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ω-Conotoxin GVIA mimetics based on an anthranilamide core: Effect of variation in ammonium side chain lengths and incorporation of fluorine

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ABSTRACT

A number of ω-conotoxin GVIA mimetics based on an anthranilamide core were prepared and tested for their affinity for rat brain $Ca_v2.2$ channels. Features such as the presence of hydroxyl and fluoro substituents on the tyrosine side chain mimic, the length of the chains on the lysine/arginine side chain mimics and the use of diguanidino and diamino substituents rather than mono-guanidine/mono-amine substitution were examined. The diguanidinylated compounds proved to be the most active and deletion of the hydroxyl substituent had a limited influence on activity. The SAR associated with variation in the lysine/arginine side chain mimics was not strong. The introduction of a fluoro substituent into the tyrosine mimic produced the most active compound prepared in this study (**2g**), with an EC_{50} at rat brain $Ca_v2.2$ channels of 6 μM.

1. Introduction

Neuropathic pain is a hypersensitive pain response that is often dysregulated and self-perpetuating. It results from nerve injury associated with limb amputation, certain types of viral infections, cancer, stroke, spinal cord injury and lower back pain caused by disk compression or herniation. It is estimated that 26 million people worldwide are affected by this condition,[1a] with the quality of life of sufferers being greatly impaired. Neuropathic pain is often unresponsive to existing therapies. Typically, a combination of drugs such as opioids, antidepressants and anticonvulsants are prescribed, but these generally only provide relief in 50% of cases, and even in these cases only a 30–50% pain reduction is experienced.[1]

The transmission and regulation of pain is a complicated process involving ascending and descending spinal cord signals. Neuronal voltage-gated N-type calcium channels ($Ca_v2.2$) concentrated in presynaptic terminals are an important component in the regulation of nociceptive neurons and pain signal transmission. They play a critical role in synaptic neurotransmitter release. These calcium channels are validated targets for the treatment of neuropathic pain, primarily due to the success of Prialt (Ziconotide), a synthetic peptide identical to ω-conotoxin MVIIA, a component of the venom of the marine cone snail, *Conus magnus*. This peptide is known to bind to mammalian $Ca_v2.2$ channels. Prialt shows non-addictive properties and is used clinically for the treatment of chronic pain where opioids are not effective. This drug however, has a narrow therapeutic window and must be administered intrathecally.[2] The GABA analogues Gabapentin (Neurontin) and Pregabalin (Lyrica) are known to bind to the α2–δ sub-unit of $Ca_v2.2$ and are considered by some physicians to be the best available treatment for neuropathic pain,[1a] further validating the $Ca_v2.2$ channels as targets for therapeutic intervention.

A number of industry and academic groups have investigated selective, low molecular weight binders of $Ca_v2.2$ as potential drug leads for the effective treatment of neuropathic pain, either for oral or intravenous administration. This includes a large campaign by the Parke–Davis laboratories[3] and concerted efforts by Ono Pharmaceutical Co.,[5] Ajinomoto Co.,[6] Ionix Pharmaceuticals,[7] the Beijing Institute of Pharmacology[8] and a team at the University of Firenze.[9] The most successful to date is Neuromed Technologies, who produced NMED-160 which reached Phase II clinical trials.[10] Although no adverse effects were observed with NMED-160, further development of this compound was halted in 2007 as it did not demonstrate 'ideal pharmaceutical characteristics'.[11] With few exceptions,[12] the initial hit structures for these investigations have been identified through the screening of peptide or proprie-

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† J. E. Graham performed all of the organic synthesis described in this article.

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tary compound libraries, or through the modification of existing CNS-active drugs.

Given the high selectivity of some conotoxins for $Ca_v2.2$ channels,[13] and in particular ω-conotoxin GVIA, which is present in the venom of *Conus geographus*, we have developed $Ca_v2.2$ binders which mimic important features of these peptides. The constrained nature of these conotoxins makes them highly amenable to the development of small molecule mimetics. The method used follows the approach of Bartlett and Lauri,[14] and involves matching the α,β-bond vectors of important amino acid residues on ω-conotoxin GVIA, with bond projections on synthetic scaffolds.[15,16] Two mimetic classes were prepared in this way and the focus of the present study are the mimetics based on an anthranilamide core **1a** and **1b** (Fig. 1).[17] While the mono-guanidinylated compound **1a** shows impressive binding affinity (3.5 μM), its large polar surface area (190 Å^2)‡ and number of hydrogen bond donors means that it is unlikely to penetrate the CNS.[18] Given the narrow therapeutic window of Prialt, however, a small molecule drug with greater selectivity for $Ca_v2.2$, even if it required intrathecal administration, would still be a major advance. Thus, before addressing the issue of CNS penetration, we are using relatively simple changes to the hit structure to better define the optimum chemical properties that promote strong association of these anthranilamide-based compounds with the $Ca_v2.2$ channel. Along these lines, we have recently shown that activity is retained if one of the ether links in **1b** is changed to an amide.[19] Encouraged by the calcium channel affinity shown by long-chain aliphatic amines like dodecylamine,[20] here we describe the preparation and $Ca_v2.2$ affinity of a series of analogues of **1a** and **1b** where variation occurs in the length of ammonium side chains. This has been extended to the preparation and testing of an analogue that bears a fluorine substituent on the peripheral aromatic moiety.

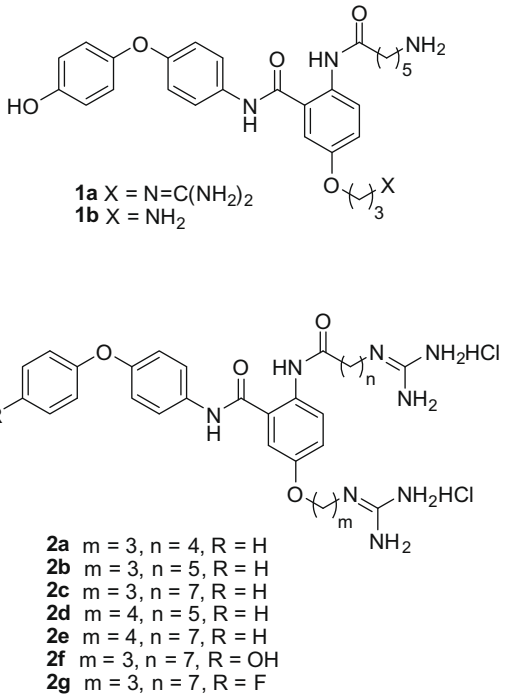
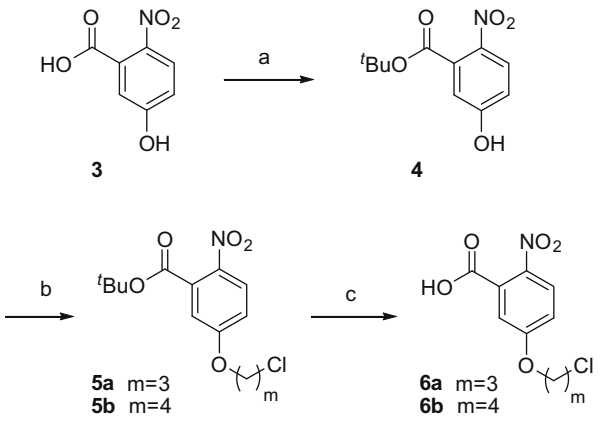


Figure 1. Previously tested anthranilamide-based ω-conotoxin GVIA mimetics **1a** and **1b** (EC_{50} 3.5 and 13.1 μM, respectively),[17] and analogues **2a–g** prepared and tested in this study.

2. Chemistry

Previous results obtained with a ω-conotoxin GVIA mimic based on a benzothiazole scaffold suggested that $Ca_v2.2$ affinity, although reduced, could be retained when the hydroxyl group on the peripheral aromatic moiety was deleted.[21] Thus, most of the analogues of **1a** and **1b** described here also lack the *p*-hydroxyl substituent on the peripheral aromatic group. One example was prepared with the *p*-hydroxyl substituent present (**2f**) and another with a *p*-fluoro substituent (**2g**). In addition, while the original mimic (**1a**) possessed both a primary amine and a guanidinium side chain, here the diamino and diguanidinylated compounds were prepared. Our initial target compounds were therefore **2a–g** with the corresponding diamino analogues being precursors to these compounds.

To allow the rapid preparation of **2a–g** a new synthetic route was developed beginning with 5-hydroxy-2-nitrobenzoic acid (**3**, Scheme 1). Protection of the acid as a *tert*-butyl ester (**4**), followed by alkylation of the phenol with 1-bromo-3-chloropropane or 1-bromo-4-chlorobutane gave the chloro compounds **5a** and **5b**. Cleavage of the *tert*-butyl esters gave the acids **6a–b**, which were coupled with the *p*-phenoxyanilines[21,22] (**7a–c**, Scheme 2) using EDC activation furnishing the nitro-amides **8a–d**. The nitro groups in **8a**,**b** and **d** were then reduced by hydrogenation over palladium on carbon, whereas the compound bearing the benzyloxy substituent **8c** was reduced with sodium dithionite. The subsequent anilines **9a–d** were then acylated with either an appropriate bromocarboxylic acid using carbodiimide activation or with 6-bromohexanoyl chloride to furnish the corresponding dihalides **10a–g**. These dihalides were then converted to diamines **12a–g** in two steps involving initial conversion to the diazides **11a–g** with tetra-*n*-butylammonium azide, generated in situ from trimethylsilyl azide and tetra-*n*-butylammonium fluoride,[23] then hydrogenation over palladium on carbon. Guanidinylation to afford **2a–g** was achieved by treatment with 1*H*-pyrazole-1-carboximidamide hydrochloride.[24] Hydrogenation for an extended period (1.5–2 days) was used to remove the benzyl protecting groups from **2h** and **12f** to furnish **2f** and **12h**, respectively (Scheme 3).

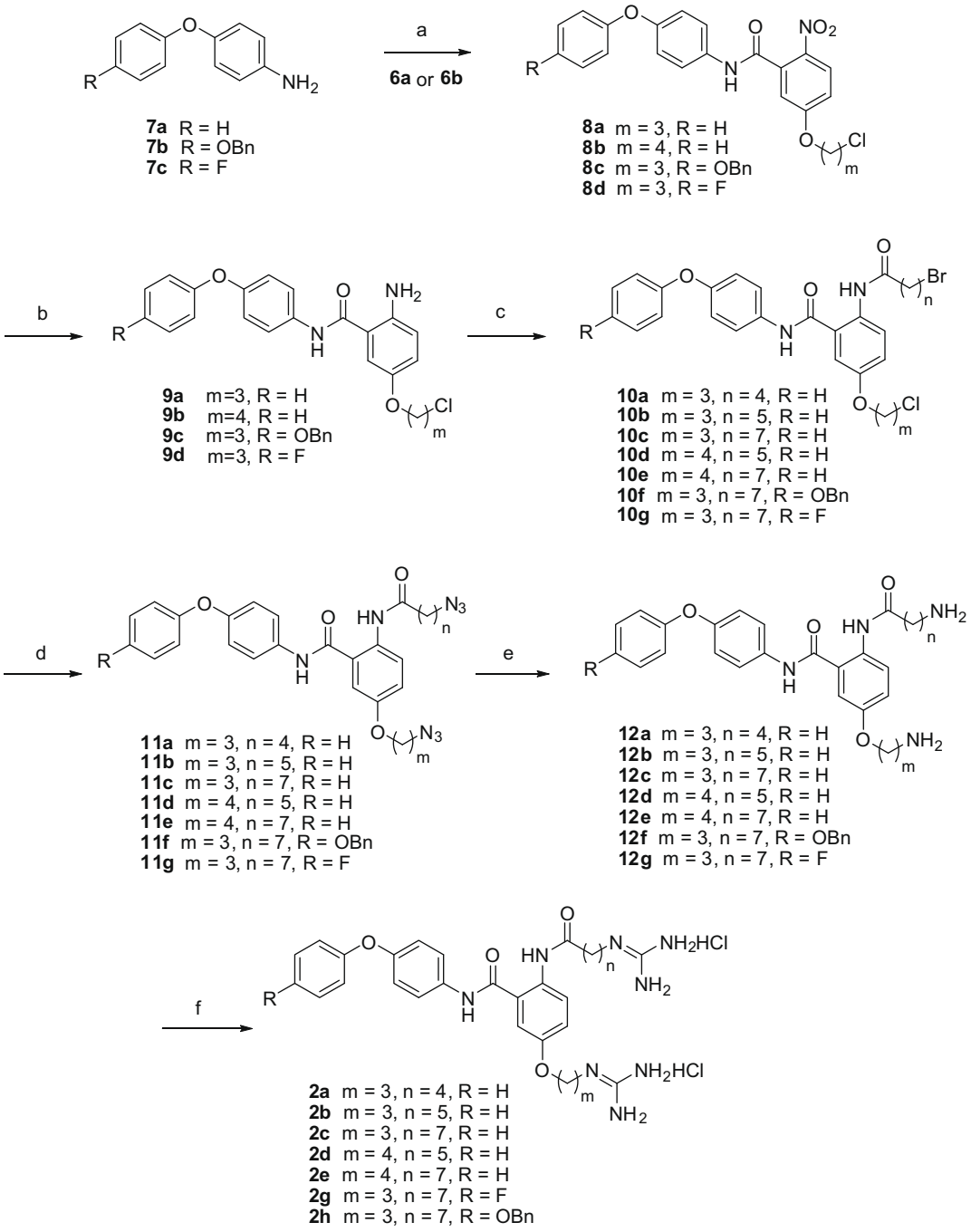


Scheme 1. Reagents and yields: (a) $MgSO_4$, H_2SO_4, *t*-BuOH, DCM, 70%; (b) K_2CO_3, DMF, 1-bromo-3-chloropropane; **5a** 67%; 1-bromo-4-chlorobutane; **5a** 84%; (c) TFA, DCM; **6a** 78%; **6b** 66%.

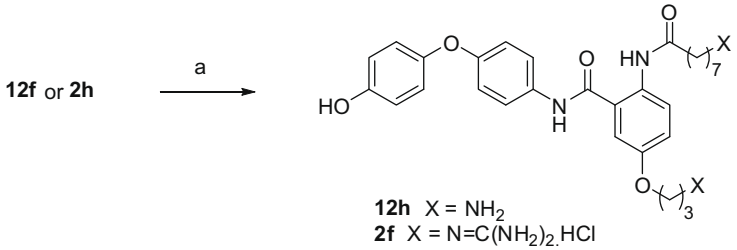
3. Results and discussion

The synthesised compounds, diamino (**12a–g**) and diguanidinium (**2a–g**), were evaluated for their ability to bind to rat brain $Ca_v2.2$ channels using a previously described radio-ligand displacement assay.[17,19,21,28] The results are summarised in Table 1.

‡ tPSA; ChemBioDraw Ultra 11.0.



Scheme 2. Reagents and yields: (a) TEA, DMAP, EDCI·HCl, DCM; **8a** 40%, **8b** 87%: or TEA, DCC, DMAP, DCM, **8c** 58%, **8d** 47%; (b) H_2, Pd/C, THF; **9a** 48%, **9b** 95%, **9d** 90%: or $Na_2S_2O_4$, EtOH, THF; **9c** 97%; (c) TEA, DMAP, EDCI·HCl, DCM, bromocarboxylic acid; **10a** 91%, **10b** 89%, **10c** 96%, **10e** 96%: or 6-bromohexanoyl chloride, TEA, DMAP, DCM; **10d** 70%: or TEA, DMAP, DCC, DCM, bromocarboxylic acid; **10f** 20%, **10g** 11%; (d) TMS azide, TBAF, THF; **11a** 68%, **11b** 94%, **11c** 95%, **11d** 89%, **11e** 98%, **11f** 47%, **11g** 28%; (e) Pd/C, H2(g), THF, MeOH; **12a** 98%, **12b** 80%, **12c** 96%, **12d** 83%, **12e** 81%, **12f** 97%, **12g** 87%; (f) 1*H*-pyrazole-1-carboximidamide hydrochloride, DIEA, DMF; **2a** 33%, **2b** 69%, **2c** 46%, **2d** 96%, **2e** 52%, **2g** 63%, **2h** 47%.



Scheme 3. Reagents and yields: (a) Pd/C, H_2(g), MeOH, DMF; **12h** 36 h 74%; **2f** 48 h 84%.

Table 1
$Ca_v2.2$ binding affinities of diamino and diguanidinium anthranilamides (95% confidence intervals are shown in parentheses)

Diamino compound	EC_{50} $Ca_v2.2$ (μM)	Diguanidinium compound	EC_{50} $Ca_v2.2$ (μM)
12a	77 (56–106)	**2a**	116 (95–141)
12b	107 (85–134)	**2b**	16 (12–21)
12c	72 (62–85)	**2c**	13 (9–17)
12d	99 (80–122)	**2d**	17 (13–22)
12e	90 (70–115)	**2e**	15 (13–17)
12h	Weak	**2f**	16 (12–21)
12g	Weak	**2g**	6 (4–11)

In the original investigation of the use of the anthranilamide scaffold in ω-conotoxin GVIA mimicry, the design strategy was tested with two compounds (**1a** and **1b**).[17] The observation now of several analogues of **1a** with $Ca_v2.2$ affinities of <20 μM supports the α,β-bond vector approach to N-type channel blockers and confirms the suitability of the anthranilamide core as a scaffold with which to develop lead structures.

The majority of synthesised compounds lack the hydroxyl group on the peripheral aromatic moiety. The effect of this simplification can be gauged by comparison of the activities of direct analogues **12b** and **1b**,[17] and **2f** and **2c**. With the diamines (**12b** and **1b**) a sixfold loss in activity was observed while the diguanidines (**2f** and **2c**) showed essentially identical activity. Taken together, these results do not represent large differences and validate the deletion of the peripheral hydroxyl group from the target compounds.

The diguanidines generally showed the strongest activities, with all but one (**2a**), having a $Ca_v2.2$ affinity of <20 μM. The same compound (**2a**) was also the only diguanidine not to have significantly stronger affinity than the corresponding diamine.

The SAR uncovered here demonstrates that chain length variation in these anthranilamide based compounds is well tolerated, with the diguanidine with the shortest chains (**2a**) being the only strongly non-preferred analogue. There is only a weak correlation between side chain lengths and binding affinity but as the propoxy octanamides (**12c** and **2c**) gave the lowest measured IC_{50} values for the diamino and diguanidino compounds, respectively, it was decided to make and test their hydroxylated analogues (**12h** and **2f**). As discussed above, this did not lead to a significant improvement in activity. Fluorine is widely used as a hydroxyl surrogate in bioactive discovery both for electronic and metabolic reasons. It is also known that phenoxy groups are very quickly metabolized in the liver and this pathway is delayed if the phenoxy group is fluorinated at the 4 position.[25] This substitution to give **2g** led to the lowest measured IC_{50} value in this study, although the 95% confidence interval for this number does overlap slightly with that determined for **2c**. This compound has comparable activity to the most active ω-conotoxin GVIA mimics reported to date.[17,21]

4. Conclusions

In summary, we have developed a new synthetic route to anthranilamide-based ω-conotoxin GVIA mimics which has allowed the ready production of an expanded set of analogues. There was evidence from previous work[21] that deletion of the hydroxyl group from the original mimic[15,17] may not lead to a significant drop in activity. It was also unclear from the original work[15,17] if a single guanidinium group was necessary for good activity or if diguanidinylated compounds would be suitable. Thus, diguanidinylated compounds were the targets here. This approach also allowed for a shortened the synthetic approach.

Six of the synthesised compounds, the diguanidinylated compounds (**2b**–**g**,) had $Ca_v2.2$ affinities of <20 μM, strongly validating the original mimetic design and the synthetic simplifications introduced here. In addition, the deletion of the hydroxyl substituent had a limited effect on activity. In one case, a fluorine substituent was incorporated in place of the hydroxyl group (**2g**) and this led to the most active compound prepared in this study. The effect of chain length variation on activity was initially a major focus of this study however this did not lead to strong a SAR and demonstrated that such structural variation is well tolerated in the $Ca_v2.2$ channel. Only the compound with the shortest combined length of the two flexible chains (**2a**) was strongly non-preferred. Given that the contact surface between the conotoxins and the $Ca_v2.2$ channel is likely to be quite large, it would be interesting to study the binding of mimics with even longer side chains than those investigated here. The use of correctly oriented rigidification in these side chains will also be critical in the achievement of submicromolar binding.

5. Experimental

Starting materials and reagents were purchased from Sigma–Aldrich and were used without purification. Tetrahydrofuran (THF) was distilled under a nitrogen atmosphere from sodium benzophenone ketal. Dry DCM, methanol and DMF were obtained by passage through two alumina columns on the Solvent Dispensing System built by J. C. Meyer and based on the original design by Grubbs and co-workers.[26] Solutions were dried over anhydrous magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4). Flash chromatography was performed on Merck silica gel No. 9385. Melting points were recorded on a Stuart melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrometer or a Bruker IFS 55 Equinox FTIR fitted with a Golden Gate single bounce diamond micro-ATR (Attenuated Total Reflectance) cell and were recorded as Nujol mulls, solutions in chloroform applied as a thin film on NaCl plates or neat samples, as indicated. Proton (^1H) NMR spectra were acquired at 400 MHz and carbon (^{13}C) NMR spectra at 100 MHz on a Bruker Av400 spectrometer. NMR spectra were referenced to residual solvent peak [chloroform (δ_H 7.26, δ_C 77.0), acetone (δ_H 2.05, δ_C 29.8, 205.9), methanol (δ_H 4.87, 3.30, δ_C 49.86)]. To aid the assignment of NMR spectra COSY and HMQC spectroscopy were used. The units for all coupling constants (J) are hertz (Hz). Low resolution mass spectra were recorded on a Micromass Platform spectrometer or VG Platform spectrometer. Accurate mass determinations were carried out at high resolution on an Agilent G1969A LC-TOF system with reference and mass correction at 4000 V capillary voltage for ESI. Microanalysis was performed at the Campbell Microanalytical Laboratory, University of Otago, Dunedin, New Zealand.

5.1. *tert*-Butyl-5-hydroxy-2-nitrobenzoate (4)

The title compound (**4**) was prepared following the method for the synthesis of *tert*-butyl esters reported by Wright et al.[4] Magnesium sulfate (33.1 g, 0.275 mol) vigorously stirring was extensively dried in vacuo with a heat gun for 30 min. Dry DCM (220 mL) was then added to the flask under a dry nitrogen atmosphere and the mixture stirred for 5 min before the addition of the benzoic acid (**3**) (10.0 g, 0.055 mol) and *tert*-butyl alcohol (26.0 mL, 0.275 mol). Concentrated sulfuric acid (5.50 mL, 0.0550 mol) was then carefully added and the RBF tightly sealed. The reaction was stirred at room temperature for 36 h after which magnesium sulfate was removed from the reaction mixture by filtration and the residues washed with DCM. The reaction mixture was cooled to 0 °C and then carefully neutralised by addition of satd $NaHCO_{3(aq)}$ (300 mL). The product was then extracted into DCM (3 × 50 mL), the combined extracts dried, and the solvent removed in vacuo

to yield the product as a brown solid. Recrystallization from DCM/hexanes yielded the product (9.1 g, 70%) as a pale yellow crystalline solid. Mp 100–103 °C; ν_{max} (Nujol)/cm^{-1} 3336br (OH), 2928s and 2854s (CH), 1702s (CO), 1598s (Ar), 1522s and 1360w (NO_2); δ_H (400 MHz, $CDCl_3$) 1.61 (s, 9H, *t*-Bu), 6.91 (dd, *J* = 2.7 and 8.9, 1H, H4), 6.97 (d, *J* = 2.7, 1H, H6), 7.93 (d, *J* = 8.9, 1H, H3); δ_C (100 MHz, $CDCl_3$) 27.7 (C3′), 85.0 (C2′), 115.5 and 117.1 (C4 and C6), 126.9 (C3), 132.4 (C1), 139.1(C2), 161.2 (C5), 166.8 (C1′); HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{11}H_{13}NO_5Na$ 262.0691 found 262.0691. Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.30; H, 5.48; N, 5.94.

5.2. *tert*-Butyl-5-(3-chloropropoxy)-2-nitrobenzoate (5a)

A solution of 1-bromo-3-chloropropane (1.97 g, 12.5 mmol) in dry DMF (10 mL) was added dropwise under an atmosphere of nitrogen to a flask containing nitrophenol (**4**) (3.00 g, 12.5 mmol), potassium carbonate (5.10 g, 37.6 mmol) and DMF (120 mL). The mixture was stirred at room temperature until no starting material remained (typically 36 h) after which the reaction mixture was poured into 1 M $HCl_{(aq)}$ (200 mL) on ice and the product extracted into ether (5 × 100 mL). The combined ether extracts were then washed with water (3 × 150 mL), dried, and the solvent removed in vacuo to yield a pale yellow oil which, after purification by flash chromatography (4:1, hexanes/ethyl acetate) gave the phenyl ether (**5a**) (2.51 g, 67%) as a colourless oil. ν_{max} (ATR)/cm^{-1} 2979w (CH), 1723vs (CO), 1584s and 1477w (Ar), 1525vs and 1370s (NO_2), 845w (CCl); δ_H (400 MHz, $CDCl_3$) 1.57 (s, 9H, *t*-Bu), 2.24–2.31 (m, 2H, H2′), 3.74 (t, *J* = 6.2, 2H, H3′), 4.22 (t, *J* = 5.8, 2H, H1′), 6.99 (dd, *J* = 2.8 and 9.0, 1H, H4), 7.05 (d, *J* = 2.7, 1H, H6), 7.97 (d, *J* = 9.0, 1H, H3); δ_C (100 MHz, $CDCl_3$) 28.4 (C3″), 33.2 (C2′), 42.5 (C3′), 67.1 (C1′), 84.2 (C2″), 116.3 (C6), 117.3 (C4), 127.9 (C3), 133.7, 141.7, 164.1, 165.7; HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{14}H_{18}NO_5Na$ 338.0777 found 338.0763.

5.3. *tert*-Butyl 5-(4-chlorobutoxy)-2-nitrobenzoate (5b)

Following the same procedure used to prepare **5a**, the phenyl ether (**5b**) was isolated as a colourless oil after purification by flash chromatography (7:1, hexanes/ethyl acetate) (6.7 g, 84%). ν_{max} (ATR)/cm^{-1} 2979s (CH), 1728vs (CO), 1584s and 1487w (Ar), 1524vs and 1370s (NO_2), 844 m (CCl); δ_H (400 MHz, $CDCl_3$) 1.56 (s, 9H, *t*-Bu), 1.96–1.99 (m, 4H, H2′ and H3′), 3.60 (t, *J* = 6.1, 2H, H4′), 4.08 (t, *J* = 5.9, 2H, H1′), 6.95 (dd, *J* = 2.7 and 9.0, 1H, H4), 7.00 (d, *J* = 2.7, 1H, H6), 7.95 (d, *J* = 9.0, 1H, H3); δ_C (100 MHz, $CDCl_3$) 26.3, 27.7, 29.0, 44.4, 68.1, 83.6, 114.5, 115.5, 126.4, 132.6, 139.9, 162.6, 164.9; *m/z* (ESI$^+$, 50 eV): *m/z* (%): 352 (20) [M+Na]$^+$.

5.4. 5-(3-Chloropropoxy)-2-nitrobenzoic acid (6a)

The cleavage of the *tert*-butyl ester (**5a**) was achieved using a procedure similar to that used by Banwell, Easton and co-workers [27] TFA (4 mL, 52.6 mmol) was added dropwise to a flask maintained at 0 °C containing a stirred solution of ester **5a** (2.5 g, 7.92 mmol) in DCM (3 mL). The reaction was maintained at 0 °C for 1 h then stirred at room temperature until TLC analysis showed no starting material remained (typically 4 h). The reaction mixture was then diluted with DCM (20 mL), washed with 1 M $HCl_{(aq)}$ and dried before removal of the solvent in vacuo to yield a white solid. Recrystallisation from DCM/hexanes gave the title compound (**6a**) (2.0 g, 78%) as a white powder. Mp 93–94 °C; ν_{max} (Nujol)/cm^{-1} 3381b (OH), 2957s and 2926s (CH), 1732s (CO), 1657w and 1487w (Ar), 1524 s and 1342s (NO_2), 847 (CCl); δ_H (400 MHz, methanol-d_4) 2.29–2.23 (m, 2H, H2′), 3.76 (t, *J* = 6.4, 2H, H3′), 4.26 (t, *J* = 5.9, 2H, H1′), 7.16 (dd, *J* = 2.7 and 8.7, 1H, H4), 7.18 (d, *J* = 2.7, 1H, H6), 8.12 (d, *J* = 8.7, 1H, H3); δ_C (100 MHz, acetone-d_6) 32.6 (C2′), 42.4 (C3′), 64.2 (C1′), 116.3, 118.6, 132.6, 133.6, 137.7, 164.0, 167.7; HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{10}H_{16}ClNNaO_5$ 282.0145 found 282.0140. Anal. Calcd for $C_{10}H_{10}ClNO_5$: C, 46.26; H, 3.88; N, 5.39. Found: C, 46.61; H, 3.91; N, 5.49.

5.5. 5-(4-Chlorobutoxy)-2-nitrobenzoic acid (6b)

Following the same procedure described for the preparation of **6a**, the benzoic acid (**6b**) (3.2 g, 66%) was isolated as a white powder. Mp 66–69 °C; ν_{max} (Nujol)/cm^{-1} 3382b (OH), 2954s and 2924s (CH), 1707s (CO), 1591w and 1490w (Ar), 1515s and 1378s (NO_2), 836w (CCl); δ_H (400 MHz, methanol-d_4) 1.82–1.85 (m, 4H, H2′ and H3′), 3.52 (t, *J* = 6.0, 2H, H4′), 4.02 (t, *J* = 5.7, 2H, H1′), 7.01 (dd, *J* = 2.7 and 8.9, 1H, H4), 7.03 (d, *J* = 2.7, 1H, H6), 7.87 (d, *J* = 8.9, 1H, H3); δ_C (100 MHz, methanol-d_4) 26.1, 28.9, 44.0, 68.2, 114.4 (C6), 115.5, 126.2, 131.8, 140.0, 162.7, 167.7; HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{10}H_{16}ClNNaO_5$ 296.0302 found 296.0305. Anal. Calcd for $C_{10}H_{10}ClNO_5$: C, 48.28; H, 4.42; N, 5.12. Found: C, 48.00; H, 4.34; N, 5.12.

5.6. 5-(3-Chloropropoxy)-2-nitro-*N*-(4-phenoxyphenyl)-benzamide (8a)

The anthranilamide **8a** was prepared following a procedure similar to that used by Banwell, Easton and co-workers.[27] A solution of nitrobenzoic acid (**6a**) (3.2 g, 12.4 mmol) in DCM (300 mL) was maintained at 0 °C under a nitrogen atmosphere and Et_3N (2.4 mL, 17.3 mmol) and 4-DMAP (0.61 g, 4.94 mmol) were added and stirred for 15 min before addition of EDC·HCl (2.84 g, 14.8 mmol). After stirring for a further 45 min a solution of 4-phenoxyaniline (**7a**) (2.74 g, 14.8 mmol) in DCM (20 mL) was added dropwise. The resulting mixture was stirred for 1 h at 0 °C before being allowed to warm to room temperature. Stirring was continued until TLC analysis showed no starting material remained (typically 16 h). The reaction mixture was then washed with water (3 × 200 mL), dried, and the solvent removed in vacuo to yield a brown oil. Purification by flash chromatography (2:1, hexanes/ethyl acetate) yielded the title compound (**8a**) (3.1 g, 40%) as a white powder. Mp 82–84 °C; ν_{max} (Nujol)/cm^{-1} 3390 m and 3222 m (NH), 2925s and 2854s (CH), 1660w (CO), 1636w and 1505 (NO_2), 1589 m and 1485s (Ar), 870 m (CCl); δ_H (400 MHz, $CDCl_3$) 2.31–2.25 (m, 2H, H2′), 3.73 (t, *J* = 6.1, 2H, H3′), 4.23 (t, *J* = 5.9, 2H, H1′), 6.93–7.01 (m, 4H, H4, H6, H4″ and H7″), 7.10 (t, *J* = 7.4, 1H, H9′), 7.33 (t, *J* = 8.4, 2H, H8″), 7.46 (d, *J* = 8.88, 2H, H3″), 7.90 (br s, 1H, NH), 8.05, (d, *J* = 9.10, 1H, H3); δ_C (100 MHz, $CDCl_3$) 31.7, 40.9, 65.5, 114.1, 115.6, 118.6, 119.5, 122.3, 123.3, 127.2, 129.8, 132.7, 135.2, 138.6, 154.2, 157.3, 163.0, 164.6. HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{22}H_{19}ClN_2O_5Na$ 449.0880 found 449.0878. Anal. Calcd for $C_{22}H_{19}ClN_2O_5$: C, 61.90; H, 4.49; N, 6.56. Found: C, 61.92; H, 4.60; N, 6.60.

5.7. 5-(4-Chlorobutoxy)-2-nitro-*N*-(4-phenoxyphenyl)-benzamide (8b)

Following the procedure used to prepare **8a** the title compound (**8b**) was prepared from **6b** and **7a**. The product was isolated as a brown oil and further purified by flash chromatography (4:1, hexanes/ethyl acetate) to yield **8b** (4.5 g, 89%) as a white powder. Mp 127–128 °C; ν_{max} (Nujol)/cm^{-1} 3390 m and 3222 m (NH), 3019s (CH), 1666 m (CO), 1589w and 1506 (Ar), 1486s and 1324w (NO_2); δ_H (400 MHz, $CDCl_3$) 1.93–1.95 (m, 4H, H2′ and H3′), 3.59 (t, *J* = 5.9, 2H, H4′), 4.03 (t, *J* = 5.3, 2H, H1′), 6.86 (dd, *J* = 9.1 and 2.2, 1H, H4), 6.92–6.89 (m, 3H, H4″ and H6), 6.96 (d, *J* = 7.7, 2H, H7″), 7.08 (t, *J* = 7.4, 1H, H9″), 7.29–7.33 (m, 2H, H8″), 7.42 (d, *J* = 9.0, 2H, H3″), 7.95 (d, *J* = 9.1, 1H, H3), 8.45 (br s, 1H, NH); δ_C

(100 MHz, $CDCl_3$) 26.3, 28.9, 44.5, 68.3, 113.9, 115.5, 118.5, 119.4, 122.2, 123.2, 127.0, 129.8, 133.0, 135.2, 138.3, 153.9, 157.4, 163.2, 164.8. *m/z* (ESI^-) 439.1 ($[M-H]^-$). Anal. Calcd for $C_{23}H_{21}ClN_2O_5$: C, 62.66; H, 4.80; N, 6.35. Found: C, 62.66; H, 4.82; N, 6.35.

5.8. *N*-[4-(4-Benzyloxy-phenoxy)-phenyl]-5-(3-chloro-propoxy)-2-nitro-benzamide (8c)

The title compound (**8c**) was prepared from **6a** and 4-(4-benzyloxyphenoxy)phenylamine (**7b**)[21] by application of the procedure used for the preparation of **8a**, with the substitution of DCC for EDC·HCl and THF as the solvent. The product was isolated as a brown oil and further purified by flash chromatography (6:1, hexanes/ethyl acetate) to yield **8c** (0.6 g, 58%) as a white powder. Mp 122–124 °C; ν_{max} (ATR)/cm^{-1} 3282s (NH), 2927w and 2850w (CH), 1658s (CO), 1607w and 1588w and 1542s (Ar) 1494s and 1335s (NO_2); δ_H (400 MHz, $CDCl_3$) 2.24 (m, 2H, H2′), 3.72 (t, *J* = 5.9, 2H, H3′), 4.18 (t, *J* = 5.6, 2H, H1′), 5.04 (s, 2H, H1‴), 6.88 (d, *J* = 8.8, 2H, H8″), 6.90–7.00 (m, 6H, H4, H6, H4″ and H7″), 7.34 (d, *J* = 6.9, 1H, H5‴), 7.37–7.43 (m, 6H, H3″, H3‴ and H4‴), 8.00 (d, *J* = 9.2, 1H, H3), 8.28 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 33.7, 41.0, 65.5, 70.6, 114.1, 115.5, 116.0, 118.3, 120.4, 122.4, 127.1, 127.5, 128.0, 128.6, 132.2, 135.3, 136.9, 138.6, 150.6, 155.0, 155.3, 162.9, 164.7; *m/z* (ESI^-, 50 eV): *m/z* (%): 531 (100) $[M-H]^-$, 567 (82) $[M+Cl]^-$, 613 (5) $[M+EtOH+Cl]^-$.

5.9. 5-(3-Chloro-propoxy)-*N*-[4-(4-fluoro-phenoxy)-phenyl]-2-nitro-benzamide (8d)

Following the same procedure as that used to prepare **8c** the title compound (**8d**) was prepared from **6a** and 4-(4-fluoro-phenoxy)-phenylamine (**7c**).[22] The product was isolated as a brown oil and further purified by flash chromatography (6:1, hexanes/ethyl acetate) to yield **8d** (0.41 g, 47%) as a white powder. Mp 137–140 °C; ν_{max} (ATR)/cm^{-1} 3263s (NH), 3069w and 2959w (CH), 1648s (CO), 1607w and 1588w and 1533s (Ar) 1494s and 1343s (NO_2); δ_H (400 MHz, $CDCl_3$) 2.29 (m, 2H, H2′), 3.75 (t, *J* = 6.0, 2H, H3′), 4.24 (t, *J* = 5.7, 2H, H1′), 6.96–7.04 (m, 7H, H4, H3″, H4″ and H7″), 7.52 (d, 2H, *J* = 8.7, 2H, H8″), 7.57 (s, 1H, H6), 8.13 (d, *J* = 8.9, 1H, H3); δ_C (100 MHz, $CDCl_3$) 31.7, 40.9, 65.4, 114.2, 115.5, 116.4 (d, *J* = 23.4, C7″), 119.0, 120.2 (d, *J* = 8.2, C6″), 122.4, 127.1, 132.7, 135.2, 138.6, 153.0, 154.5, 158.8 (d, *J* = 241.6, C8″), 160.0, 163.0, 164.6. *m/z* (ESI^-, 50 eV): *m/z* (%): 443 (100) $[M-H]^-$.

5.10. 2-Amino-5-(3-chloropropoxy)-*N*-(4-phenoxyphenyl) benzamide (9a)

The title compound was prepared following a procedure used by Banwell, Easton and co-workers.[27] A vigorously stirred flask containing a mixture of the nitro compound (**8a**) (0.67 g, 1.57 mmol) and 10% wt palladium on carbon (15 mg, 0.45 mmol) in THF (5 mL) was degassed, flushed with hydrogen and stirred under an atmosphere of hydrogen for 3 h. The flask was then flushed with nitrogen and filtered though Celite. This solution was used immediately for subsequent transformations without further purification. One batch of the aniline (**9a**) (0.30 g, 48%) after solvent removal in vacuo was obtained as a white solid. Mp 116–118 °C; ν_{max} (Nujol)/cm^{-1} 3427 w and 3323w (NH), 2824s and 2853s (CH), 1643w (CO), 1591s and 1490s (Ar), 1516s and 1460 (NO_2); δ_H (400 MHz, $CDCl_3$) 2.15 (m, 2H, H2′), 3.10 (br s, 2H, NH_2) 3.69 (t, *J* = 6.3, 2H, H3′), 4.09 (t, *J* = 5.9, 2H, H1′), 6.66 (d, *J* = 8.8, 1H, H3), 6.86 (dd, *J* = 2.8 and 8.8, 1H, H4), 6.93–6.97 (m, 4H, H4″ and H7″), 7.03 (t, *J* = 7.4, 1H, H9″), 7.07 (d, *J* = 2.8, 1H, H6), 7.50 (m, 2H, H8″), 7.50 (d, *J* = 8.9, 2H, H3″); δ (100 MHz, methanol-d_4) 33.8 (C2′), 42.5 (C3′), 66.7 (C1′), 115.1 (C6), 119.4, 119.5 (C3), 119.6, 120.4 (C4), 121.7, 124.4 (C9″), 124.5 (C3″), 131.0 (C8″), 135.6, 144.4, 152.0, 155.3, 159.3, 170.1.(C1″); HRMS (ESI^+) $[M+H]^+$ calcd for $C_{22}H_{22}ClN_2O_3$ 397.1319 found 397.1330.

5.11. 2-Amino-5-(4-chlorobutoxy)-*N*-(4-phenoxyphenyl) benzamide (9b)

The title compound (**9b**) was prepared from **8b** according to the procedure used to prepare **9a**. One batch of the aniline (**9b**) (1.4 g, 95%) was isolated as a white solid. ν_{max} (ATR)/cm^{-1} 3421w and 3414w and 3278br (NH), 2986w and 2857w (CH), 1642w (CO), 1592s and 1500s and 1478vs (Ar), 800 (CCl); δ_H (400 MHz, $CDCl_3$) 1.90–1.99 (m, 4H, H2′ and H3′), 3.62 (t, *J* = 6.1, 2H, H4′), 3.96 (t, *J* = 6.0, 2H, H1′), 6.71 (d, *J* = 8.8, 1H, H3), 6.90 (d, *J* = 8.8 and 2.6, 1H, H4), 6.99–7.08 (m, 5H, H6, H4″ and H7″), 7.09–7.11 (m, 1H, H9″), 7.33 (t, *J* = 7.7, 2H, H8″), 7.54 (d, *J* = 8.9, 2H, H3″), 8.08 (br s, 1H, NH); δ (100 MHz, $CDCl_3$) 26.7, 29.3, 44.7, 68.1, 113.2, 118.1, 118.5, 119.5, 119.6, 120.3, 122.3, 123.1, 129.7, 133.2, 141.8, 151.0, 153.7, 157.5, 166.9; HRMS (ESI^+) $[M+H]^+$ calcd for $C_{23}H_{24}ClN_2O_3$ 411.1476 found 411.1472.

5.12. 2-Amino-*N*-(4-(4-(benzyloxy)phenoxy)phenyl)-5-(3-chloropropoxy)benzamide (9c)

The aniline (**9c**) was prepared following our previously reported procedure.[17] To a solution of the nitrobenzene (**8c**) (250 mg, 0.464 mmol) in THF (15 mL) and EtOH (20 mL) at reflux was added $Na_2S_2O_4$ (326 mg, 1.88 mmol) and H_2O (4 mL). The mixture was stirred at reflux until no starting material was evident by TLC (typically 2 h) at which time the solvent was removed, the residues dissolved in ethyl acetate (150 mL) and washed with satd $NaHCO_{3(aq)}$ (3 × 100 mL). The organic layer was then dried and the solvent removed in vacuo to yield the product **9c** (230 mg, 97%) as a beige solid which was used for subsequent steps without further purification. *m/z* (ESI^+, 50 eV): *m/z* (%): 525 (50) $[M+Na]^+$, 541 (11) $[M+K]^+$.

5.13. 2-Amino-5-(3-chloropropoxy)-*N*-(4-(4-fluorophenoxy) phenyl)benzamide (9d)

The title compound (**9d**) was prepared from **8d** according to the procedure used to prepare **9a.** After filtration through a plug of Celite the solvent was removed and the aniline (**9d**) (0.34 g, 90%) was used in subsequent transformations without further purification. HRMS (ESI^+) $[M+H]^+$ calcd for $C_{22}H_{21}ClFN_2O_3$ 415.1224 found 415.12143.

5.14. 2-(5-Bromopentanamido)-5-(3-chloropropoxy)-*N*-(4-phenoxyphenyl)benzamide (10a)

To a stirred solution of 5-bromovaleric acid (0.22 g, 1.33 mmol) in DCM (50 mL) maintained at 0 °C under a nitrogen atmosphere was added TEA (0.24 mL, 1.4 mmol) and 4-DMAP (0.138 g, 0.20 mmol). After stirring for 5 min EDC·HCl (0.231 g, 1.21 mmol) was added and the mixture stirred for a further 15 min after which a solution of the aniline (**9a**) (0.218 g, 1.21 mmol) in THF (10 mL) was added. When TLC analysis showed no starting material remained (typically 36 h) the reaction mixture was washed with brine (3 × 50 mL), satd $NaHCO_{3(aq)}$ (3 × 50 mL) and 5% citric $acid_{(aq)}$ (3 × 50 mL). The organic solution was dried and the solvent removed in vacuo to yield a brown oil which was purified by flash chromatography (3:1 hexanes/ethyl acetate). The title compound (**10a**) (2.3 g, 91%) was obtained as a white powder. Mp 131–133 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3284 m and 3044 m (NH), 2936w (CH), 1731s and 1660s (CO), 1588s and 1505s and 1489s (Ar), 844w (CCl), 752s (CBr); δ_H (400 MHz, $CDCl_3$) 1.84–1.92 (m, 2H),

1.92–1.97 (m, 2H), 2.20–2.26 (m, 2H, H2′), 2.40 (t, *J* = 7.2, 2H, H2‴), 3.42 (t, *J* = 6.5, 2H, H5‴), 3.74 (t, *J* = 6.2, 2H, H3′), 4.13 (t, *J* = 5.9, 2H, H1′), 6.99 (dd, *J* = 2.8 and 9.1, 1H, H4), 7.01–7.14 (m, 6H, H6, H4″, H7″ and H9″), 7.32–7.36 (m, 2H, H8″), 7.58 (d, *J* = 8.8, 2H, H3″), 8.21 (br s, 1H, NH), 8.35 (d, *J* = 9.1, 1H, H3), 10.30 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 23.8, 24.1, 32.1, 33.0, 36.9, 41.3, 64.9, 113.3, 117.8, 118.7, 119.5, 122.5, 123.1, 123.3, 123.8, 129.8, 132.4, 132.5, 154.2, 154.3, 157.2, 166.8, 171.2; HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{27}H_{28}BrClN_2NaO_4$ 581.0819 found 581.0820.

5.15. 2-(6-Bromohexanamido)-5-(3-chloropropoxy)-*N*-(4-phenoxyphenyl)benzamide (10b)

The title compound (**10b**) was prepared from **9a** using 6-bromohexanoic acid according to the procedure used to prepare **10a**. The crude product was obtained as a pale yellow solid and purified by flash chromatography (2:1 hexanes/ethyl acetate) then recrystallised from DCM/hexanes to yield the product (**10b**) (0.49 g, 89%) as white fluffy crystals. Mp 128–131 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3280s (NH), 3016 m and 2940 m (CH), 1660s (CO), 1600s and 1504vs (Ar); δ_H (400 MHz, $CDCl_3$) 1.49–1.55 (m, 2H, H4‴), 1.70–1.78 (m, 2H, H3‴), 1.85–1.92 (m, 2H, H5‴), 2.18–2.24 (m, 2H, H2′), 2.37 (t, *J* = 7.6, 2H, H2‴), 3.40 (t, *J* = 6.7, 2H, H6‴), 3.73 (t, *J* = 6.2, 2H, H3′), 4.11 (t, *J* = 5.8, 2H, H1′), 6.96 (dd, *J* = 2.7 and 9.1, 1H, H4), 7.02–7.13 (m, 6H, H6, H4″, H7″ and H9″), 7.35–7.37 (m, 2H, H8″), 7.61 (d, *J* = 8.9, 1H, H3″), 8.28 (d, *J* = 9.1, 1H, H3), 8.50 (br s, 1H, NH), 10.25 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 24.6, 27.7, 32.1, 32.5, 33.5, 37.7, 41.3, 64.9, 113.6, 117.6, 118.7, 119.5, 122.4, 123.3, 123.4, 123.7, 129.8, 132.1, 132.8, 154.2, 154.3, 166.8, 171.7; HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{28}H_{30}BrClN_2NaO_4$ 595.0975 found 595.0975.

5.16. 2-(8-Bromooctanamido)-5-(3-chloropropoxy)-*N*-(4-phenoxyphenyl)benzamide (10c)

The title compound (**10c**) was prepared from **9a** using 8-bromooctanoic acid according to the procedure used to prepare **10a**. The product **10c** (0.60 g, 96%) was obtained as white crystals after purification by flash chromatography (2:1 hexanes/ethyl acetate) and recrystallisation from DCM/hexanes. Mp 133–134 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3314b (NH), 3019w and 2933w (CH), 1654w and 1604w (CO), 1506s and 1490s (Ar); δ_H (400 MHz, $CDCl_3$) 1.31–1.46 (m, 6H, H4‴, H5‴ and H6‴), 1.67–1.75 (m, 2H, H3‴) 1.79–1.89 (m, 2H, H7‴), 2.30–2.23 (m, 2H, H2′), 2.35 (t, *J* = 7.4, 2H, H2‴), 3.38 (t, *J* = 6.8, 2H, H8‴), 3.73 (t, *J* = 6.2, 2H, H3′), 4.13–4.10 (m, 2H, H1′), 6.97 (dd, *J* = 2.8 and 9.1, 1H, H4), 7.02–7.07 (m, 4H, H4″ and H7″), 7.10 (d, *J* = 2.66, 1H, H6), 7.11–7.14 (m, 1H, H9″), 7.34–7.38 (m, 2H, H8″), 7.61 (d, *J* = 8.9, 2H, H3″), 8.34 (d, *J* = 9.1, 1H, H3), 8.37 (br s, 1H, NH), 10.24 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 25.4, 28.0, 28.4, 29.0, 32.1, 32.7, 33.9, 38.0, 41.3, 64.9, 113.4, 117.3, 118.5, 119.5, 122.4, 123.3, 122.7, 123.8, 129.8, 132.3, 132.7, 154.3, 154.1, 157.2, 166.8, 172.1; *m/z* (ESI$^-$, 50 eV): *m/z* (%): 599 (100) [M−H]$^{--}$. Anal. Calcd for $C_{30}H_{34}BrClN_2O_4$: C, 59.86; H, 5.69; N, 4.65. Found: C, 59.60; H, 5.80; N, 4.55.

5.17. 2-(6-Bromohexanamido)-5-(4-chlorobutoxy)-*N*-(4-phenoxyphenyl)benzamide (10d)

A solution of 6-bromohexanoyl chloride (0.231 g, 1.17 mmol) in DCM (20 mL) was added dropwise to a stirring solution of the aniline (**9b**) (400 mg, 0.976 mmol) in DCM (70 mL) at 0 °C under a nitrogen atmosphere. When TLC analysis indicated the absence of starting material (typically 10 min) the reaction mixture was washed with brine (3 × 50 mL), satd $NaHCO_{3(aq)}$ (3 × 50 mL) and 5% citric $acid_{(aq)}$ (3 × 50 mL). The organic solution was then dried and the solvent removed in vacuo to yield a brown oil. After purification by flash chromatography (3:1 hexanes/ethyl acetate) and recrystallisation from DCM/hexanes the title compound (**10d**) (0.40 g, 70%) was isolated as white crystals. Mp 145–146 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3270br (NH), 3017w and 2937w (CH), 1656vs and 1603s (CO), 151506s and 1490s (Ar); δ_H (400 MHz, $CDCl_3$) 1.51 (m, 2H, H4‴), 1.68–1.75 (m, 4H, H3‴ and H5‴), 1.87–1.93 (m, 4H, H2′ and H3′), 2.36 (t, *J* = 7.36, 2H, H2‴), 3.39 (t, *J* = 6.7, 2H, H6‴), 3.60 (t, *J* = 5.7, 2H, H4′), 3.97 (t, *J* = 5.5, 2H, H1′), 6.90 (dd, *J* = 2.3 and 9.0, 1H, H4), 7.02–7.07 (m, 5H, H6, H4″ and H7″), 7.11 (t, *J* = 7.5, 1H, H9″), 7.33 (t, *J* = 7.5, 2H, H8″), 7.62 (d, *J* = 8.7, 2H, H3″), 8.26 (d, *J* = 9.0, 1H, H3), 8.55 (br s, 1H, NH), 10.24 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 24.6, 26.6, 27.8, 29.2, 32.4, 33.5, 37.7, 44.6, 67.6, 113.7, 117.3, 118.7, 119.5, 122.3, 123.3, 123.4, 123.7, 129.7, 132.0, 132.9, 154.2, 154.3, 157.4, 166.1, 171.7; HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{29}H_{32}BrClN_2O_4Na$ 611.1111 found 611.1107. Anal. Calcd for $C_{30}H_{34}BrClN_2O_4$: C, 59.24; H, 5.49; N, 4.76. Found: C, 59.19; H, 5.42; N, 4.75.

5.18. 2-(8-Bromooctanamido)-5-(4-chlorobutoxy)-*N*-(4-phenoxyphenyl)benzamide(10e)

The title compound (**10e**) was prepared from **9b** using 8-bromooctanoic acid according to the procedure used to prepare **10a**. The product (**10e**) (0.6 g, 96%) was obtained as white crystals after purification by flash chromatography (2:1 hexanes/ethyl acetate) then recrystallisation from DCM/hexanes. Mp 133–134 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3299br (NH), 3017 and 2935 and 2858 (CH), 1652 and 1591 (CO), 1595 and 1487 (Ar); δ_H (400 MHz, $CDCl_3$) 1.32–1.43 (m, 6H, H4‴, H5‴and H6‴), 1.71 (m, 2H, H3‴), 1.83 (m, 2H, H7‴), 1.93–1.97 (m, 4H, H2′ and H3′), 2.35 (t, *J* = 7.6, 2H, H2‴), 3.38 (t, *J* = 6.9, 2H, H5‴), 3.62 (t, *J* = 5.9, 2H, H4′), 3.97 (t, *J* = 5.83, 2H, H1′), 6.90 (dd, *J* = 2.9 and 9.1, 1H, H4), 7.01–7.04 (m, 4H, H4″ and H7″), 7.06–7.11 (m, 1H, H9″), 7.33–7.37 (m, 3H, H6 and H8″), 7.59 (d, *J* = 9.0, 2H, H3″), 8.26 (br s, 1H, NH), 8.33 (d, *J* = 9.1, 1H, H, H3), 10.23 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 25.4, 26.6, 28.0, 28.5, 29.0, 29.2, 32.7, 33.9, 38.1, 44.6, 67.6, 113.5, 117.7, 118.6, 118.8, 119.5, 122.5, 123.4, 123.9, 129.8, 132.3, 132.8, 154.4, 157.3, 166.9, 172.1; *m/z* (ESI$^+$, 50 eV): *m/z* (%): 615 (100) [M+H]$^+$ Anal. Calcd for $C_{31}H_{36}BrClN_2O_4$: C, 60.44; H, 5.89; N, 4.55. Found: C, 60.50; H, 5.61; N, 4.71.

5.19. *N*-(4-(4-(Benzyloxy)phenoxy)phenyl)-2-(8-bromooctanamido)-5-(3-chloropropoxy)benzamide (10f)

The title compound (**10f**) was prepared from **9c** using 8-bromooctanoic acid according to the procedure used to prepare **8c**. The product (**10f**) (44 mg, 20%) was obtained as white crystals after purification by flash chromatography (2:1 hexanes/ethyl acetate) then recrystallisation from DCM/hexanes. Mp 111–113 °C; ν_{max} (ATR)/cm^{-1} 3396w and 3323w (NH), 2927w and 2851w (CH), 1686w and 1623w (C=O), 1586w, 1511w, 1493s (Ar); δ_H (400 MHz, $CDCl_3$) 1.35–1.38 (m, 4H, H4‴ and H5‴), 1.42 (m, 2H, H6‴), 1.71 (m, 2H, H6‴), 1.83 (m, 2H, H7‴), 2.20 (m, 2H, H2′), 2.34 (t, *J* = 7.5, 2H, H2‴), 3.38 (t, *J* = 6.9, 2H, H8‴), 3.71 (t, *J* = 6.2, 2H, H3′), 4.08 (t, *J* = 5.9, 2H, H1′), 5.06 (s, 2H, H1‴), 6.92 (dd, *J* = 2.8 and 9.1, 1H, H4), 6.94–7.00 (m, 6H, H4″ and H7″ and H8″), 7.33 (d, *J* = 7.1, 1H, H5‴‴), 7.40 (m, 2H, H4‴‴), 7.44 (m, 2H, H3‴‴), 7.57 (d, *J* = 8.9, 2H, H3″), 8.29 (d, *J* = 9.1, 1H, H3), 8.52 (br s, 1H, NH), 10.25 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 25.4, 28.0, 28.5, 29.0, 32.1, 32.7, 33.9, 38.0, 41.3, 64.9, 70.6, 113.6, 116.0, 117.6, 118.3, 120.5, 121.6, 122.4, 123.4, 123.7, 127.5, 128.0, 128.6, 132.2, 136.9, 150.5, 154.1, 155.1, 155.5, 166.8, 172.1; HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{37}H_{41}BrClN_2O_5$ 707.18874 found 707.18743.

5.20. 2-(8-Bromooctanamido)-5-(3-chloropropoxy)-*N*-(4-(4-fluorophenoxy)phenyl)benzamide (10g)

The title compound (**10g**) was prepared from **9d** using 8-bromooctanoic acid according to the procedure used to prepare **8c**. The product (**10g**) (62 mg, 11%) was obtained as a pale brown solid after purification by flash chromatography (2:1 hexanes/ethyl acetate) then recrystallisation from DCM/hexanes. Mp 101–105 °C; ν_{max} (ATR)/cm^{-1} 3427w and 3307w (NH), 2928w and 2855w (CH), 1687w and 1641w (C=O), 1590w, 1511w and 1493s (Ar); δ_H (400 MHz, $CDCl_3$) 1.25–1.43 (m, 4H, H4‴, H5‴ and H6‴), 1.68–1.71 (m, 2H, H3‴), 1.81–1.85 (m, 2H, H7‴), 2.17–2.20 (m, 2H, H2′), 2.33 (t, *J* = 7.6, 2H, H2‴), 3.37 (t, 2H, *J* = 6.8, 2H, H8‴), 3.70 (t, *J* = 6.2, 2H, H3′), 4.08 (t, *J* = 5.8, 2H, H1′), 6.9 (dd, *J* = 2.6 and 9.1, 1H, H4), 6.97–7.04 (m, 8H, H4″, H6″, H7″ and H8″), 7.07 (d, *J* = 2.6, 1H, H6), 7.61 (d, *J* = 8.8, 2H, H3″), 8.23 (d, *J* = 8.5, 1H, H3), 8.71 (br s, 1H, NH), 10.22 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 25.4, 28.0, 28.5, 29.0, 32.1, 32.7, 33.9, 38.0, 41.3, 64.7, 113.7, 116.3 (*J* 23.3, C8″), 117.5, 118.9, 120.3 (*J* 8.3, C7″), 122.4, 123.4, 123.7, 132.1, 132.9, 152.9, 154.1, 154.6, 158.8 (*J* 241.8, C9″), 166.8, 172.1; HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{30}H_{33}BrClFN_2O_4Na$ 641.1194 found 641.1187.

5.21. 2-(5-Azidopentanamido)-5-(3-azidopropoxy)-*N*-(4-phenoxyphenyl)benzamide (11a)

The diazide (**11a**) was prepared from the dihalide (**10a**) following the method of Takaya.[23] To a stirred solution of the dihalide (100 mg, 0.17 mmol) in THF (5 mL), maintained at 0 °C under an atmosphere of nitrogen was added trimethylsilylazide (60 mg, 0.52 mmol) then *tetra*-butylammonium fluoride (1 M) in THF (0.52 mL, 0.52 mmol). The reaction mixture was then allowed to warm slowly to room temperature then heated at 45 °C until NMR analysis showed no starting material remained (typically 50 h). The solvent was then removed in vacuo to give a brown oil which was purified by flash chromatography (4:1 hexanes/ethyl acetate) then recrystallised from DCM/hexanes to yield the title compound (**11a**) (62 mg, 68%) as white crystals. Care was taken to ensure the dry diazide was not subjected to shock or heat. ν_{max} ($CHCl_3$)/cm^{-1} 3322br (NH), 3017s and 2960s (CH), 2099vs (N_3), 1656s and 1591s (CO), 1505vs and 1489vs (Ar); δ_H (400 MHz, $CDCl_3$) 1.66 (m, 2H, H3‴), 1.80 (m, 2H, H4‴), 2.06 (m, 2H, H2′), 2.42 (t, *J* = 7.2, 2H, H2‴), 3.32 (t, *J* = 6.6, 2H, H5‴), 3.52 (t, *J* = 6.5, 2H, H3′), 4.06 (t, *J* = 6.1, 2H, H1′), 6.99–7.14 (m, 7H, H4, H6, H4″, H7″ and H9″) 7.35 (m, 2H, H8″), 7.78 (d, *J* = 8.9, 2H, H3″), 8.18 (br s, 1H, NH), 8.42 (d, *J* = 9.1, 1H, H3), 10.47 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 22.6, 28.4, 28.7, 37.3, 48.1, 51.1, 65.2, 113.5, 117.7, 118.7, 119.5, 122.5, 123.1, 123.4, 123.7, 129.8, 132.4, 132.6, 154.1, 154.4, 157.2, 166.8, 171.2; HRMS (ESI$^+$) [M+H]$^+$ calcd for $C_{27}H_{29}N_8O_4$ 529.2312 found 529.2339.

5.22. 2-(6-Azidohexanamido)-5-(3-azidopropoxy)-*N*-(4-phenoxyphenyl)benzamide (11b)

The diazide (**11b**) was prepared from the dihalide (**10b**) according to the method used to prepare **11a**. The product (**11b**) (280 mg, 94%) was isolated as white crystals. ν_{max} ($CHCl_3$)/cm^{-1} 3310br (NH), 3019s and 2934s (CH), 2100vs (N_3), 1655w and 1592w (CO), 1521s and 1506vs (Ar); δ_H (400 MHz, $CDCl_3$) 1.54 (m, 2H, H4‴), 1.71 (m, 2H, H3‴), 1.81 (m, 2H, H5‴), 2.15 (m, 2H, H2′), 2.48 (t, *J* = 7.40, 2H, H2‴), 3.41 (t, *J* = 6.9, 2H, H6‴), 3.66 (t, *J* = 6.7, 2H, H3′), 4.23 (t, *J* = 6.1, 2H, H1′), 7.09–7.15 (m, 4H, H4″and H7″), 7.19–7.23 (m, 2H, H4 and H9″), 7.47 (m, 2H, H8″), 7.51 (d, *J* = 2.9, 1H, H6), 7.88 (d, *J* = 9.0, 2H, H3″), 8.50 (d, *J* = 9.1, 1H, H3), 9.84 (br s, 1H, NH), 10.56 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 25.0, 26.3, 28.6, 37.8, 48.1, 51.2, 53.8, 65.2, 113.6, 117.6, 118.7, 119.5, 119.6, 122.4, 123.3, 123.7, 129.8, 132.2, 132.8, 154.1, 154.2, 157.2, 166.8, 171.7 (C1″); HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{28}H_{30}N_8O_4Na$ 565.2288 found 565.2282.

5.23. 2-(8-Azidooctanamido)-5-(3-azidopropoxy)-*N*-(4-phenoxyphenyl)benzamide (11c)

The diazide (**11c**) was prepared from the dihalide (**10c**) according to the method used to prepare **11a**. The product (**11c**) (28 mg, 95%) was isolated as white crystals. ν_{max} ($CHCl_3$)/cm^{-1} 3300br (NH), 2933s (CH), 2097vs (N_3), 1653w and 1591s (CO), 1521s and 1506vs and 1489s (Ar); δ_H (400 MHz, $CDCl_3$) 1.35 (m, 4H, H4‴ and H5‴), 1.44 (m, 2H, H6‴), 1.58 (m, 2H, H3‴), 1.69 (m, 2H, H7‴), 2.02 (m, 2H, H2′), 2.46 (t, *J* = 7.5, 2H, H2‴), 3.23 (t, *J* = 6.9, 2H, H8‴), 3.50 (t, *J* = 6.6, 2H, H3′), 4.03 (t, *J* = 5.9, 2H, H1′), 6.93 (dd, *J* = 2.7 and 9.1, 1H, H4), 7.01–7.14 (m, 6H, H6, H4″, H7″ and H9″), 7.35 (m, 2H, H8″), 7.55 (d, *J* = 8.9, 2H, H3″), 8.42 (d, *J* = 9.1, 1H, H3), 8.54 (br s, 1H, NH), 10.27 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 25.4, 26.5, 28.71, 28.74, 28.8, 29.0, 38.1, 48.1, 51.4, 65.1, 113.5, 117.6, 118.4, 118.7, 119.5, 122.4, 123.3, 123.7, 129.8, 132.3, 132.8, 154.0, 154.2, 157.3, 166.8, 172.0; HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{30}H_{34}N_8O_4Na$ 593.2601 found 593.2593.

5.24. 5-(4-Azidobutoxy)-2-(6-azidohexanamido)-*N*-(4-phenoxyphenyl)benzamide(11d)

The diazide (**11d**) was prepared from the dihalide (**10d**) according to the method used to prepare **11a**. The product (**11d**) (0.34 g, 89%) was isolated as white crystals. ν_{max} ($CHCl_3$)/cm^{-1} 3280br (NH), 3014w and 2933s (CH), 2098vs (N_3), 1655s and 1591s (CO), 1521s and 1506vs and 1488s (Ar); δ_H (400 MHz, $CDCl_3$) 1.45 (m, 2H, H4‴), 1.63 (m, 2H, H3‴), 1.71–1.83 (m, 4H, H3′ and H5‴), 1.84–1.89 (m, 2H, H2′), 2.38 (t, *J* = 7.5, 2H, H2‴), 3.26 (t, *J* = 6.9, 2H, H6‴), 3.37 (t, *J* = 6.5, 2H, H4′), 4.00 (t, *J* = 6.0, 2H, H1′), 6.98 (dd, *J* = 2.8 and 9.1, 1H, H4), 7.02–7.07 (m, 4H, H4″ and H7″), 7.09 (d, *J* = 2.8, 1H, H6), 7.12 (m, 1H, H9″), 7.33–7.37 (m, 2H, H8″), 7.56 (d, *J* = 8.9, 2H, H3″), 8.16 (br s, 1H, NH), 8.37 (d, *J* = 9.1, 1H, H3), 10.28 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 25.0, 25.6, 26.3, 26.5, 28.6, 37.8, 51.2, 53.9, 65.2, 113.7, 117.4, 118.7, 119.5, 119.6, 122.4, 123.4, 123.7, 129.8, 132.0, 132.8, 154.29, 154.31, 157.3, 166.8, 171.6; HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{29}H_{32}N_8O_4Na$ 579.2444 found 579.2444.

5.25. 5-(4-Azidobutoxy)-2-(8-azidooctanamido)-*N*-(4-phenoxyphenyl)benzamide (11e)

The diazide (**11e**) was prepared from the dihalide (**10e**) according to the method used to prepare **11a**. The product (**11e**) (0.14 mg, 98%) which was isolated as white crystals. ν_{max} ($CHCl_3$)/cm^{-1} 3320br (NH), 3028s and 2933s (CH), 2100vs (N_3), 1652s and 1591s (CO), 1521s and 1505vs and 1489s (Ar); δ_H (400 MHz, $CDCl_3$) 1.32–1.41 (m, 6H, H4‴and H5‴ and H6‴), 1.54–1.59 (m, 2H, H3‴), 1.67–1.72 (m, 2H, H7‴), 1.74–1.80 (m, 2H, H3′) 1.82–1.89 (m, 2H, H2′), 2.35 (t, *J* = 7.5, 2H, H2‴), 3.26 (t, *J* = 6.9, 2H, H8‴), 3.37 (t, *J* = 6.6, 2H, H4′), 4.00 (t, *J* = 5.9, 2H, H1′), 6.98 (dd, *J* = 2.7 and 9.1, 1H, H4), 7.07–7.02 (m, 4H, H4″ and H7″), 7.09 (d, *J* = 2.7, 1H, H6), 7.12 (t, *J* = 7.5, 1H, H9″), 7.35 (m, 2H, H8″), 7.61 (d, *J* = 8.8, 2H, H3″), 8.30 (d, *J* = 9.1, 1H, H3), 8.48 (br s, 1H, NH), 10.22 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 25.4, 25.6, 26.4, 26.5, 28.7, 28.9, 29.0, 38.0, 51.1, 51.4, 67.8, 113.7, 117.2, 118.7, 119.5, 119.6, 122.3, 123.3, 123.6, 129.8, 131.7, 132.8, 154.21, 154.24, 157.3, 166.9, 172.1; HRMS (ESI$^+$) [M+Na]$^+$ calcd for $C_{31}H_{36}N_8O_4Na$ 607.2757 found 607.2756.

5.26. 2-(8-Azidooctanamido)-5-(3-azidopropoxy)-*N*-(4-(4-(benzyloxy)phenoxy)phenyl)benzamide (11f)

The diazide (**11f**) was prepared from the dihalide (**10f**) according to the method used to prepare **11a** (53 mg, 47%). ν_{max} (ATR)/cm^{-1} 3244w and 3123w and 3039w (NH), 2930s and 2857w (CH), 2091s (N_3), 1656s and 1639s (CO), 1600vs and 1547s and 1493s (Ar); δ_H (400 MHz, $CDCl_3$) 1.35 (m, 6H, H4‴, H5‴ and H6‴), 1.58 (m, 2H, H3‴), 1.71 (m, 2H, H7‴), 1.02 (m, 2H, H2′), 2.34 (t, J = 7.6, 2H, H2‴), 3.23 (t, J = 7.0, 2H, H8‴), 3.49 (t, J = 6.6, 2H, H3′), 4.02 (t, J = 6.1, 2H, H1′), 5.06 (s, 2H, H1‴′), 6.92 (dd, J = 2.7 and 9.4, 2H, H4), 6.78–7.00 (m, 6H, H4″, H7″ and H8″), 7.08 (d, J = 2.7, 1H, H6), 7.33–7.38 (m, 1H, H5‴′), 7.39–7.45 (m, 4H, H3‴′ and H4‴), 7.56 (d, J = 8.9, 2H, H3″), 8.30 (d, J = 9.1, 1H, H3), 8.49 (br s, 1H, NH), 10.26 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 25.4, 26.6, 28.7, 28.8, 28.9, 29.1, 38.0, 48.1, 51.4, 65.2, 70.6, 113.6, 115.0, 117.6, 118.4, 120.5, 121.5, 123.7, 127.5, 128.0, 128.6, 132.2, 132.3, 136.9, 150.5, 154.1, 155.1, 155.5, 166.8, 172.1; HRMS (ESI$^+$) $[M+Na]^+$ calcd for $C_{37}H_{41}N_8O_5Na$ 699.3019 found 699.3013.

5.27. 2-(8-Azidooctanamido)-5-(3-azidopropoxy)-*N*-(4-(4-fluorophenoxy)phenyl)benzamide (11g)

The diazide (**11g**) was prepared from the dihalide (**10g**) according to the method used to prepare **11a**. The product (**11g**) (50 mg, 28%) which was isolated as white crystals. ν_{max} (ATR)/cm^{-1} 3309br and 3241s (NH), 2928s (CH), 2096s (N_3), 1645s and 1589s (CO), 1520s and 1593vs and 1466s (Ar); δ_H (400 MHz, $CDCl_3$) 1.35 (m, 6H, H4‴, H5‴ and H6‴), 1.58 (m, 2H, H3‴), 1.71 (m, 2H, H7‴), 2.04 (m, 2H, H2′), 2.35 (t, J = 7.5, 2H, H2′), 3.23 (t, J = 6.9, 2H, H8‴), 3.51 (t, J = 6.3, 2H, H3′), 4.05 (t, J = 5.9, 2H, H1′), 6.97–7.04 (m, 7H, H4, H4″, H7″ and H8″), 7.09 (d, J = 2.5, 1H, H6), 7.57 (d, J = 8.8, 2H, H3″), 8.25 (br s, 1H, NH), 8.35 (d, J = 9.1, 1H, H3), 10.23 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 25.4, 26.5, 28.7, 28.7, 28.9, 29.0, 38.0, 48.1, 51.4, 65.2, 113.4, 116.4 (J = 23.4, C8″), 117.8, 118.9, 120.4 (J = 8.3, C7″), 122.5, 123.1, 123.8, 132.5, 132.6, 151.0, 154.1, 154.8, 158.6 (J = 241.4, C9″), 166.8, 171.6; HRMS (ESI$^+$) $[M+Na]^+$ calcd for $C_{30}H_{33}N_8O_4Na$ 611.25065 found 611.24969.

5.28. 2-(5-Aminopentanamido)-5-(3-aminopropoxy)-*N*-(4-phenoxyphenyl)benzamide (12a)

A flask containing a solution of the diazide (**11a**) (48 mg, 0.10 mmol) and 10% wt palladium on carbon (16 mg, 0.071 mmol) in THF/methanol (1:1) (4 mL) was degassed, flushed with hydrogen and stirred with an atmosphere of hydrogen for 3 h. After this time the reaction mixture was filtered through Celite and the solvent removed in vacuo to give a pale yellow oil. After recrystallisation from methanol/ethyl acetate the title compound (**12a**) (43 mg, 98%) was isolated as a white powder. Mp 152 °C (decomposed); ν_{max} (ATR)/cm^{-1} 3228b (NH), 2930s and 2857s (CH), 1636s and 1600s (CO), 1528vs and 1501vs and 1485vs (Ar). δ_H (400 MHz, methanol-d_4) 1.50 (m, 2H, H3‴), 1.66 (m, 2H, H4‴), 1.95 (m, 2H, H2′), 2.38 (t, J = 7.4, 2H, H2‴), 2.62 (t, J = 7.1, 2H, H5‴), 2.85 (t, J = 6.8, 2H, H3′), 4.11 (t, J = 6.1, 2H, H1′), 6.96–6.99 (m, 4H, H4″ and H7″), 7.06–7.10 (m, 1H, H9″), 7.28 (d, J = 2.7, 1H, H6), 7.34 (m, 2H, H8″), 7.63 (d, J = 8.9, 2H, H3″), 7.90 (d, J = 9.0, 1H, H3); δ_C (100 MHz, methanol-d_4) 22.5, 23.9, 31.9, 37.8, 39.5, 41.7, 67.5, 115.2, 118.7, 119.6, 120.2, 124.1, 124.4, 126.0, 128.6, 130.9, 131.4, 135.1, 155.4, 156.9, 158.9, 168.8, 174.0; HRMS (ESI$^+$) $[M+H]^+$ calcd for $C_{27}H_{33}N_4O_4$ 477.2502 found 477.2498.

5.29. 2-(6-Aminohexanamido)-5-(3-aminopropoxy)-*N*-(4-phenoxyphenyl)benzamide (12b)

The diamine (**12b**) was prepared from the diazide (**11b**) according to the method used to prepare **12a**. The product (**12b**) (66 mg, 80%) was isolated as a white powder. Mp 147 °C (decomposed); ν_{max} (ATR)/cm^{-1} 3258b and 3150b and 3057b (NH), 2928s and 2860s (CH), 1649s and 1587s (CO), 1503vs and 1485vs (Ar); δ_H (400 MHz, methanol-d_4) 1.41 (m, 2H, H4‴), 1.53 (m, 2H, H3‴), 1.69 (m, 2H, H5‴), 1.98 (m, 2H, H2′), 2.38 (t, J = 7.2, 2H, H2‴), 2.69 (t, J = 7.2, 2H, H6‴), 2.89 (t, J = 6.9, 2H, H3′), 4.13 (t, J = 6.1, 2H, H1′), 6.97–7.01 (m, 4H, H4″ and H7″), 7.08–7.11 (m, 2H, H4 and H9″), 7.30 (d, J = 2.6, 1H, H6), 7.35 (m, 2H, H8″), 7.64 (d, J = 8.9, 2H, H3″), 7.91 (d, J = 9.0, 1H, H3); δ_C (100 MHz, methanol-d_4) 25.2, 26.0, 31.5, 31.7, 36.7, 38.2, 40.7, 66.1, 113.7, 117.2, 118.2, 118.8, 122.6, 122.9, 124.6, 127.3, 129.5, 131.1, 133.7, 154.0, 155.6, 157.5, 167.4, 173.0; HRMS (ESI$^+$) $[M+H]^+$ calcd for $C_{28}H_{35}N_4O_4$ 491.2658 found 491.2658.

5.30. 2-(8-Aminooctanamido)-5-(3-aminopropoxy)-*N*-(4-phenoxyphenyl)benzamide (12c)

The diamine (**12c**) was prepared from the diazide (**11c**) according to the method used to prepare **12a**. The product (**12c**) (156 mg, 96%) was isolated as a white powder. Mp 132 °C (decomposed); ν_{max} (ATR)/cm^{-1} 3262b and 3043b (NH), 2927s and 2854s (CH), 1728s and 1589s (CO), 1503vs and 1486vs (Ar); δ_H (400 MHz, methanol-d_4) 1.29–1.33 (m, 6H, H4‴ and H5‴ and H6‴), 1.39 (m, 2H, H7‴), 1.64 (m, 2H, H3‴), 1.94 (m, 2H, H2′), 2.36 (t, J = 7.4, 2H, H2‴), 2.66 (t, J = 7.2, 2H, H8‴), 2.88 (t, J = 7.0, 2H, H3′), 4.13 (t, J = 6.0, 2H, H1′), 6.97–7.01 (m, 4H, H4″ and H7″), 7.08–7.11 (m, 2H, H4 and H9″), 7.29 (d, J = 2.7, 1H, H6), 7.33 (m, 2H, H8″), 7.64 (d, J = 8.6, 2H, H3″), 7.90 (d, J = 9.0, 1H, H3); δ_C (100 MHz, methanol-d_4) 27.0 (C3‴), 28.0, 30.4, 30.5, 33.5 (C2′), 34.0 (C7‴), 38.4 (C2‴), 39.8 (C3′), 42.7 (C8‴), 67.7 (C1′), 115.1 (C4), 118.6 (C6), 119.6, 120.4, 123.9 (C9″), 124.1 (C3), 124.4 (C3″), 126.2, 131.1 (C8″), 131.2, 135.5, 155.3, 157.2, 159.1, 169.0, 174.8; HRMS (ESI$^+$) $[M+Na]^+$ calcd for $C_{30}H_{39}N_4O_4Na$ 519.2971 found 519.2970.

5.31. 5-(4-Aminobutoxy)-2-(6-aminohexanamido)-*N*-(4-phenoxyphenyl)benzamide (12d)

The diamine (**12d**) was prepared from the diazide (**11d**) according to the method used to prepare **12a**. The product (**12d**) (101 mg, 83%) was isolated as a white powder. Mp 106 °C (decomposed); ν_{max} (ATR)/cm^{-1} 3270b and 3047b (NH), 2925s and 2852s (CH), 1708s and 1624s (CO), 1503vs and 1486vs (Ar); δ_H (400 MHz, methanol-d_4) 1.31 (m, 2H, H4‴), 1.40 (m, 2H, H3‴), 1.55–1.62 (m, 4H, H3′ and H5‴), 1.76 (m, 2H, H2′), 2.23 (t, J = 7.4, 2H, H2‴), 2.53 (t, J = 7.1, 2H, H6‴), 2.66 (t, J = 7.2, 2H, H4′), 4.00 (t, J = 6.3, 2H, H1′), 6.93–6.91 (m, 4H, H4″ and H7″), 7.02 (dd, J = 2.7 and 9.0, 1H, H4), 7.06 (t, J = 7.4, 1H, H9″), 7.20–7.25 (m, 2H, H6), 7.26–7.30 (m, 2H, H8″), 7.58–7.60 (d, J = 7.85, 2H, H3″), 7.89 (d, J = 8.49, 1H, H3); δ_C (100 MHz, methanol-d_4) 26.7 (C3‴), 27.5 (C4‴), 27.8 (C2′), 30.6 (C3′), 33.7 (C5‴), 38.3 (C2‴), 42.38 (C6″), 42.43 (C4′), 69.4 (C1′), 115.2 (C6), 118.6 (C4), 119.6 (C4″), 120.3 (C7″), 124.0 (C3″), 124.3, 125.8 (C3), 128.4, 130.9 (C8″), 131.5 (C3″), 135.3, 155.3, 156.9, 158.9, 168.8, 174.3; HRMS (ESI$^+$) $[M+H]^+$ calcd for $C_{29}H_{37}N_4O_4$ 505.2815 found 505.2815.

5.32. 5-(4-Aminobutoxy)-2-(8-aminooctanamido)-*N*-(4-phenoxyphenyl)benzamide (12e)

The diamine (**12e**) was prepared from the diazide (**11e**) according to the method used to prepare **12a**. The product (**12e**) (59 mg,

81%) was isolated as a white powder. Mp 122 °C (decomposed); ν_{max} (ATR)/cm^{-1} 3325b and 3230b and 3125b (NH), 2929s and 2851s (CH), 1644s and 1602s (CO), 1511vs and 1488vs (Ar); δ_H (400 MHz, methanol-d_4) 1.35–1.37 (m, 6H, H4‴, H5‴ and H6‴), 1.45 (m, 2H, H7‴), 1.69–1.71 (m, 4H, H3′ and H3‴), 1.89 (m, 2H, H2′), 2.39 (t, J = 6.3, 2H, H2‴), 2.60 (t, J = 7.2, 2H, H8‴), 2.76 (t, J = 6.2, 2H, H4′), 4.13 (m, 2H, H1′), 7.03 (m, 4H, H4″ and H7″), 7.09–7.15 (m, 2H, H4 and H9″), 7.36–7.40 (m, 3H, H6 and H8″), 7.66 (d, J = 8.0, 2H, H3″), 7.93 (d, J = 8.7, 1H, H3); δ_C (100 MHz, methanol-d_4) 26.9, 27.8, 27.9, 30.2, 30.3, 30.6, 34.0, 38.5, 42.4, 42.6, 69.4, 115.2, 118.6, 119.5, 120.3, 124.0, 124.8, 125.9, 129.5, 130.1, 130.9, 135.9, 155.1, 157.0, 159.1, 168.9, 174.5; HRMS (ESI$^+$) [M+H]$^+$ calcd for $C_{31}H_{41}N_4O_4$ 533.3128 found 533.3119.

5.33. 2-(8-Aminooctanamido)-5-(3-aminopropoxy)-*N*-(4-(4-(benzyloxy)phenoxy)phenyl)benzamide (12f)

The diamine (**12f**) was prepared from the diazide (**11f**) according to the method used to prepare **12a**. The product (**12f**) (49 mg, 97%) was isolated as a colourless oil. δ_H (400 MHz, methanol-d_4) 1.28–1.38 (m, 6H, H4‴, H5‴ and H6‴), 1.45 (m, 2H, H7‴), 1.65 (m, 2H, H3‴), 1.96 (m, 2H, H2′), 2.34 (t, J = 7.4, 2H, H2‴), 2.63 (t, J = 7.3, 2H, H8‴), 2.86 (t, J = 7.0, 2H, H3′), 4.11 (t, J = 6.6, 2H, H1′), 5.05 (s, 2H, H1⁗), 6.87–7.00 (m, 6H, H4″, H7″ and H8″), 7.08 (dd, J = 2.7 and 8.9, 1H, H4), 7.27 (m, 1H, H6), 7.30 (d, J = 7.2, 1H, H5⁗), 7.34–7.44 (m, 4H, H3⁗ and H4⁗), 7.59 (d, J = 9.0, 2H, H3″), 7.90 (d, J = 8.9, 1H, H3); δ_C (100 MHz, methanol-d_4) 25.4, 26.4, 28.8, 29.0, 31.8, 31.9, 36.8, 38.2, 41.0, 66.2, 70.1, 114.2, 115.8, 116.1, 117.6, 119.8, 121.6, 122.5, 124.7, 127.2, 127.5, 128.1, 129.8, 133.1, 137.3, 148.9, 150.7, 155.2, 155.6, 167.4, 173.2; m/z (ESI$^+$, 50 eV): m/z (%): 625 (65) [M+H]$^+$.

5.34. 2-(8-Aminooctanamido)-5-(3-aminopropoxy)-*N*-(4-(4-fluorophenoxy)phenyl)benzamide (12g)

The diamine (**12g**) was prepared from the diazide (**11g**) according to the method used to prepare **12a**, using a 4 h reaction time. The product (**12g**) (46 mg, 87%) was isolated as a white powder. Mp 84 °C (decomposed); ν_{max} (ATR)/cm^{-1} 3282b (NH), 2952s and 2864w (CH), 1730s and 1629s (CO), 1503w and 1459s (Ar); δ_H (400 MHz, methanol-d_4) 1.25–1.37 (m, 6H, H4‴, H5‴ and H6‴), 1.41 (m, 2H, H3‴), 1.65 (m, 2H, H7‴), 1.94 (m, 2H, H2′), 2.35 (t, J = 7.4, 2H, H2‴), 2.58 (t, J = 7.0, 2H, H8‴), 2.89 (t, J = 7.0, 2H, H3′), 4.11 (t, J = 6.6, 2H, H1′), 6.96–7.02 (m, 5H, H4, H4″ and H7″), 7.09 (J = 8.4, 2H, H8″), 7.29 (d, J = 2.3, 1H, H6), 7.63 (d, J = 8.8, 2H, H3″), 7.84 (d, J = 8.9, 1H, H3); δ_C (100 MHz, methanol-d_4) 26.8, 27.8, 30.2, 30.3, 33.4, 33.8, 38.4, 39.7, 42.6, 67.6, 115.1, 117.3 (J = 8.3, C8″), 118.7, 119.8, 121.2 (J = 8.3, C7″), 124.0, 126.0, 128.7, 131.4, 135.2, 151.0, 154.9, 160.1 (J = 240.0, C9″), 162.6, 166.9, 174.6; HRMS (ESI$^+$) [M+H]$^+$ calcd for $C_{30}H_{38}FN_4O_4$ 537.2877 found 537.2876.

5.35. 2-(8-Aminooctanamido)-5-(3-aminopropoxy)-*N*-(4-(4-hydroxyphenoxy)phenyl)benzamide (12h)

The phenol (**12h**) was prepared from the benzyl ether (**12f**) according to the method used to prepare **12a**, using a 36 h reaction time. The product (**12h**) (17 mg, 74%) was isolated as a white powder. Mp 100 °C (decomposed); ν_{max} (ATR)/cm^{-1} 3310b (OH), 3278b (NH), 2929s and 2855s (CH), 1654s (CO), 1598s and 1503w and 1498vs (Ar); δ_H (400 MHz, methanol-d_4) 1.09–1.19 (m, 10H, H3‴, H4‴, H5‴, H6‴ and H7‴), 1.48 (m, 2H, H2′), 1.78 (m, 2H, H2‴), 2.16–2.25 (m, 2H, H3′ and H8‴), 4.00 (m, 2H, H1′), 6.71–6.75 (m, 2H, H4″), 6.79–6.87 (m, 4H, H7″ and H8″), 7.01 (m, 1H, H4), 7.24 (m, 1H, H6), 7.61 (m, 2H, H3″), 7.93 (m, 1H, H3); δ_C (100 MHz, methanol-d_4) 26.7, 28.5, 28.8, 29.0, 32.6, 33.3, 36.9, 38.5, 41.6, 65.9, 114.1, 116.2, 117.2, 120.2, 120.5, 122.2, 127.6, 128.3, 133.8, 137.0, 148.2, 154.2, 160.7, 166.5, 166.5, 175.1; HRMS (ESI$^+$) [M+H]$^+$ calcd for $C_{30}H_{39}N_4O_5$ 535.2921 found 535.2906.

5.36. 2-(5-Guanidinopentanamido)-5-(3-guanidinopropoxy)-*N*-(4-phenoxyphenyl)benzamide dihydrochloride (2a)

The diamine (**12a**) (43 mg, 0.091 mmol), DIEA (0.031 mL, 0.18 mmol), 1H-pyrazole-1-carboximidamide hydrochloride (26 mg, 0.18 mmol) and DMF (3 mL) were combined and stirred under a nitrogen atmosphere overnight. The solvent was then removed in vacuo and the residues recrystallised twice from ether/methanol to yield the title compound (**2a**) (20 mg, 33%) as colourless crystals. Mp 76–80 °C; ν_{max} (ATR)/cm^{-1} 3242b and 3290b and 3159b (NH), 2950s and 2862s (CH), 1631s (CO), 1504 and 1487 and 1471 (Ar); δ_H (500 MHz, methanol-d_4) 1.60 (m, 2H, H4‴), 1.69 (m, 2H, H3‴), 2.06 (m, 2H, H2′), 2.39 (t, J = 7.3, 2H, H2‴), 3.12 (t, J = 7.1, 2H, H5‴), 3.40 (t, J = 6.8, 2H, H3′), 4.16 (t, J = 5.8, 2H, H1′), 6.95–6.98 (m, 4H, H4″ and H7″), 7.08 (m, 1H, H9″), 7.14 (dd, J = 2.7 and 9.0, 1H, H4), 7.34–7.37 (m, 3H, H6 and H8″), 7.65 (d, J = 8.7, 2H, H3″), 7.87 (d, J = 9.0, 1H, H3); δ_C (100 MHz, methanol-d_4) 23.8 (C4‴), 29.4 (C3‴), 29.8 (C2′), 37.5 (C2‴), 39.7 (C5‴), 42.3 (C3′), 66.7 (C1′), 115.3 (C6), 118.8 (C4), 119.7 (C4″), 119.8 (C7″), 120.4 (C3″), 124.2 (C9″), 126.4 (C3), 129.5 (C1), 131.1 (C8″), 131.4 (C2″), 135.2 (C2), 155.6, 157.0 (C6″), 158.7 (C6‴), 158.9 (C4′), 159.1, 169.0, 174.4; HRMS (ESI$^+$) [M+H]$^+$ calcd for $C_{29}H_{37}N_8O_4$ 561.2938 found 561.2941.

5.37. 2-(5-Guanidinohexanamido)-5-(3-guanidinopropoxy)-*N*-(4-phenoxyphenyl)benzamide dihydrochloride (2b)

The diguanidinium compound (**2b**) was prepared from the diamine (**12b**) according to the method used to prepare **2a**. The product (**2b**) (30 mg, 69%) was isolated as colourless crystals. Mp 106–111 °C; ν_{max} (ATR)/cm^{-1} 3316b (=N–H), 3241b and 3159b (NH), 2950s and 2863s (CH), 1632s (CO), 1562w (C=N), 1504s and 1486s and 1471s (Ar); δ_H (400 MHz, methanol-d_4) 1.43 (m, 2H, H4‴), 1.59 (m, 2H, H5‴), 1.61 (m, 2H, H3‴), 2.10 (m, 2H, H2′), 2.41 (t, J = 7.3, 2H, H2‴), 3.14 (t, J = 7.1, 2H, H6‴), 3.45 (t, J = 6.7, 2H, H3′), 4.18 (t, J = 5.8, 2H, H1′), 6.99–7.03 (m, 4H, H4″ and H7″), 7.13 (m, 1H, H9″), 7.15 (dd, J = 2.8 and 9.0, 1H, H4), 7.35–7.39 (m, 3H, H6 and H8″), 7.69 (d, J = 8.9, 2H, H3″), 7.89 (d, J = 9.0, 1H, H3); δ_C (100 MHz, methanol-d_4) 26.3, 27.2, 29.5, 29.7, 37.9, 39.6, 42.3, 66.7, 115.3, 118.8, 119.6, 120.2, 124.1, 124.4, 126.3, 129.3, 130.9, 131.3, 135.1, 155.5, 156.9, 158.6, 158.8, 158.9, 168.9, 174.4; HRMS (ESI$^+$) [M+2H]$^{2+}$ calcd for $C_{30}H_{39}N_8O_4$ 288.1586 found 288.1577.

5.38. 2-(5-Guanidino-octanamido)-5-(3-guanidinopropoxy)-*N*-(4-phenoxyphenyl)benzamide dihydrochloride (2c)

The diguanidinium compound (**2c**) was prepared from the diamine (**12c**) according to the method used to prepare **2a**. The product (**2c**) (26 mg, 46%) was isolated as colourless crystals. Mp 117–119 °C; ν_{max} (ATR)/cm^{-1} 3316b (=N–H), 3241b and 3159b (NH), 2950s and 2863s (CH), 1632s (CO), 1562w (C=N), 1504s and 1486s and 1471s (Ar); δ_H (400 MHz, methanol-d_4) 1.43 (m, 2H, H4‴), 1.59 (m, 2H, H5‴), 1.61 (m, 2H, H3‴), 2.10 (m, 2H, H2′), 2.41 (t, J = 7.3, 2H, H2‴), 3.14 (t, J = 7.1, 2H, H6‴), 3.45 (t, J = 6.7, 2H, H3′), 4.18 (t, J = 5.8, 2H, H1′), 6.99–7.03 (m, 4H, H4″ and H7″), 7.13 (m, 1H, H9″), 7.15 (dd, J = 2.8 and 9.0, 1H, H4), 7.35–7.39 (m, 3H, H6 and H8″), 7.69 (d, J = 8.9, 2H, H3″), 7.89 (d, J = 9.0, 1H, H3); δ_C (100 MHz, methanol-d_4) 26.3, 27.2, 29.5, 29.7, 37.9, 39.6, 42.3, 66.7, 115.3, 118.8, 119.6, 120.2, 124.1, 124.4, 126.3, 129.3, 130.9, 131.3, 135.1, 155.5, 156.9, 158.6, 158.8, 158.9, 168.9, 174.4; HRMS (ESI$^+$) [M+2H]$^{2+}$ calcd for $C_{30}H_{39}N_8O_4$ 288.1586 found 288.1577.

5.39. 2-(5-Guanidinohexanamido)-5-(3-guanidinobutoxy)-*N*-(4-phenoxyphenyl)benzamide dihydrochloride (2d)

The diguanidinium compound (**2d**) was prepared from the diamine (**12d**) according to the method used to prepare **2a**. The product (**2d**) (81 mg, 96%) was isolated as colourless crystals. Mp 106–113 °C; ν_{max} (ATR)/cm^{-1} 3320b (=N–H), 3247b and 3150b and 3065b (NH), 2938s and 2869s (CH), 1634s (CO), 1543s (C=N), 1597vs, 1502vs and 1489vs (Ar); δ_H (400 MHz, methanol-d_4) 1.39 (m, 2H, H4‴), 1.56 (m, 2H, H5‴), 1.67 (m, 2H, H3‴), 1.78 (m, 2H, H3′), 1.86 (m, 2H, H2′), 2.37 (t, J = 7.3, 2H, H2‴), 3.11 (t, J = 7.1, 2H, H6‴), 3.27 (t, J = 7.0, 2H, H4′), 4.05 (t, J = 6.1, 2H, H1′), 6.96–7.00 (m, 4H, H4″ and H7″), 7.07–7.11 (m, 2H, H4 and H9″), 7.26 (d, J = 2.7, 1H, H6), 7.34 (m, 2H, H8″), 7.64 (d, J = 8.9, 2H, H3″), 7.83 (d, J = 8.9, 1H, H3); δ_C (100 MHz, methanol-d_4) 26.3 (C3‴), 26.7 (C4‴), 27.2 (C3′), 27.5 (C2′), 29.5 (C5‴), 37.9 (C2‴), 42.30 (C6‴), 42.38 (C4′), 69.0 (C1′), 115.2 (C6), 118.8 (C4), 119.6 (C4″), 120.2 (C7″), 124.2 (C9″), 124.4 (C3″), 126.3 (C3), 129.3 (C1), 130.9 (C8″), 131.0 (C2″), 135.1 (C2), 155.4 (C5″), 157.1 (C6″), 158.6 (C7‴), 158.7 (C5′), 158.9 (C5), 168.9 (C1‴), 174.7 (C1″); HRMS (ESI$^+$) [M+H]$^+$ calcd for $C_{31}H_{41}N_8O_4$ 589.3251 found 589.3247.

5.40. 2-(5-Guanidino-octanamido)-5-(3-guanidinobutoxy)-*N*-(4-phenoxyphenyl)benzamide dihydrochloride (2e)

The diguanidinium compound (**2e**) was prepared from the diamine (**12e**) according to the method used to prepare **2a**. The product (**2e**) (41 mg, 52%) was isolated as colourless crystals. Mp 61–65 °C; ν_{max} (ATR)/cm^{-1} 3320b (=N–H), 3251b and 3150b and 3065b (NH), 2934s and 2899s (CH), 1645s (CO), 1605 (C=N), 1597vs, 1504vs and 1487vs (Ar); δ_H (400 MHz, methanol-d_4) 1.31–1.40 (m, 6H, H4‴, H5‴, H6‴ and H7‴), 1.55 (m, 2H, H3‴), 1.67 (m, 2H, H7‴), 1.80 (m, 2H, H3′), 1.88 (m, 2H, H2′), 2.36 (t, J = 7.4, 2H, H2‴), 3.12 (t, J = 7.1, 2H, H8‴), 3.30 (t, J = 6.9, 2H, H4′), 4.10 (t, J = 6.0, 2H, H1′), 6.96–7.00 (m, 4H, H4″ and H7″), 7.11 (m, 2H, H9″), 7.09 (dd, J = 2.6 and 9.0, 1H, H4), 7.28 (d, J = 2.6, 1H, H6), 7.35 (m, 2H, H8″), 7.64 (d, J = 8.9, 2H, H3″), 7.85 (d, J = 9.0, 1H, H3); δ_C (100 MHz, methanol-d_4) 25.2, 25.3, 25.99, 26.02, 28.3, 28.5, 28.6, 36.7, 40.8, 41.0, 67.6, 115.2, 118.7, 119.5, 120.3, 124.0, 124.4, 126.3, 129.4, 130.9, 131.1, 135.2, 155.4, 157.2, 158.6, 158.7, 159.0, 168.8, 174.7; HRMS (ESI$^+$) [M+H]$^+$ calcd for $C_{33}H_{45}N_8O_4$ 617.3564 found 617.3559.

5.41. *N*-(4-(4-Fluorophenoxy)phenyl)-2-(8-guanidinooctanamido)-5-(3-guanidinopropoxy)benzamide dihydrochloride (2g)

The diguanidinium compound (**2g**) was prepared from the diamine (**12g**) according to the method used to prepare **2a**. The product (**2g**) (33 mg, 63%) was isolated as colourless crystals. Mp 73–79 °C; ν_{max} (ATR)/cm^{-1} 3320b (=N–H), 3253b and 3150b (NH), 2931s and 2857s (CH), 1648s (CO), 1604s (C=N), 1508s and 1492vs (Ar); δ_H (400 MHz, methanol-d_4) 1.32–1.38 (m, 6H, H4‴, H5‴ and H6‴), 1.55 (m, 2H, H3‴), 1.66 (m, 2H, H7‴), 2.09 (m, 2H, H2′), 2.36 (t, J = 7.4, 2H, H2‴), 3.13 (t, J = 7.0, 2H, H8‴), 3.42 (t, J = 6.8, 2H, H3′), 4.15 (t, J = 5.8, 2H, H1′), 6.97–7.02 (m, 4H, H4″ and H8″), 7.08–7.14 (m, 3H, H4 and H7″), 7.32 (d, J = 2.3, 1H, H6), 7.64 (d, J = 8.6, 2H, H3″), 7.87 (d, J = 8.7, 1H, H3); δ_C (100 MHz, methanol-d_4) 26.7, 27.5, 29.7, 29.8, 29.9, 30.0, 38.1, 39.6, 42.4, 66.7, 115.3 (d, J = 23.7, H8″), 117.3, 118.6, 119.8 (d, J = 8.3, C7″), 121.3, 124.1, 126.2, 129.2, 131.4, 135.1, 154.8, 156.3, 158.6, 158.8, 160.2 (d, J = 240.3, C9″), 161.4, 168.8, 174.7; HRMS (ESI$^+$) [M+H]$^+$ calcd for $C_{32}H_{42}N_8O_4$ 621.3313 found 621.3308.

5.42. *N*-(4-(4-(Benzyloxy)phenoxy)phenyl)-2-(8-guanidinooctanamido)-5-(3-guanidinopropoxy)benzamide dihydrochloride (2h)

The diguanidinium compound (**2h**) was prepared from the diamine (**12f**) according to the method used to prepare **2a**. The product (**2h**) (25 mg, 47%) was isolated as colourless crystals. Mp 75–81 °C; ν_{max} (ATR)/cm^{-1} 3363b (=N–H), 3248b and 3150b (NH), 2931s and 2858s (CH), 1643s (CO), 1603 (C=N), 1493vs (Ar); δ_H (400 MHz, methanol-d_4) 1.19–1.26 (m, 6H, H4‴, H5‴ and H6‴), 1.40 (m, 2H, H3‴), 1.52 (m, 2H, H7‴), 1.92 (m, 2H, H2′), 2.25 (t, J = 6.5, 2H, H2‴), 3.04 (m, 2H, H8‴), 3.29 (m, 2H, H3′), 4.11 (t, J = 4.9, 2H, H1′), 5.06 (s, 2H, H1‴), 6.80–7.03 (m, 8H, H4″, H7″ and H8″), 7.10 (d, J = 8.9 1H, H4), 7.29–7.33 (m, 1H, H5‴), 7.33–7.45 (m, 5H, H6, H3‴ and H4‴), 7.90 (br s, 1H, NH), 7.94 (d, J = 8.8, 1H, H3), 8.10 (br s, 1H, NH); δ_C (100 MHz, DMSO-d_6) 24.9 (C5‴), 25.8 (C4‴), 28.1 (C6‴), 28.2 (C3‴), 28.3 (C7‴), 36.6 (C2′), 37.6 (C2‴), 38.8 (C3′), 40.5 (C8‴), 65.2 (C1′), 69.6 (C1‴), 114.1 (C6), 115.9 (C4″), 116.1 (C4), 117.8 (C7″), 119.8 (C8″), 122.4 (C3″), 126.2 (C3), 127.5 (C3‴), 127.7 (C5‴), 128.3 (C4‴), 130.7 (C1), 133.4 (C2‴), 133.8 (C2″), 137.0 (C2), 148.3 (C9″), 150.2 (C5″), 153.6 (C6″), 154.3 (C5), 157.1 (C9‴), 157.2 (C4′), 166.1 (C1‴), 170.8 (C1″); HRMS (ESI$^+$) [M+H]$^+$ calcd for $C_{33}H_{45}N_8O_4$ 709.3826 found 709.3805.

5.43. 2-(8-Guanidinooctanamido)-5-(3-guanidinopropoxy)-*N*-(4-(4-hydroxyphenoxy)phenyl)benzamide dihydrochloride (2f)

The phenol (**2f**) was prepared from the benzyl ether (**2h**) according to the method used to prepare **12a**, using DMF/methanol (1:2) (1.5 mL) as the reaction solvent and a 48 h reaction time. The product (**2f**) (20 mg, 84%) was isolated as a white powder. Mp 169 °C (decomposed); ν_{max} (ATR)/cm^{-1} 3351b (=N–H), 3260b and 3169b and 3065b (NH), 2933s and 2859s (CH), 1650s (CO), 1603 (C=N), 1496vs and (Ar). δ_H (400 MHz, DMSO-d_6) 1.19–1.28 (m, 6H, H4‴, H5‴ and H6‴), 1.37 (m, 2H, H3‴), 1.56 (m, 2H, H7‴), 1.90 (m, 2H, H2′), 2.26 (t, J = 7.1, 2H, H2‴), 3.00 (t, J = 6.8, 2H, H8‴), 3.25 (t, J = 6.3, 2H, H3′), 4.03 (t, J = 5.9, 2H, H1′), 6.75 (d, J = 8.8, 2H, H8″), 6.83–6.86 (m, 4H, H4″ and H7″), 7.02 (dd, J = 2.8 and 8.7, 1H, H4), 7.48 (d, J = 2.4, 1H, H6), 7.61 (d, J = 8.8, 2H, H3″), 8.01 (d, J = 8.8, 1H, H3). δ_C (100 MHz, DMSO-d_6) 26.6, 28.3, 28.5, 28.5, 28.6, 29.7, 32.0, 40.5, 45.0, 69.5, 114.5, 115.8, 116.3, 117.2, 118.8, 122.8, 123.7, 127.7, 128.3, 134.3, 137.0, 154.0, 157.1, 157.8, 158.0, 160.7, 161.4, 170.6; HRMS (ESI$^+$) [M+H]$^+$ calcd for $C_{32}H_{43}N_8O_5$ 619.3356 found 619.3332.

5.44. $Ca_v2.2$ binding assay

Radioligand binding assays were run in triplicate in 96-well plates at room temperature as previously described.[28] Each assay contained the test compound, radiolabelled peptide (^{125}I-GVIA) and 8 μg of crude rat brain membrane, added last. All dilutions were made in assay buffer (20 mM HEPES, 75 mM NaCl, 0.2 mM EDTA, 0.2 mM EGTA, 2 μM leupeptin, 2 μL apoprotinin (to 30 mL assay buffer) and 0.1% BSA, pH 7.4). The final volume in each well was 150 μL. After shaking for 1 h, the membrane was filtered (Wallac, Finland glass fibre filters pre-soaked in 0.6% polyethyleneimine) and washed with 20 mM HEPES, 125 mM NaCl, pH 7.4 on a Tomtec harvester. After addition of scintillant, radioactivity bound to the filter was counted using a 1450 MicroBeta (Wallac, Finland). The data were analysed using GraphPad Prism 2.0 (GraphPad Software, Inc, San Diego, USA).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.07.063.

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