The Synthesis of Oxa-Analogues and Homologues of Naturally Occurring Polyamines

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In the memory of Romeo V. Yordanov

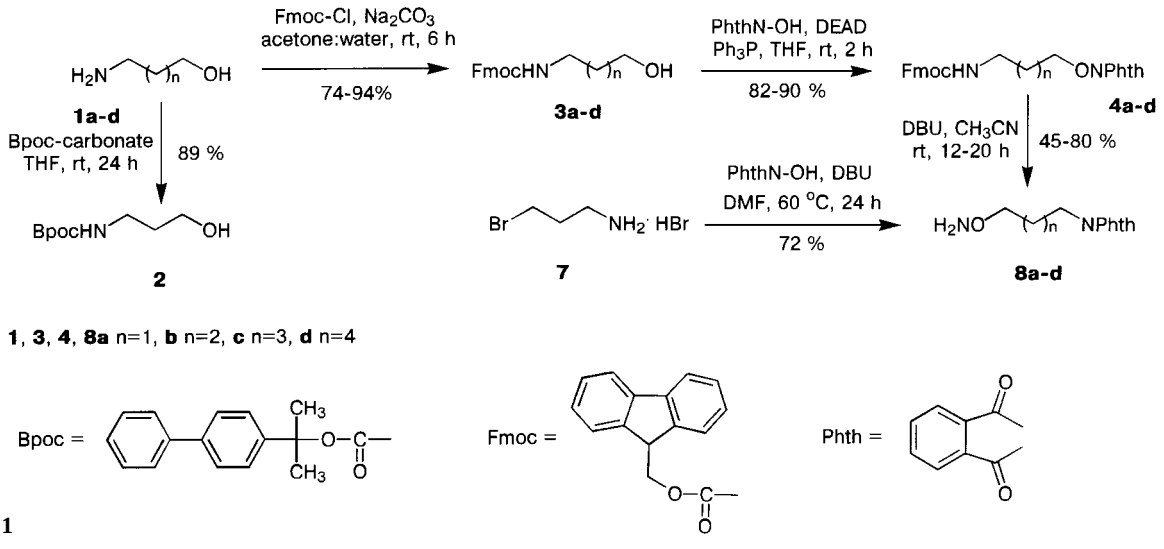
Abstract: A number of polyamine oxa-analogues **14a–d**, **19** have been synthesised. Spermidine oxa-analogues and homologues **14** were made from *N*-(aminooxypropyl)phthalimide **8**a which was obtained either from the Fmoc-deprotection of *N*-[3-(Fmoc-amino)propoxy]phthalimide **4a** or from the reaction between 3-bromopropylamine and *N*-hydroxyphthalimide, both reactions involving an unusual rearrangement mechanism. Sulphonated derivatives **9**, **16**, upon Mitsunobu condensation with *N*-protected 3-aminopropanol or *N*-alkylation with *N*-(bromoalkyl)phthalimides, afforded the fully protected spermidine and spermine oxa-analogues and homologues. Subsequent sequential deprotection gave spermidine analogues **14**. Using the same strategy, spermine oxa-analogue **19** was synthesised.

Key words: polyamines, oxa-analogues of polyamines, polyamine homologues, rearrangement, synthesis

Natural polyamines such as putrescine [$NH_2(CH_2)_4NH_2$], spermidine [$NH_2(CH_2)_3NH(CH_2)_4NH_2$] and spermine [$NH_2(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$] are ubiquitous biomolecules in living cells. Their presence is vital for the proper function and proliferation of cells.[1–3] During the last decade there has been intense interest in developing specific inhibitors to target enzymes which take part in polyamine biosynthesis, in order to elucidate the precise biological function of cellular polyamines and to develop new anticancer agents.[4] For example, a number of *N*-alkylated polyamine analogues such as N^1,N^{14}-diethylspermine demonstrated very good in vitro and in vivo activity against cancer cells[5–9] while dibenzylpolyamine analogues have been shown to be potential antimalarial and antitrypanosomal drugs.[10–13] More recently a number of reports have revealed that polyamine analogues bearing an oxyamino moiety, for example aminooxypropylamine (APA), *N*-(2-aminooxyethyl)butane-1,4-diamine and 3-aminooxy-*N*-(3-aminopropyl)propylamine, have interesting biological activity.[4–16] Furthermore, analogues of APA have also been evaluated as potential anticancer agents.[17] At physiological pH these drugs are partially deprotonated since the pKa values of the oxyamino group are in the region of 4.5–5.0[16] and this may facilitate their transport through the cell membrane. Other workers have synthesised polyamine analogues with electron-withdrawing groups either on or adjacent to the nitrogen to generate the same effect.[18, 19]

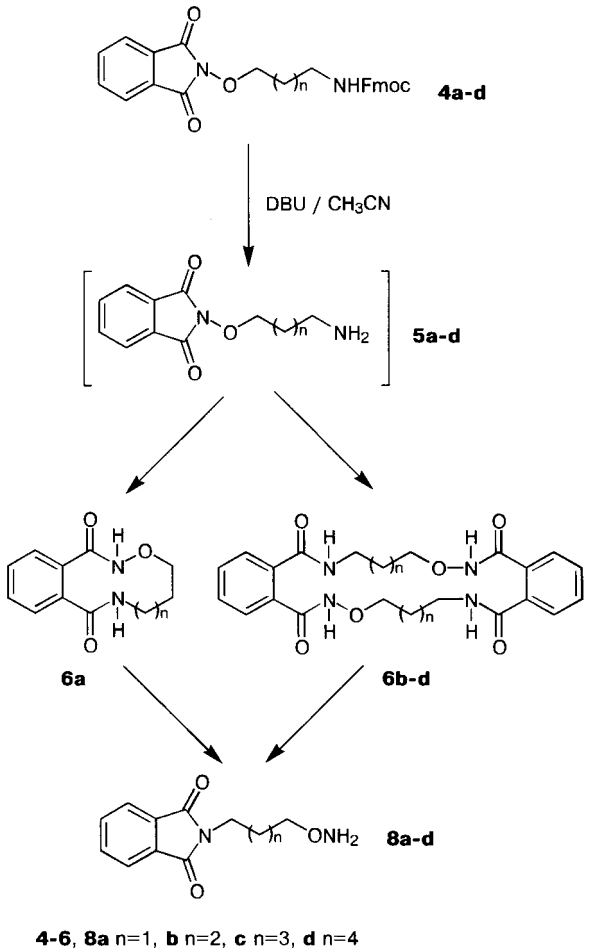
In this paper we report the synthesis of a number of polyamine oxa-analogues and homologues with the aminooxy group located within the polyamine chain.

In a recent publication[20] we reported the facile synthesis of *N*-(aminooxypropyl)phthalimide starting from 3-bromopropylamine hydrobromide (**7**) and *N*-hydroxyphthalimide in the presence of base (DBU), as shown in Scheme 1. This reaction involves firstly the nucleophilic substitution of bromine by the *N*-hydroxyphthalimide anion. Subsequent intramolecular rearrangement affords *N*-(aminooxypropyl)phthalimide (**8a**) in 72% yield. It is interesting to note that the *N*-(aminooxyalkyl)phthalimides with four, five, and six carbon chains cannot be obtained from the corresponding aminoalkyl bromide salts, In these reactions with *N*-hydroxyphthalimide, no characterisable product was isolated. However, *N*-(aminooxyalkyl)phthalimides **8b–d** were successfully obtained by the deprotection and rearrangement of the corresponding *N*-[ω-(Fmoc-amino)alkoxy]phthalimides 4 by DBU. The reac-



Scheme 1

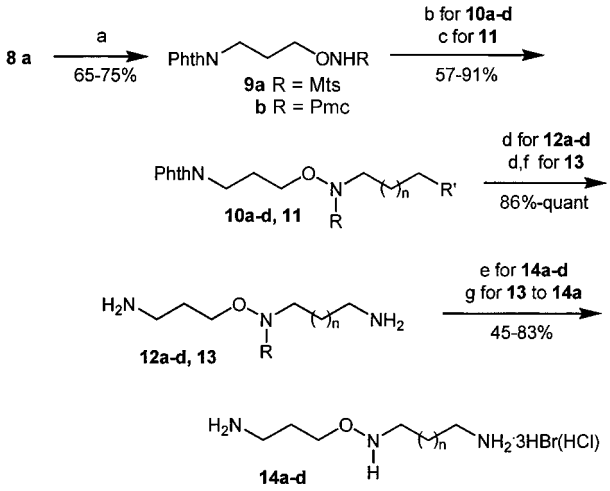
tion mechanism proposed for the formation of the *N*-(aminooxyalkyl)phthalimides is depicted in Scheme 2. The reaction mechanism proposed for the deprotection of **4a** to form **8a** is analogous to the reaction between aminopropyl bromide and *N*-hydroxyphthalimide discussed above. However for the formation of **8b–d**, the nucleophilic addition of two molecules of *N*-(aminoalkoxy)phthalimide to give large ring intermediates **6b–d** is suggested; this intermediate subsequently undergoes ring opening to give the corresponding *N*-(aminooxyalkyl)phthalimides **8b–d**. This proposal is supported by the isolation and characterisation of macrocycle **6d**. During deprotection of **4d**, if glacial acetic acid was added to the reaction mixture soon after the addition of DBU, this resulted in the formation of a precipitate in 9% yield. The mass spectrum of the precipitate gave a molecular ion at 525 m.u. and the ^{13}C NMR spectrum showed resonances at δ = 167.4, 165.2, 136.6, 133.5, 129.5, 129.3, 127.6, 127.4, suggesting two different spatial arrangements of the phthaloyl groups. This spectroscopic evidence suggests that **6d** is a macrocycle.



Scheme 2

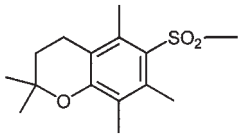
Typically the ^1H NMR spectrum of *N*-(aminooxyalkyl)phthalimides **8** showed a broad signal at δ ~5.5 which disappeared in the presence of D_2O and was hence assigned as the aminooxy group (ONH_2). The methylene groups adjacent to the aminooxy and phthalimido groups showed two groups of triplets between δ = 4.0 and 4.5 while the central methylene groups were usually located in the region of δ = 1.0–2.0. The IR spectra of **8** showed characteristic absorption bands at 3460, 3320, 1710 cm^{-1}.

In the synthesis of the spermidine analogue **14a** and homologues **14b–d**, *N*-(aminooxypropyl)phthalimide (**8a**) was used as the precursor. The aminooxy group was first activated by sulphonation and extension of the chain was effected by two methods (Scheme 3).



Compound	n	R[a]	R′	Compound	n	R[a]
10a	1	Mts	NPhth	**12a**	1	Mts
10b	2	Mts	NPhth	**12b**	2	Mts
10c	3	Mts	NPhth	**12c**	3	Mts
10d	4	Mts	NPhth	**12d**	4	Mts
11	1	Pmc	NHBpoc	**13**	1	Pmc

[a] Mts = SO_2Mes, Pmc =

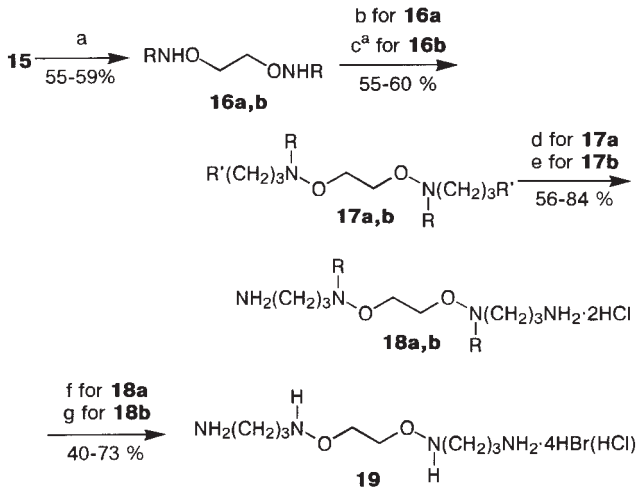


a: RCl, Et_3N, CH_2Cl_2, r.t., 24 h. **b**: $PhthN(CH_2)_nBr$, K_2CO_3, DMF, 80 °C, 12 h. **c**: **2**, DEAD, Ph_3P, THF, r.t., 2 h. **d**: $N_2H_4 \bullet H_2O$, EtOH, r.t., 24 h. **e**: HBr/HOAc, CH_2Cl_2, r.t., 24 h. **f**: HCl, MeOH, r.t., 2 h. **g**: HCl/HOAc, 80 °C, 12 h.

Scheme 3

Firstly *N*-(sulphonylaminooxypropyl)phthalimide **9b** was condensed with Bpoc-amino-protected propyl alcohol **2** under Mitsunobu conditions to give the fully protected polyamine oxa-analogue **11**. Subsequent deprotection with alcoholic hydrazine hydrate, HCl/diethyl ether and then HCl/HOAc gave the parent compound **14a**. The second method involved direct *N*-alkylation of **9a** with the appropriate *N*-(bromoalkyl)phthalimide[22] in the presence of K_2CO_3 in anhydrous DMF. Removal of the phthaloyl groups followed by treatment with HBr/HOAc gave **14**.

For the oxa-analogue of spermine **19** (Scheme 4), 1,2-bis(aminooxy)ethane dihydrochloride (**15**) was prepared



[a] Mixture DMF-THF was used. [b] Reaction conditions and reagents used were the same as shown in Scheme 3.

Compound	R	Compound	R	R′
16a, 18a	Mts	**17a**	Mts	NPhth
16b, 18b	Pmc	**17b**	Pmc	NHBpoc

a: RCl, Et_3N, CH_2Cl_2, r.t., 24 h. **b**: PhthN$(CH_2)_n$Br, K_2CO_3, DMF, 80 °C, 12 h. **c: 2**, DEAD, Ph_3P, DMF, THF, r.t., 12 h. **d**: N_2H_4•H_2O, EtOH, r.t., 24 h. **e**: HCl, MeOH, r.t., 2 h. **f**: HBr/HOAc, CH_2Cl_2, r.t., 24 h. **g**: HCl/HOAc, 80 °C, 12 h.

Scheme 4[b]

from the reaction between 1,2-dibromoethane and *N*-hydroxyphthalimide followed by acid hydrolysis.[21] Extension from both sides of the chain was done via condensation under Mitsunobu conditions or *N*-alkylation as discussed above.

In this paper we have introduced a new method to synthesise *N*-(aminooxyalkyl)phthalimides **8**, versatile precursors to oxa-analogues and homologues of naturally occurring polyamines. The synthetic strategies we have employed have generated polyamine oxa-analogues with orthogonal protection. For example the phthaloyl groups in compounds **10** can be selectively removed with hydrazine, leaving the mesityl group intact, thus introducing the possibility of extending the chain from both sides. In compound **11** the Bpoc group can be selectively removed with acid thereby allowing chain extension on one side. Furthermore, oxa-analogues of polyamines are a new family of compounds which can be used in the design of a number of biologically active compounds and they can be also applied to the synthesis of novel oxa-azamacrocycles, an area in which we are currently working.

Unless otherwise stated all reagents were purchased from Aldrich, Fluka and Lancaster and were used without further purification. Mps were determined on a Gallenkamp melting point apparatus in open capillaries and are uncorrected. TLC was performed on Kieselgel plates (Merck) 60 F_{254} in either $CHCl_3$/MeOH (97:3 or 99:1) or hexane/acetone (3:1). Plates were visualised using UV-light or an iodine vapour bath. Silica gel Kieselgel 60 (230–400 mesh ASTM) was used for column chromatography. IR spectra were recorded on a Nicolet 5ZDX FT-IR spectrophotometer or on a Perkin–Elmer 781 IR spectrophotometer. ^1H and ^{13}C spectra were recorded on a JEOL JNM-EX90 FT NMR spectrometer. FAB-MS were obtained on a VG Analytical AutoSpec (25 kV) spectrometer, EI/CI-MS spectra were performed on Micromass Quattro II (low resolution) or VG Analytical ZAB-E instruments (accurate mass). DMF was distilled prior to use. CH_2Cl_2 and THF were distilled over P_2O_5. Compounds 1,2-bis(aminooxy)ethane (**15**),[21] *ω*-bromoalkylphthalimides,[22] 1-(biphenyl-4-yl)-1-methylethyl 4-methoxycarbonylphenyl carbonate (Bpoc-carbonate),[23] and 2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-chromen-6-ylsulphonyl chloride (Pmc-Cl)[24] were synthesised as described in the literature.

3-[1-(Biphenyl-4-yl)-1-methylethoxycarbonylamino]propanol (2):
To a solution of 3-aminopropanol (**1a**) (1.08 g, 14.4 mmol) in THF (32 mL), Bpoc-carbonate (5.61 g, 14.4 mmol) was added and the mixture was stirred at r.t. for 24 h. Solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (30 mL) and washed with 1 M NaOH (5 × 50 mL), water (100 mL), and dried (Na_2SO_4). Evaporation of $CHCl_3$ gave 4.03 g (89%) of product which was used without further purification; mp 118–119 °C (MeCN).
^1H NMR ($CDCl_3$): δ = 7.33–7.61 (m, 9H), 5.03 (s, 1H, N*H*), 3.60 (t, 2H), 3.14–3.35 (m, 2H), 2.51 (s, 1H, OH), 1.79 (s, 6H), 1.55–1.69 (m, 2H).
^{13}C NMR ($CDCl_3$): δ = 157.6 (*C*=O), 145.4, 140.6, 139.5, 128.6, 127.0, 126.9, 126.8, 124.5 (arom. *C*), 80.6, 59.2, 38.2, 32.4, 28.9.
IR (Nujol): ν = 3290 (NH), 3240 (OH), 1678 cm^{-1} (C=O).

***N*-(9-Fluorenylmethoxycarbonyl)-*ω*-amino Alcohols 3; General Procedure:**
Amino alcohol, (11 mmol) was dissolved in aq acetone (1:1, 20 mL) followed by the addition of sat. aq Na_2CO_3 (2.5 mL) and a solution of 9-fluorenylmethyl chloroformate (Fmoc-Cl) (10 mmol) in acetone (10 mL). The mixture was stirred for 6 h at r.t. and the solvent was then removed under reduced pressure. The crude product was dissolved in $CHCl_3$ (40 mL) and was washed with water (2 × 40 mL); the organic layer was dried (anhyd Na_2SO_4) and filtered. After removal of solvent in vacuo, Fmoc-protected amino alcohol was obtained as a white solid which was used without further purification. An analytical sample was prepared by recrystallisation from MeCN (Table 1).

***ω*-[*N*-(9-Fluorenylmethoxycarbonyl)amino]-*O*-phthalimido Alcohols 4 (Mitsunobu Reaction); General Procedure:**
A solution of DEAD (5.57 mg, 32 mmol) in anhyd THF (10 mL) was added dropwise with stirring to a suspension of Fmoc-amino alcohol **3** (16 mmol), *N*-hydroxyphthalimide (PhthN-OH) (5.22 g, 32 mmol), and Ph_3P (8.39 g, 32 mmol). The mixture was stirred for 2 h at r.t. and after removal of solvent under reduced pressure, the residue was taken up into $CHCl_3$ (100 mL) and washed with sat. $NaHCO_3$ (4 × 100 mL) and water (100 mL). The organic layer was dried (Na_2SO_4) and evaporation of solvent followed by the addition of MeOH (100 mL) afforded a white precipitate. The latter was filtered off, washed with cold MeOH and dried to give the product. For analytical purposes a sample was recrystalised from MeCN (Table 1).

***N*-[*ω*-(Aminooxy)alkyl]phthalimides 8 (Fmoc-Deprotection); General Procedure:**
A solution of DBU (0.85 g, 5.58 mmol) in anhyd MeCN (7 mL) was added dropwise with stirring to a suspension of Fmoc-amino-*O*-phthalimido alcohol **4a–d** (5.58 mmol) in MeCN (10 mL). The mixture was allowed to stir for 12–20 h at r.t. Removal of the solvent in vacuo followed by column chromatography on silica gel ($CHCl_3$) afforded the pure oxyamine as a yellow oil (Table 2).

***N*-[3-(Aminooxy)propyl]phthalimide (8a) (*O*-Alkylation of *N*-Hydroxyphthalimide):**
DBU (10.6 g, 69.5 mmol) was added dropwise to stirred mixture of 3-bromopropylamine hydrobromide (**7**) (6.92 g, 31.6 mmol), and *N*-hydroxyphthalimide (5.51 g, 33.8 mmol) in anhyd DMF (60 mL). The re-

Table 1. *N*-(9-Fluorenylmethoxycarbonyl)-ω-amino Alcohols **3** and ω-[*N*-(9-Fluorenylmethoxycarbonyl)amino]-*O*-phthalimido Alcohols **4**

Product	Yield (%)	mp (°C)	IR (Nujol) ν (cm^{-1})	^{1}H NMR ($CDCl_3$) δ	^{13}C NMR ($CDCl_3$) δ	HRMS (FAB) *m/z*
3a	91	126–127	3440 (OH), 3321 (NH), 1688 (C=O)	7.23–7.90 (m, 8H), 5.38 (t, 1H, N*H*), 4.16–4.73 (m, 3H), 3.71 (t, 2H), 3.26–3.52 (m, 2H), 3.14 (s, 1H, O*H*), 1.62–1.87 (m, 2H)	157.2 (*C*=O), 143.8, 141.2, 127.6, 126.9, 124.9, 119.8 (arom. *C*), 66.5, 59.5, 47.2, 38.0, 32.3	–
3b	91	112–113	3338 (OH), 3324 (NH), 1693 (C=O)	7.09–7.71 (m, 8H), 4.83 (s, 1H, N*H*), 4.02–4.36 (m, 3H), 3.54 (t, 2H), 2.98–3.20 (m, 2H), 1.73 (s, 1H, O*H*), 1.21–1.53 (m, 4H)	156.1 (*C*=O), 143.5, 140.9, 127.2, 126.5, 124.5, 119.5 (arom. *C*), 66.1, 61.9, 46.9, 40.0, 29.2, 26.1	–
3c	95	106–107 (dec)	3430 (OH), 3324 (NH), 1693 (C=O)	7.02–7.70 (m, 8H), 4.97 (t, 1H, N*H*), 4.02–4.36 (m, 3H), 3.49 (t, 2H), 2.89–3.23 (m, 2H), 2.23 (s, 1H, O*H*), 1.11–1.64 (m, 6H)	156.5 (*C*=O), 143.9, 141.2, 127.5, 126.9, 124.9, 119.8 (arom. *C*), 66.4, 62.3, 47.2, 40.8, 32.0, 29.6, 22.8	–
3d	74	127–128 (dec)	3389 (OH), 3342 (NH), 1688 (C=O)	7.15–7.71 (m, 8H), 4.67 (t, 1H, N*H*), 4.02–4.36 (m, 3H), 3.38–3.62 (t, 2H), 2.96–3.18 (m, 2H), 1.03–1.58 (m, 9H)	156.5 (*C*=O), 144.0, 141.4, 127.6, 127.0, 125.0, 119.9 (arom. *C*), 67.0, 62.7, 47.3, 41.0, 32.6, 30.0, 26.4, 25.3	–
4a	83	143–144	3328 (NH), 1726, 1681 (C=O)	7.09–7.84 (m, 12H), 5.76 (br t, 1H, N*H*), 4.12–4.35 (m, 5H), 3.33–3.46 (m, 2H), 1.83–1.96 (m, 2H)	163.7, 156.6 (*C*=O), 144.7, 141.3, 134.6, 128.9, 127.6, 126.9, 125.2, 123.6, 119.9 (arom. *C*), 76.2, 66.6, 47.3, 37.7, 27.8	Calcd ($C_{26}H_{22}N_2O_5$) 442.471. Found 443.151 [MH]$^+$
4b	90	158–159 (dec)	3325 (NH), 1724, 1685 (C=O)	7.11–7.80 (m, 12H), 5.00 (br t, 1H, N*H*), 4.13–4.36 (m, 5H), 3.02–3.37 (m, 2H), 1.38–1.80 (m, 4H)	163.2, 156.0 (*C*=O), 143.6, 140.9, 134.0, 128.5, 127.1, 126.5, 124.6, 123.0, 119.4 (arom. *C*), 77.6, 66.1, 46.9, 40.2, 25.8, 25.0	Calcd ($C_{27}H_{24}N_2O_5$) 456.498. Found 457.178 [MH]$^+$
4c	83	188–189 (dec)	3340 (NH), 1727, 1692 (C=O)	7.17–7.83 (m, 12H), 4.97 (br t, 1H, N*H*), 4.05–4.34 (m, 5H), 3.07–3.30 (m, 2H), 1.25–1.89 (m, 6H)	163.5, 156.4 (*C*=O), 143.6, 141.2, 134.3, 128.8, 127.5, 126.9, 124.9, 123.3, 119.8 (arom. *C*), 78.1, 66.4, 47.2, 41.2, 29.3, 27.6, 22.6	Calcd ($C_{28}H_{26}N_2O_5$) 470.525. Found 471.193 [MH]$^+$
4d	86	157–158 (dec)	3343 (NH), 1734, 1688 (C=O)	7.11–7.79 (m, 12H), 4.81 (br t, 1H, N*H*), 4.05–4.36 (m, 5H), 2.92–3.25 (m, 2H), 1.25–1.89 (m, 8H)	164.0, 157.0 (*C*=O), 144.1, 141.3, 134.4, 129.0, 127.6, 127.0, 125.0, 123.4, 119.9 (arom. *C*), 78.3, 66.0, 47.3, 40.1, 29.7, 28.0, 26.2, 25.2	Calcd ($C_{29}H_{28}N_2O_5$) 484.552. Found 485.107 [MH]$^+$

action was left at 60 °C for 24 h. DMF was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (50 mL), washed with sat. $NaHCO_3$ (4 × 50 mL) and brine (50 mL), dried (Na_2SO_4), and filtered through silica gel. Removal of solvent in vacuo yielded 5.00 g (72%) of a yellow oil, which crystallised on standing (mp 67–69 °C). The compound obtained showed spectroscopic properties identical to **8a**.
Anal.: Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.90; H, 5.57; N, 12.86.

Cyclic Amide 6d:
To a suspension of **4d** (2.34 g, 4.82 mmol) in anhyd MeCN (20 mL) was added DBU (0.73 g, 4.79 mmol). After all the precipitate had dissolved, glacial HOAc (0.58 g, 9.66 mmol) was added. The precipitate formed was filtered off, washed with MeCN and dried to give 0.23 g (9%) of macroheterocycle **6d**, which was recrystallised from DMF.
^{1}H NMR ($CDCl_3$): δ = 7.91–8.20 (m, 8H, phthaloyl), 3.97 (m, 4H, CH_2-11,24), 3.39 (m, 4H, CH_2-5,18), 1.47 (m, 16H, CH_2-6,7,8,9,19,20,21,22).
^{13}C NMR ($CDCl_3$): δ = 167.4, 165.2 (*C*=O), 136.6, 133.5, 129.5, 129.3, 127.6, 127.4 (phthaloyl *C* and *CH*), 75.0 (*C*-11,24), 39.1 (*C*-5,18), 28.9, 27.5, 26.0, 25.2 (*C*-6,7,8,9,19,20,21,22).
IR (Nujol): ν = 3252, 3115 (N–H), 1627 cm^{-1} (C=O).
LRMS (FAB): calcd for $C_{28}H_{36}N_4O_6$ 524.62, found 525.00 [MH]$^+$.

***N*-{3-[(Mesitylsulphonyl)aminooxy]propyl}phthalimides 9; General Procedure:**
Mesitylsulphonyl chloride (26.2 mmol) was added portionwise to a stirred solution of **8a** (5.49 g, 24.9 mmol) and Et_3N (2.68 g, 26.5 mmol) in anhyd CH_2Cl_2 (20 mL) at 0 °C. After 24 h at r.t., $CHCl_3$ (50 mL) was added and the solution was washed with 1 M HCl (50 mL), sat. $NaHCO_3$ (2 × 50 mL), and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered through silica gel and, after removal of solvent under reduced pressure, Et_2O (40 mL) was added to the residue. The mixture was allowed to stir for 30 min and then cooled; the crystals formed were filtered off, washed with cold Et_2O, and dried to give the product as a white solid.

N-*{3-[(Mesitylsulphonyl)aminooxy]propyl}phthalimide* (**9a**): yield: 75%; mp 137–138 °C (Et_2O/THF).
^{1}H NMR ($CDCl_3$): δ = 7.67–7.91 (m, 4H), 7.55 (s, 1H, ON*H*), 6.97 (s,

Table 2. *N*-[ω-(Aminooxy)alkyl]phthalimides **8**

Product	Yield (%)	Time (h)	IR ν (cm^{-1})	^1H NMR δ	^{13}C NMR δ	HRMS (FAB) *m/z*
8a	55–72	12	3460, 3320 (N–H), 1710 (C=O), 1592, 1055 (neat)	7.48–7.76 (m, 4H), 5.33 (br s, 2H, ONH_2), 3.34–3.71 (m, 4H), 1.60–1.89 (m, 2H) ($CDCl_3$)	167.6 (*C*=O), 133.3, 131.5, 122.5 (arom. *C*), 72.4, 34.6, 26.9 ($CDCl_3$)	Calcd[a] ($C_{11}H_{13}ClN_2O_3$) 256.689. Found 221.082 $[MH–HCl]^+$
8b[a]	42	12	2667 (NH_3^+), 1713 (C=O), 1597, 1042 (Nujol)	11.02 (br s, 3H, ONH_3^+), 7.82 (m, 4H), 4.02 (t, 2H), 3.50 (t, 2H), 1.40–1.80 (m, 4H) (DMSO-d_6)	167.9 (*C*=O), 134.3, 131.6, 122.9 (arom. *C*), 73.5, 37.0, 24.6, 24.3 (DMSO-d_6)	Calcd[a] ($C_{12}H_{15}ClN_2O_3$) 270.716. Found 235.109 $[MH–HCl]^+$
8c	74	12	3463, 3320 (N–H), 1710 (C=O), 1596, 1055 (neat)	7.64–7.90 (m, 4H), 5.37 (br s, 2H, ONH_2), 3.58–3.77 (m, 4H), 1.26–1.85 (m, 6H) ($CDCl_3$)	168.6 (*C*=O), 134.0, 132.4, 123.3 (arom. *C*), 75.9, 38.0, 28.6, 28.1, 23.5 ($CDCl_3$)	Calcd[a] ($C_{13}H_{17}ClN_2O_3$) 284.742. Found 249.125 $[MH–HCl]^+$
8d	80	24	202 (NH_3^+), 1712 (C=O), 1597, 1060 (Nujol)[a]	7.62–7.84 (m, 4H), 5.39 (br s, 2H, ONH_2), 3.37–3.73 (m, 4H), 1.20–1.85 (m, 8H) ($CDCl_3$)	168.4 (*C*=O), 133.8, 132.2, 123.1 (arom. *C*), 77.2, 37.9, 28.6, 28.2, 26.7, 25.6 ($CDCl_3$)	Calcd[a] ($C_{14}H_{19}ClN_2O_3$) 298.769. Found 263.152 $[MH–HCl]^+$

[a] For the hydrochloride salt.

2H), 3.94 (t, 2H), 3.72 (t, 2H), 2.67 (s, 6H), 2.32 (s, 3H), 1.78–2.13 (m, 2H).
^{13}C NMR ($CDCl_3$): δ = 168.1 (*C*=O), 143.2, 140.5, 133.8, 131.9, 130.8, 123.1 (arom. *C*), 74.3, 34.7, 27.1, 22.9, 20.9.
IR (Nujol): ν = 3244 (N–H), 1695 (C=O), 1338, 1162 cm^{-1} (SO_2).

N-*{3-[(2,2,5,7,8-Pentamethyl-3,4-dihydro-2*H*-chromen-6-ylsulphonyl)aminooxy]propyl}phthalimide* (**9b**): yield: 65%; mp 129–130 °C (Et_2O/THF).
^1H NMR ($CDCl_3$): δ – 7.70–7.93 (m, 4H), 7.41 (s, 1H, N*H*), 4.02 (t, 2H), 3.77 (t, 2H), 2.61 (s, 6H), 2.40–2.82 (t, 2H), 2.18 (s, 3H), 1.61–2.18 (m, 4H), 1.40 (s, 6H).
^{13}C NMR ($CDCl_3$): δ = 167.9 (C=O), 155.1, 137.9, 137.7, 133.6, 131.6, 125.7, 124.4, 122.8, 118.3 (arom. *C*), 74.0, 73.9, 34.6, 32.2, 27.0, 26.4, 21.0, 18.3, 17.3, 11.9.
IR (Nujol): ν = 3220 (N–H), 1710 (C=O), 1322, 1162 cm^{-1} (SO_2).

5-(Mesitylsulphonyl)-α,ω-diphthalimido-4-oxa-5-azaalkanes 10; General Procedure (Alkylation Reaction):
A mixture ofmesitylsulphonyl amide **9a** (3.13 mmol), *N*-(bromoalkyl)-phthalimide (3.13 mmol), and anhyd K_2CO_3 (0.91 g, 6.58 mmol) in anhyd DMF (8 mL) was allowed to stir at 80 °C for 12 h. DMF was removed under reduced pressure and the residue was taken up in $CHCl_3$ (50 mL), washed with 2 M HCl (2 × 50 mL), sat. $NaHCO_3$ (50 mL), and water (2 × 50 mL), dried (Na_2SO_4), and filtered through silica gel. Solvent was removed in vacuo followed by the addition of Et_2O (30 mL). The mixture was allowed to stir for 20 min, cooled, and the crystals formed were filtered off, washed with cold Et_2O, and dried to give the product as a white solid, which was used without further purification. An analytical sample was prepared by recrystallization from Et_2O/THF (Table 3).

8-[1-(Biphenyl-4-yl)-1-methylethoxycarbonylamino]-5-(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-chromen-6-ylsulphonyl)-1-phthalimido-4-oxa-5-azaoctane (11) (Mitsunobu Reaction):
11 was obtained from **2** and **9b** using the Mitsunobu method described above and was purified by column chromatography on silica gel ($CHCl_3$) to give pure product as a yellow oil; yield 80%.
^1H NMR ($CDCl_3$): δ = 7.2–8.1 (m, 13H), 5.38 (t, 1H, N*H*), 3.1–3.9 (m, 8H), 1.5–3.0 (m, 8H), 2.61 (s, 6H), 2.18 (s, 3H), 1.89 (s, 6H), 1.35 (s, 6H).
^{13}C NMR ($CDCl_3$): δ = 167.6, 155.3 (C=O), 145.4, 140.3, 138.9, 138.8, 138.7, 133.5, 131.4, 128.2, 126.6, 126.5, 124.6, 124.5, 124.4, 122.7, 118.4 (arom. *C*), 80.0, 73.9, 73.8, 47.5, 38.5, 34.7, 32.1, 28.7, 27.0, 26.2, 25.2, 21.0, 18.2, 17.2, 11.7.
IR (Nujol): ν = 3400 (N–H), 1710 (C=O), 1340; 1160 cm^{-1} (SO_2).

α,ω-Diamino-5-(mesitylsulphonyl)-4-oxa-5-azaalkanes 12; General Procedure (Removal of the Phthaloyl Protecting Group):
Phthaloyl-protected oxapolyamine **10** (1.94 mmol) was dissolved in EtOH (30 mL) at 70°C and $N_2H_4 \bullet H_2O$ (0.20 g, 4.00 mmol) was added. The reaction was left to stir at r.t. for 24 h. The precipitate formed was filtered off and the filtrate was evaporated in vacuo. The residue was treated with $CHCl_3$ (20 mL), filtered, and the filtrate was evaporated again to yield the compound as a yellow oil in quantitative yield (Table 3). To form the dihydrochloride salt, diamine was dissolved in Et_2O/MeOH (5:1, 10 mL) and sat. HCl/Et_2O (3 mL) was added. The mixture was then cooled, precipitate formed was filtered off and washed with cold Et_2O and dried to afford the dihydrochloride salt as a white solid.

5-(2,2,5,7,8-Pentamethyl-3,4-dihydro-2*H*-chromen-6-ylsulphonyl)-4-oxa-5-azaoctane-1,8-diamine Dihydrochloride (13):
*8-[I-(Biphenyl-4-yl)-1-methylethoxycarbonylamino]-5-(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-chromen-6-ylsulphonyl)-4-oxa-5-azaoctan-1-amine:*
The phthaloyl group of **11** was removed using the same procedure as for **12** to give the product as a yellow oil; yield: 86%.
^1H NMR ($CDCl_3$): δ = 7.3–7.9 (m, 9H), 3.0–3.8 (m, 6H), 2.3–3.0 (m, 10H), 2.2 (s, 3H), 1.4–2.1 (m, 4H), 1.86 (s, 6H), 1.38 (s, 6H).
^{13}C NMR ($CDCl_3$): δ = 155.7, 155.2, 145.4, 140.6, 139.3, 139.0, 128.5, 126.9, 126.8, 126.8, 124.8, 124.6, 118.6 (arom. *C*), 80.4, 74.2, 73.5, 38.6, 38.4, 38.3, 32.3, 28.9, 27.2, 26.5, 21.2, 18.4, 17.4, 12.0.

5-*(2,2,5,7,8-Pentamethyl-3,4-dihydro-2*H*-chromen-6-ylsulphonyl)-4-oxa-5-azaoctane-1,8-diamine Dihydrochloride* (**13**):
The NPhth-deprotected material was used directly for the deprotection of the Bpoc group. To a suspension of the amine (2.38 g, 3.6 mmol) in MeOH (15 mL) was added a solution of sat. HCl in MeOH (10 mL) and the mixture stirred for 2 h min. After removal of most of the MeOH, cold EtOAc was added to precipitate the product. After

Table 3. 5-(Mesitylsulphonyl)-α,ω-diphthalimido-4-oxa-5-azaalkanes **10** and α,ω-Diamino-5-(arylsulphonyl)-4-oxa-5-azaalkanes **12**, **13**

Product	Yield (%)	mp (°C)	IR (Nujol) ν (cm^{-1})	^1H NMR δ	^{13}C NMR δ	MS *m/z*
10a	75	116–117	1710 (C=O), 1332, 1183 (SO_2)	7.55–7.92 (m, 8H), 6.94 (s, 2H), 3.27–3.88 (m, 8H), 2.66 (s, 6H), 2.26 (s, 3H), 1.96–2.20 (m, 2H), 1.67–1.92 (m, 2H) ($CDCl_3$)	167.5, 167.4 (*C*=O), 143.4, 141.1, 133.4, 131.5, 129.3, 122.6, 122.5 (arom. *C*), 73.4, 47.2, 35.3, 34.5, 27.0, 25.5, 22.6, 20.6 ($CDCl_3$)	Calcd ($C_{31}H_{31}N_3O_7S$) 589.6670. Found 607.2230 $[M+NH_4]^+$ HRMS (CI)
10b	57	121–122	1709 (C=O), 1333, 1151 (SO_2)	7.69–7.99 (m, 8H), 6.99 (s, 2H), 3.36–3.80 (m, 8H), 2.72 (s, 6H), 2.33 (s, 3H), 1.66–2.07 (m, 6H) ($CDCl_3$)	168.0, 167.8 (*C*=O), 143.5, 141.7, 133.7, 133.6, 131.9, 131.8, 129.8, 122.9 (arom. *C*), 73.6, 48.9, 37.3, 34.9, 27.2, 25.9, 24.2, 22.9, 20.8 ($CDCl_3$)	Calcd ($C_{32}H_{33}N_3O_7S$) 603.6939. Found 621.2380 $[M+NH_4]^+$ HRMS (CI)
10c	91	130–132	1713, 1700 (C=O), 1348, 1164 (SO_2)	7.67–7.92 (m, 8H), 6.94 (s, 2H), 3.20–3.79 (m, 8H), 2.66 (s, 6H), 2.27 (s, 3H), 1.40–1.89 (m, 8H) ($CDCl_3$)	167.6, 167.4 (*C*=O), 143.2, 141.3, 133.4, 131.6, 131.5, 131.4, 129.6 (arom. *C*), 73.2, 48.9, 37.2, 34.5, 27.6, 26.9, 26.0, 23.8, 22.6, 20.5 ($CDCl_3$)	Calcd ($C_{33}H_{35}N_3O_7S$) 617.7208. Found 635.2540 $[M+NH_4]^+$ HRMS (CI)
10d	64	133–134	1705 (C=O), 1330, 1160 (SO_2)	7.71–7.95 (m, 8H), 6.99 (s, 2H), 3.23–3.82 (m, 8H), 2.72 (s, 6H), 2.32 (s, 3H), 1.34–1.83 (m, 10H) ($CDCl_3$)	168.3, 168.0 (*C*=O), 143.6, 141.8, 133.9, 133.8, 132.2, 132.1, 131.8, 130.2, 123.1 (arom. *C*), 73.7, 49.6, 37.8, 35.1, 28.4, 27.4, 26.8, 26.6, 26.4, 23.0, 21.0 ($CDCl_3$)	Calcd ($C_{34}H_{37}N_3O_7S$) 631.7477. Found 649.2696 $[M+NH_4]^+$ HRMS (CI)
12a	>95		3328, 3280 (N–H), 1338, 1162 (SO_2) (neat)	7.05 (s, 2H), 3.22–3.62 (m, 4H), 2.90 (t, 2H), 2.74 (s, 6H), 2.59 (t, 2H), 2.38 (s, 3H), 1.90 (m, 2H), 1.62 (m, 2H) ($CDCl_3$)	143.7, 141.9, 131.9, 130.1 (arom. *C*), 73.9, 47.3, 39.6, 38.7, 32.0, 30.7, 23.1, 21.0 ($CDCl_3$)	Calcd[a] ($C_{15}H_{29}Cl_2N_3O_3S$) 402.385. Found 331 $[MH–2HCl]^+$ LRMS (FAB)
12b	>95		2020 (NH_3^+), 1605 (N–H), 1330, 1160 (SO_2)[a]	6.91 (s, 2H), 3.37 (t, 2H), 3.20 (t, 2H), 2.30–2.72 (m, 4H), 2.61 (s, 6H), 2.24 (s, 3H), 1.12–1.82 (m, 6H) ($CDCl_3$)	143.5, 141.1, 131.8, 130.1 (arom. *C*), 73.8, 49.3, 41.6, 38.8, 32.1, 30.9, 24.2, 22.9, 20.9 ($CDCl_3$)	Calcd[a] ($C_{16}H_{31}Cl_2N_3O_3S$) 416.412. Found 344 $[MH–2HCl]^+$ LRMS (FAB)
12c	>95		2030 (NH_3^+), 1605 (N–H), 1338, 1150 (SO_2)[a]	7.04 (s, 2H), 3.51 (t, 2H), 3.33 (t, 2H), 2.58–2.80 (m, 4H), 2.74 (s, 6H), 2.38 (s, 3H), 1.27–1.82 (m, 6H) ($CDCl_3$)	143.6, 141.8, 131.9, 130.1 (arom. *C*), 73.8, 49.4, 41.4, 38.5, 32.2, 31.7, 26.6, 24.2, 23.0, 21.0 ($CDCl_3$)	Calcd[a] ($C_{17}H_{33}Cl_2N_3O_3S$) 430.439. Found 358 $[MH–2HCl]^+$ LRMS (FAB)
12d[a]	>95		2000 (NH_3^+), 1605 (N–H), 1320, 1153 (SO_2)[a]	7.18 (s, 2H), 3.62 (t, 2H), 3.30 (t, 2H), 2.81–3.10 (m, 4H), 2.74 (s, 6H), 2.40 (s, 3H), 1.30–2.05 (m, 10H) (CD_3OD)	145.9, 142.9, 133.2, 130.9 (arom. *C*), 74.2, 50.7, 40.7, 38.3, 28.4, 27.7, 27.5, 26.9, 23.3, 21.1 (CD_3OD)	Calcd[a] ($C_{18}H_{35}Cl_2N_3O_3S$) 444.466. Found 372 $[MH–2HCl]^+$ LRMS (FAB)
13[a]	86		1950 (NH_3^+), 1600 (N–H), 1335, 1160 (SO_2)	8.38 (br s, 6H, 2 × NH_3^+), 3.59 (t, 2H), 3.36 (t, 2H), 2.56 (s, 6H), 2.4–3.2 (m, 6H), 2.16 (s, 3H), 1.5–2.15 (s, 6H, CH_2-2,7), 1.35 (s, 6H) (DMSO-d_6)	155.1, 138.8, 138.3, 124.4, 124.1, 119.2 (arom. *C*), 74.5, 72.6, 46.7, 36.7, 35.8, 31.7, 26.3, 25.9, 24.2, 20.7, 18.3, 17.3, 12.0 (DMSO-d_6)	Calcd[a] ($C_{20}H_{37}Cl_2N_3O_4S$) 486.501. Found 441.243 $[MH–2HCl]^+$ HRMS (FAB)

[a] For the dihydrochloride salt.

filtration, washing and drying the diamine salt **13** was obtained as a white powder (Table 3).

α,ω-Diamino-4-oxa-5-azaalkanes 14; General Procedure (Removal of the Mesitylsulphonyl Protecting Group):

To a solution of mesitylsulphonyl-protected oxapolyamine **12** (5.89 mmol) in CH_2Cl_2 (5 mL) 30% HBr in HOAc (5mL) was added and mixture was stirred for 24 h at r.t. The precipitate formed was filtered off, washed with EtOAc (5 × 10 mL) and dried in a desiccator ovemight to give the trihydrobromide salt as a yellow hygroscopic powder (Table 4).

4-Oxa-5-azaoctane-1,8-diamine Trihydrochloride (14a); Typical Procedure (Removal of the Pmc Protecting Group):

The dihydrochloride salt of **13** (0.52 g, 1.00 mmol) was suspended in a solution of HCl in glacial HOAc (20 mL) in a screwtop bottle and

Table 4. α,ω-Diamino-4-oxa-5-azaalkanes **14** and 5,8-Dioxa-4,9-diazadodecane-1,12-diamine (**19**)

Product	Yield (%)	IR (Nujol) ν (cm^{-1})	^1H NMR δ	^{13}C NMR δ	LRMS (FAB) *m/z*
14a	47–71	3070, 2680, 2480, 2000, 1600, 1273, 1169, 1060, 955, 850, 787	4.27 (t, 2H), 3.51 (t, 2H), 3.07–3.24 (m, 4H), 1.95–2.33 (m, 4H) (D_2O)	80.1, 54.9, 45.3, 45.0, 33.8, 30.0 (D_2O)	Calcd ($C_6H_{20}Br_3N_3O$) 389.956. Found 148 [M–3HBr+H^+]
14b	68	3080, 2730, 2505, 2495, 1600, 1310, 995, 895, 760	–	72.2, 49.5, 39.8, 37.5, 24.9, 24.8, 21.2 (D_2O)	Calcd ($C_7H_{22}Br_3N_3O$) 403.983. Found 162 [M–3HBr+H^+]
14c[a]	83	–	3.66 (t, 2H), 2.40–2.82 (m, 6H), 1.04–1.80 (m, 8H)	71.6, 51.7, 41.7, 39.2, 33.3, 32.4, 26.9, 24.2 ($CDCl_3$) ($CDCl_3$)	(EI/CI): Calcd ($C_8H_{21}N_3O$) 175.284. Found 176 [M+H^+]
14d	46	–	3.67 (t, 2H), 2.40–2.90 (m, 6H), 1.20–1.78 (m, 10H) ($CDCl_3$)	2.2, 52.2, 42.2, 39.7, 33.9, 32.9, 27.5, 27.3, 27.0 ($CDCl_3$)	Calcd ($C_9H_{24}Cl_3N_3O$) 298.683. Found 192 [M–2HCl+3H^+]
19	40–73 –		7.9–8.5 (br s, 6H), 4.35 (s, 4H), 3.1–3.45 (m, 4H), 2.7–3.1 (m, 4H), 1.8–2.22 (m, 4H) (DMSO-d_6)	70.29, 45.51, 36.28, 21.61 (DMSO-d_6)	Calcd ($C_8H_{26}Br_4N_4O_2$) 529.936. Found 228.2 [M–4HBr+Na^+]

[a] Product was isolated as the free base.

the suspension heated for 24 h at 80 °C. The mixture was cooled, concentrated in vacuo and the residue treated with MeOH, EtOAc and Et_2O to precipitate a fawn-coloured solid. After filtration and drying, 0.13 g (47%) of the salt was obtained. Spectroscopic properties were consistent to those of the trihydrobromide salt (Table 4).

1,2-Bis[(mesitylsulphonyl)aminooxy]ethane (16a):
A mixture of **15** (3.30 g, 20 mmol), mesitylsulphonyl chloride (8.75 g, 40 mmol) and Et_3N (4.05 g, 40 mmol) in CH_2Cl_2 (15 mL) was left to stir at r.t. for 24 h. The mixture was worked up as for **9a** to give crude product which was recrystallised from toluene to give **16a** as a white solid; yield: 55%; mp 116–117 °C (dec).
^1H NMR ($CDCl_3$): δ = 7.04 (s, 4H), 7.32 (s, 2H, N*H*), 4.00 (s, 4H), 2.65 (s, 12H), 3.49 (s, 6H).
^{13}C NMR ($CDCl_3$): δ = 143.6, 140.8, 132.1, 130.8 (arom. *C*), 73.8, 22.9, 21.0.
IR (Nujol): ν = 3250, 1600 (N–H), 1350, 1160 cm^{-1} (SO_2).

1,2-Bis[(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-chromen-6-ylsulphonyl)aminooxy]ethane (16b):
Reaction conditions were the same as for **16a**. The precipitate formed after reaction was filtered off and washed with water (100 mL), and MeCN (50 mL), and dried to provide the title compound as a white powder in 59% yield; mp 198–199 °C (dec) (DMF).
^1H NMR ($CDCl_3$): δ = 3.97 (s, 4H), 3.43 (s, 6H), 2.69 (s, 6H), 2.49 (s, 12H), 2.14 (s, 6H), 1.89 (t, 4H), 1.38 (s, 12H).
^{13}C NMR ($CDCl_3$): δ = 154.8, 138.1, 137.9, 127.2, 123.8, 118.8 (arom. *C*), 74.4, 73.7, 32.2, 26.6, 21.0, 18.6, 17.6, 12.2.
IR (Nujol): ν = 3230, 1665 (N–H), 1540, 1320 (SO_2), 1298, 1154 (SO_2), 1103 cm^{-1}.

4,9-Bis(mesitylsulphonyl)-1,12-diphthalimido-5,8-dioxa-4,9-diazadodecane (17a):
17a was obtained from **16a** and *N*-(3-bromopropyl)phthalimide using the procedure for **10** in 60% yield as a white solid; mp 183–184 °C (dec) (EtOH).
^1H NMR ($CDCl_3$): δ = 7.70–7.93 (m, 8H), 7.01 (s, 4H), 3.83 (t, 4H), 3.55 (s, 4H), 3.35 (t, 4H), 2.66 (s, 12H), 2.37 (s, 6H), 1.79–2.46 (m, 4H).
^{13}C NMR ($CDCl_3$): δ = 168.0 (*C*=O), 143.7, 141.9, 133.9, 132.0, 129.6, 123.1 (arom. *C*), 73.5, 47.5, 35.7, 25.6, 23.1, 21.0.
IR (Nujol): ν = 3100, 1710 (C=O), 1600, 1325, 1165 cm^{-1} (SO_2).
LRMS (FAB): calcd for $C_{42}H_{46}N_4O_{10}S_2$ 830.98, found 831 $[MH]^+$.

1,12-Bis[1-(biphenyl-4-yl)-1-methylethoxycarbonylamino]-4,9-bis(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-chromen-6-ylsulphonyl)-5,8-dioxa-4,9-diazadodecane (17b) (bis-Mitsunobu Reaction):
The bis-Pmc-oxyamine **16b** (2.81 g, 4.5 mmol) was dissolved in anhyd DMF (40 mL) at 100 °C. After cooling to r.t., anhyd THF (125 mL), Bpoc-aminopropanol **2** (3.37 g, 10.7 mmol), Ph_3P (3.54 g, 13.5 mmol), and DEAD (2.12 mL, 13.5 mmol) were added. After stirring for 1 h, more DEAD (2.34 g, 13.5 mmol) and Ph_3P (3.54 g, 13.5 mmol) were added and the mixture was stirred overnight. The THF was then removed in vacuo and the residue taken up in $CHCl_3$ (40 mL) and washed with sat. Na_2CO_3 (2 × 50 mL), sat. NH_4Cl (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo to give the crude product. This was treated with Et_2O and cooled to 0 °C to precipitate out Ph_3PO. After removal of this, the filtrate was concentrated in vacuo and purified by column chromatography (MeOH/$CHCl_3$, 1.5:98.5 and then Et_2O/CH_2Cl_2, 5:95) to provide the pure mono-Mitsunobu product and a mixture of the mono- and bis-Mitsunobu products. These products (3.48 g) were together resubjected to the Mitsunobu reaction in anhyd THF (30 mL) using **2** (2.02 g, 6.44 mmol), Ph_3P (2.12 g, 8.08 mmol) and DEAD 1.40 g (8.06 mmol) for 3 h. Following the usual workup the crude product was subjected to column chromatography, eluting with (Et_2O/CH_2Cl_2) as above, to obtain the pure bis-Mitsunobu product **17b** in 55% (3.00 g) yield as a yellow oil.
^1H NMR ($CDCl_3$): δ = 7.3–7.9 (m, 18H), 5.00 (s, 2H, N*H*), 3.42 (s, 4H), 3.33 (t, 4H), 3.21 (m, 4H), 2.4–2.9 (m, 8H), 2.65 (s, 6H), 2.3 (s, 3H), 1.79–2.37 (m, 4H), 1.89 (s, 6H), 1.4 (s, 6H).
^{13}C NMR ($CDCl_3$): δ = 155.7, 155.1, 145.5, 140.7, 139.4, 139.1, 139.0, 128.5, 126.8, 126.8, 124.74, 124.7, 124.6, 118.6 (arom. *C*), 80.4, 74.2, 73.5, 47.2, 38.4, 32.3, 28.9, 27.0, 26.6, 21.1, 18.4, 17.4, 12.0.

4,9-Bis(mesitylsulphonyl)-5,8-dioxa-4,9-diazadodecane-1,12-diamine Dihydrochloride (18a):
18a was obtained according to the procedure for **12a–d** as a white solid with 56% yield of the dihydrochloride salt.
^{1}H NMR (DMSO-d_6): δ = 8.32 (br s, 6H, 2 × NH_3^+), 7.17 (s, 4H), 4.26 (s, 4H), 2.78–3.35 (m, 8H), 2.57 (s, 12H), 2.36 (s, 6H), 1.52–2.16 (m, 4H).
^{13}C NMR (DMSO-d_6): δ = 143.9, 141.1, 131.9, 129.1 (arom. *C*), 73.0, 46.8, 37.3, 24.2, 22.5, 20.5.
IR (Nujol): ν = 3400 (N–H), 1950 (NH_3^+), 1600, 1340, 1165 cm^{-1} (SO_2).

4,9-Bis(2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-chromen-6-ylsulphonyl)-5,8-dioxa-4,9-diazadodecane-1,12-diamine Dihydrochloride (18b):
The dihydrochloride salt was obtained according to the procedure for Bpoc removal for **13** in 84% yield as a white solid.
^{1}H NMR (DMSO-d_6): δ = 2.95–4.4 (m, 14H), 2.85 (s, 4H), 2.6 (m, 4H), 2.35 (s, 12H), 2.05 (s, 6H), 1.94 (m, 4H), 1.8 (m, 4H), 1.3 (s, 12H).
^{13}C NMR (DMSO-d_6): δ = 155.4, 139.2, 138.8, 124.8, 124.3, 119.2 (arom. *C*), 74.65, 73.4, 46.8, 37.1, 32.0, 21.0, 24.5, 26.6, 18.4, 17.5, 12.1.

5,8-Dioxa-4,9-diazadodecane-1,12-diamine (19):
The tetrahydrobromide salt was prepared from **18a** using HBr/HOAc as described for the preparation of **14**. The tetrahydrochloride salt was prepared from **18b** using HCl/HOAc (procedure **13** to **14a**). Both compounds showed identical spectroscopic properties (Table 4).

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