Design, synthesis and pharmacological evaluation of active pyrrole based, nonpeptidic analogues of neurotensin(8-13)

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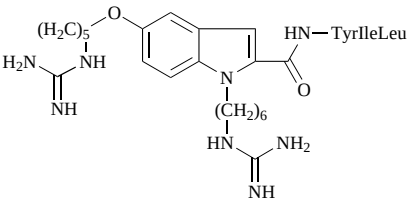
We report the design, synthesis and pharmacological analysis of pyrrole based, nonpeptidic analogues of neurotensin(8-13) for testing further our reported multiple template approach to developing nonpeptidic mimetics of neuropeptides and for developing nonpeptidic mimetics of neurotensin(8-13) as potential drug candidates for the treatments of neuropsychiatric diseases such as schizophrenia and Parkinson's disease. Three newly synthesized pyrrole analogues (mimics-4, -5 and -6) designed by the multiple template approach have been found to be more active in binding to the neurotensin receptor than the previously reported indole based mimics-1 and -2, which are a partial nonpeptidic antagonist and an agonist of neurotensin(8-13), respectively. The results support the theory of the multiple template approach and provide insights into the rational design of more potent neurotensin mimetics and into the library design for rational screening for effective nonpeptide compounds by combinatorial chemistry.

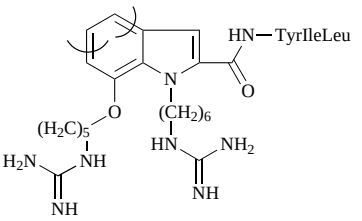
Introduction

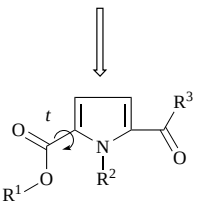
To develop nonpeptide mimetics of neurotensin(8-13), a peptide fragment of neurotensin (pGlu[1]Leu[2]Tyr[3]Glu[4]Asn[5]Lys[6]-Pro[7]Arg[8]Arg[9]Pro[10]Tyr[11]Ile[12]Leu[13]), for potential treatments of neuropsychiatric diseases such as schizophrenia and Parkinson's disease and for evaluating further the physiological and putative pathological roles of the neurotensin receptors, we proposed the multiple template approach for converting a peptide of interest into a nonpeptidic mimic.[1] The principle of this approach is to convert a vast number of conformers of a native peptide to a handful of partially flexible molecules that can individually mimic a different portion of the conformers of the peptide and altogether mimic all the conformers available to the peptide. Each of these partially flexible molecules consists of a template of different size responsible for mimicking a certain portion of the conformers of the peptide. Given the conformational flexibilities of the designed molecules and the conformational flexibility of the native peptide, one could determine how many templates are required to be tested. By testing all the partially flexible molecules, one should arrive at a molecule that covers the receptor-bound conformation of the native peptide and fits to the receptor to achieve the desired biological functions. We recently reported an inactive quinoline based nonpeptidic analogue of neurotensin(8-13) which mimics a cluster of the conformations of neurotensin(8-13) that are not compatible with the neurotensin receptor.[2] We report herein three active pyrrole based nonpeptidic analogues that mimic the receptor-compatible conformation of neurotensin(8-13).

Design

Our early effort identified serendipitously mimics-**1** and -**2** as a partial nonpeptidic antagonist and an agonist of neurotensin(8-13), respectively.[2] According to the multiple template approach, the pharmacological properties of mimic-**2** will not be significantly altered if the indole ring of mimic-**2** is replaced by a pyrrole ring. The indole ring serves, in theory, only as a molecular template to constrain the functional groups of neurotensin(8-13), which were identified by structure–activity relationship studies,[1] in the three-dimensional space for achieving effective binding by reducing entropy loss of mimic-**2** upon binding. It can therefore be substituted by the pyrrole ring which can offer similar geometric constraints for the required functional groups.







Chemical structures of mimics-**1** and -**2** and the rationale for the pyrrole template

To test further the multiple template approach and to develop nonpeptidic agonists that require less effort to synthesize, we designed mimics-**4**–**6** with the same considerations

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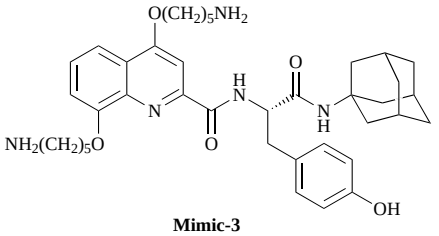
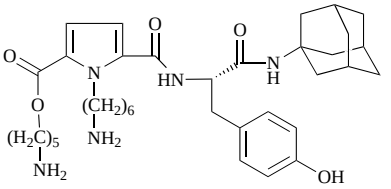
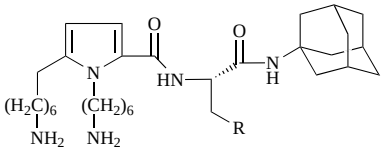


Mimic-3



Mimic-4



Mimic-5, R = 4-hydroxyphenyl
Mimic-6, R = indol-3-yl

Chemical structures of mimics-**3**–**6**

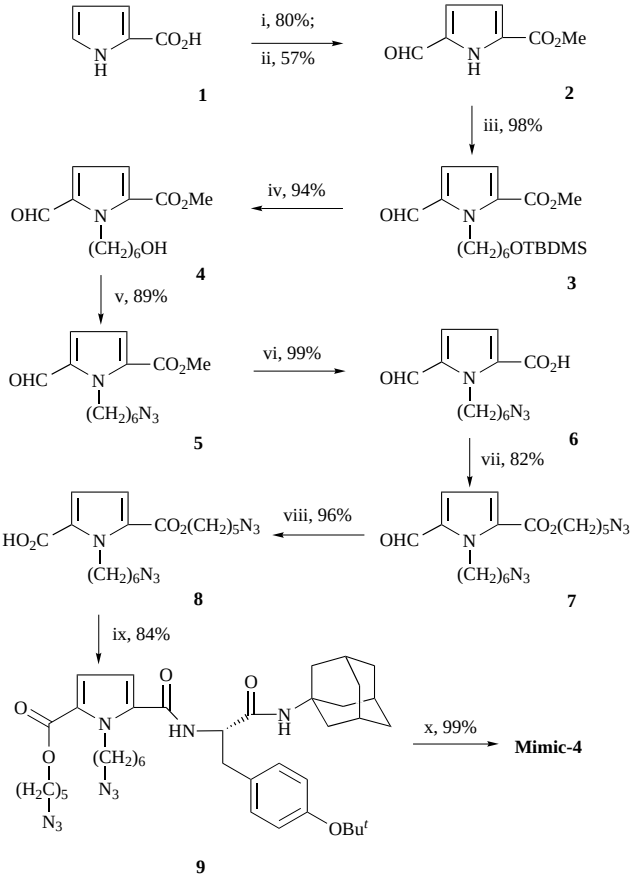
for the design of the recently reported mimic-**3**.[2] An ester group was used in mimic-**4** to constrain the torsion *t* of the alkylamino chain (N–C–C–O) at 0 or 180 degrees of arc so that mimic-**4** can better resemble mimic-**2** in terms of conformational flexibility. However, based on *ab initio* calculations at RHF/6-31G*//RHF/6-31G*, we found that the relative potential energy difference between the conformation with *t* being 0 degrees of arc and the conformation with *t* being 180 degrees of arc is 1.3 kcal mol^{-1}. This suggests that about 10% of mimic-**4** adopts the desired conformation with *t* being 0 degrees of arc. Therefore, according to our conformational selection mechanism,[3] mimic-**4** has to undergo conformational conversion (pre-organization) before binding to the neurotensin receptor. This suggests that the ester substituted pyrrole template could not constrain the functional groups as effectively as the indole template, but could achieve measurable binding of mimic-**4** to the neurotensin receptor. It is thus worthwhile to study experimentally mimic-**4** for validating the theoretical predictions.

The ester group was thus replaced by an ethylene group in mimics-**5** and -**6** to avoid the complication of the conformational conversion (pre-organization) and to investigate a new template derivatized from the indole template. This template is equivalent in size to the indole and the ester-substituted pyrrole templates, but can construct more flexible mimics than the others.

To develop agonists of neurotensin(8-13), it is necessary to design new analogues interacting at the agonist binding site. Insertion of a tryptophan residue rather than a tyrosine residue into mimic-**6** was to probe the interaction site of the pyrrole analogues on the neurotensin receptor. If the pyrrole analogues interact with the neurotensin(8-13) binding site, the pyrrole analogues should demonstrate a structure–activity relationship parallel to what was observed from neurotensin(8-13) for the tyrosine substitution.[4] Otherwise, the pyrrole template is not worth investigating.

Synthesis

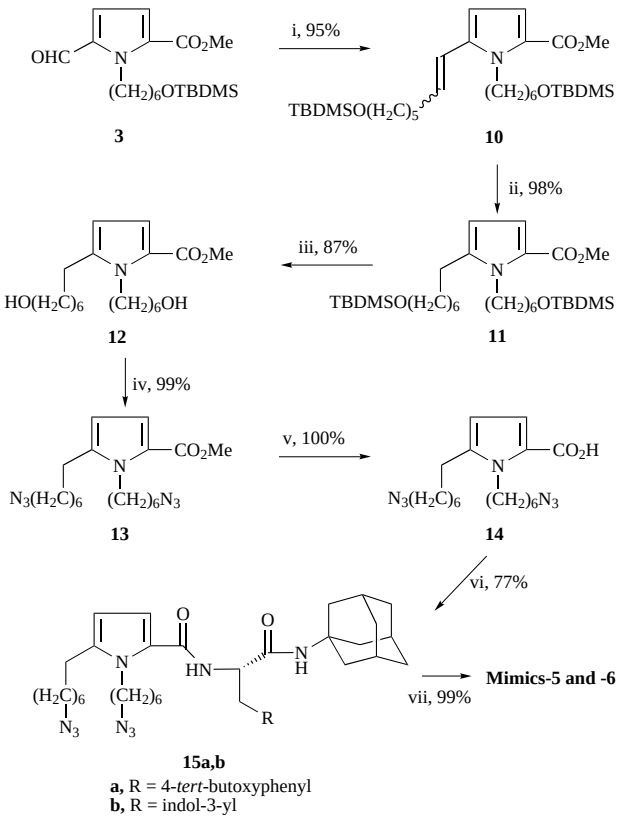
Mimic-**4** was prepared according to Scheme 1. Pyrrole-2-carboxylic acid **1** was esterified by saturated HCl gas in MeOH[5]



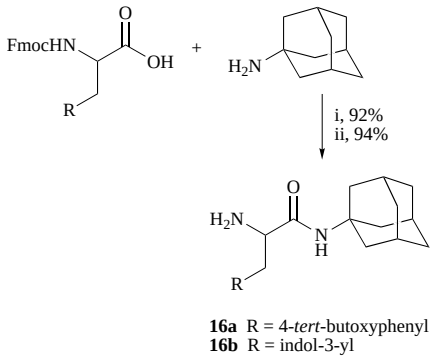
Scheme 1 Synthesis of mimic-**4**. *Reagents and conditions*: i, MeOH, HCl (gas), room temp.; ii, DMF, $POCl_3$, $ClCH_2CH_2Cl$, 50 °C; iii, $TBDMSO(CH_2)_6I$, K_2CO_3, 18-crown-6, CH_3CN, 70 °C; iv, TBAF, THF, room temp.; v, HN_3, PPh_3, DEAD, CH_2Cl_2, 0 °C; vi, 2 M KOH, MeOH, reflux; vii, $N_3(CH_2)_5OH$, DCC, DMAP, room temp.; viii, 1 M $KMnO_4$, 5% KH_2PO_4, Bu^{t}OH, room temp.; ix, O-Bu^t-Tyr-NH-Ada **16a**, DCC, HOBT, DMF, room temp.; x, H_2, 10% Pd–C, conc. HCl, MeOH, EtOAc, room temp.

followed by formylation according to a literature procedure[6] using $POCl_3$ in DMF to yield methyl 5-formylpyrrole-2-carboxylate **2** along with a small amount of methyl 4-formylpyrrole-2-carboxylate which was separated by column chromatography. *N*-Alkylation of pyrrole **2** by 1-(*tert*-butyldimethylsilyloxy)-6-iodohexane[7] gave *N*-alkylated **3**, which can be further derivatized to mimics-**5** and -**6** (*vide infra*). Deprotection of TBDMS masked intermediate **3** by TBAF at room temperature gave alcohol **4**, which was then converted to azide **5** by a Mitsunobu reaction. Hydrolysis of the first transformed ester group of intermediate **5** followed by esterification of the subsequent acid **6** with 5-azidopentan-1-ol in the presence of DCC and DMAP resulted in diazide **7**. At this stage, the previously introduced formyl group of intermediate **7** was oxidized to an acid group of intermediate **8**. Coupling of intermediate **8** to our reported intermediate of O-Bu^t-Tyr-NH-Ada[2] in the presence of DCC and hydroxybenzotriazole (HOBT) in DMF afforded the precursor of mimic-**4** (**9**). Mimic-**4** was then efficiently prepared from precursor **9** by catalytic hydrogenation in the presence of concentrated hydrochloric acid to reduce the azide group to an amino group and unmask the phenol group.

Mimics-**5** and -**6** were synthesized from the above intermediate **3** according to Scheme 2. Wittig reaction of intermediate **3** with [6-(*tert*-butyldimethylsilyloxy)hexylidene]triphenylphosphorane gave a mixture of *Z* and *E* olefins **10**, which were saturated by catalytic hydrogenation to yield intermediate **11**. Intermediate **11** was then transformed to mimic-**5** or -**6** using O-Bu^t-Tyr(or Trp)-NH-Ada (**16a** or **16b**) by the same methods used to synthesize mimic-**4**.[2] Compound **16b** was made by a similar procedure used to prepare previously reported inter-



Scheme 2 Synthesis of mimics-**5** and **-6**. *Reagents and conditions*: i, $TBDMSO(CH_2)_5CH{=}PPh_3$, THF, room temp.; ii, H_2, 10% Pd–C, MeOH, EtOAc, room temp.; iii, TBAF, THF, room temp.; iv, HN_3, PPh_3, DEAD, CH_2Cl_2, 0 °C; v, 2 M KOH, EtOH, reflux; vi, O-Bu^t-Tyr(Trp)-NH-Ada **16a** or **16b**, DCC, HOBT, DMF, room temp.; vii, H_2, 10% Pd–C, conc. HCl, MeOH, EtOAc, room temp.



Scheme 3 *Reagents and conditions*: i, DCC, HOBT, DMF, room temp., 12 h; ii, 5% piperidine in THF, room temp., 30 min

mediate **16a** (Scheme 3).[2] All final compounds were purified by reversed-phase HPLC by our reported protocol[2] and were fully characterized by IR, ^{1}H, ^{13}C-NMR, MS and HRMS.

Pharmacology

Mimics-**4**–**6** in their bis(trifluoroacetate) salt form were tested for their ability to compete for [^{3}H]neurotensin binding at the human neurotensin receptor that had been stably transfected in CHO-KI cells. Cell culture and radioligand binding assays were performed using previously described methods.[8–10] The equilibrium dissociation constants (K_d) of neurotensin(8-13) and mimics-**2**, **-4**–**6** are listed in Table 1. We present values previously derived at the mouse neurotensin receptor in intact N1E-115 cells for comparison. Neurotensin(8-13) was the most potent at both the human and mouse neurotensin receptors. The rank order of potency for neurotensin(8-13) and mimic-**2** stayed the same in both cell lines. Mimic-**4** was as potent as mimic-**2** in binding. Mimics-**5** and **-6** showed about a fivefold increase in binding over mimic-**2**. Additionally, mimic-**6** exhibited a slight increase in binding over mimic-**5**.

Discussion

The fact that mimic-**4** was as potent in binding as mimic-**2** suggests that the ester substituted pyrrole template can indeed constrain the functional groups of neurotensin(8-13) in a similar way to that done by the indole template. More active mimics-**5** and **-6** suggests that the methylene substituted pyrrole template can also constrain the functional groups in a similar fashion. However, the ester substituted pyrrole template is not as effective as the methylene substituted pyrrole template because of the conformational conversion (the torsion *t* changes from 0 to 180 degrees of arc) of the ester substituted pyrrole template as described above. This conclusion is evident from the results that mimics-**5** and **-6** were more potent in binding than mimic-**4**, for the three mimics bear the same functional groups. The results revealed importantly that the indole ring in mimic-**2**, which was identified by serendipity,[2] indeed functions only as a template to constrain the functional groups of neurotensin in binding, and *can be replaced by other rationally designed templates*. The results further validate the theory of the multiple template approach that some templates can cover the receptor compatible conformation as exemplified by the indole and pyrrole templates in the present report while others cannot as exemplified by our previous report for the inactive quinoline based mimic-**3**,[2] and that one should be able to identify a partially flexible molecule adopting the receptor-bound conformation of the native peptide by testing a relatively small number of templates that altogether mimic all the conformations of the peptide.

As expected, mimic-**6** demonstrated a slight increase in binding over mimic-**5** when the tyrosine residue in mimic-**6** was replaced by a tryptophan residue. This structure–activity relationship is parallel to the one observed from both neurotensin and neurotensin(8-13).[4] The result implies that mimics-**5** and **-6** bind to the same site as neurotensin(8-13).

Our work on nonpeptidic mimetics of neurotensin(8-13) to date suggests the pharmacophores required for binding of the neurotensin receptor. In general, the two alkylamino groups, the phenol or indole-like aromatic ring, and the adamantyl-like hydrophobic core grafted in mimics-**5** and **-6** are required for developing effective nonpeptidic ligands of the neurotensin receptor and for library design for screening effective analogues by combinatorial chemistry. Further studies on the details of how to constrain precisely these pharmacophores in the three-dimensional space, which is pivotal to developing effective nonpeptidic ligands of the neurotensin receptor, are underway and will be reported in due course.

Experimental

Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. DMSO was dried with CaH_2. Methylene chloride was distilled from P_2O_5 prior to use. Solvents used for chromatography were purchased in 5 gal drums, redistilled from an all-glass apparatus, and stored in glass bottles. Silica gel 60 (Merck, 230–400 mesh ASTM for flash chromatography) was used for column chromatography. TLC was performed on Merck silica gel 60F-254 (0.25 mm, precoated on glass). Other reagents were used as supplied by the Aldrich Chemical Co. and Lancaster Synthesis Inc. NMR spectra were taken on a Bruker AC-300 instrument (300 MHz for ^{1}H and 75.46 MHz for ^{13}C). Chemical shifts are reported in δ (ppm) with reference to Me_4Si ($\delta = 0.00$ ppm) for ^{1}H spectra or $CDCl_3$ ($\delta = 77.00$ ppm) for ^{13}C spectra as internal standards. *J* Values are recorded in Hz. Ar, φ, φ′ and Fn denote pyrrole,

Table 1 Comparison of binding affinities for neurotensin, neurotensin(8-13) and mimics-**4**–**6** at human and mouse neurotensin receptors

Compound	K_d/nM	
	Human neurotensin receptor in CHO-K1 membranes	Mouse neurotensin receptor in N1E-115 intact cells
Neurotensin(8-13)	0.14 ± 0.01 (4)	0.61 ± 0.02 (3)[11]
Mimic-**2**	14 000 ± 1 000 (4)	2 600 ± 300 (6)
Mimic-**4**	13 000 ± 2 000 (5)	nd
Mimic-**5**	3 400 ± 200 (5)	nd
Mimic-**6**	2 700 ± 200 (5)	nd

K_d = apparent equilibrium dissociation constant. Values are geometric mean ± SE; each value is the mean of duplicate determinations made in independent experiments; value in parentheses indicates *n* value; nd = no data.

phenyl, indolyl and fluorene rings, respectively. Mass spectra were obtained on a FINNIGAN MAT-900 instrument. High resolution mass data were collected by employing ESI with a reference material of PEG 400. Melting points were determined in open capillary tubes on a Gallenkamp capillary melting point apparatus.

Methyl 5-formylpyrrole-2-carboxylate 2[6]

A mixture of pyrrole-2-carboxylic acid (3.0 g, 24 mmol) in 150 ml of methanol was saturated with HCl gas and kept for two days at room temp. A brown solid residue obtained by evaporation of the solvent was then dissolved in ethyl acetate, washed with saturated aqueous $NaHCO_3$ and with brine, and dried over $MgSO_4$. Evaporation of ethyl acetate gave essentially pure methyl pyrrole-2-carboxylate (2.76 g, 80%) as a yellowish powder, mp 72.1–73.0 °C (lit.,[12] 71.5–73 °C). To methyl pyrrole-2-carboxylate (2.0 g, 16 mmol) in 1,2-dichloroethane (15 ml) were sequentially added DMF (1.9 ml, 24.6 mmol) and $POCl_3$ (2.2 ml, 24.6 mmol) *via* a syringe at 5 °C with stirring. The solution was poured into saturated aqueous $NaHCO_3$ after stirring at 50 °C for 1 h. The ethyl acetate extract was washed with water and with brine, dried ($MgSO_4$) and concentrated. Chromatography on silica gel column, eluting with ethyl acetate–hexanes (20 : 80) (R_f = 0.24), gave intermediate **2** (2.0 g, 82%) as a yellowish powder; mp 98.1–98.6 °C (lit.,[6] 92–93 °C); δ_H(300 MHz; $CDCl_3$) 3.93 (3 H, s, OCH_3), 6.94 (2 H, s, ArH), 9.67 (1 H, s, CHO) and 9.95 (1 H, s, NH); δ_H(300 MHz; [$^2H_6$]DMSO) 3.83 (3 H, s, OCH_3), 6.89 (1 H, d, *J* 3.9, 3-ArH), 6.97 (1 H, d, *J* 3.9, 4-ArH) and 9.70 (1 H, s, NH); δ_C(75.46 MHz; $CDCl_3$) 52.2, 115.6, 119.6, 128.2, 134.6, 160.9 and 180.5.

Methyl 5-formyl-1-[6-(*tert*-butyldimethylsilyloxy)hexyl]-pyrrole-2-carboxylate 3

A solution of **2** (1.4 g, 11.2 mmol), 6-(*tert*-butyldimethylsilyloxy)hexyl iodide (5.0 g, 14.6 mmol), K_2CO_3 (5 g, 36.4 mmol) and a catalytic amount of 18-crown-6 in anhydrous acetonitrile (50 ml) was stirred at 70 °C for 10 h under N_2. After cooling to room temp., it was poured into H_2O, and extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$) and concentrated. Chromatography on silica gel column, eluting with ethyl acetate–hexanes (1 : 19, R_f = 0.40), gave **3** (3.75 g, 98%) as a light yellow oil; ν_{max}(neat)/cm^{-1} 1725, 1680 and 1248; δ_H(300 MHz; $CDCl_3$) 0.01 (6 H, s, $SiCH_3$), 0.86 [9 H, s, $C(CH_3)_3$], 1.35–1.45 (4 H, m, 3-H_2 + 4-H_2), 1.45–1.55 (2 H, m, 5-H_2), 1.67–1.80 (2 H, m, 2-H_2), 3.56 (2 H, t, *J* 6.6, 6-H_2), 3.84 (3 H, s, OCH_3), 4.75 (2 H, t, *J* 7.7, NCH_2), 6.84 (1 H, d, *J* 4.3, 3-ArH), 6.90 (1 H, d, *J* 4.2, 4-ArH) and 9.68 (1 H, s, CHO); δ_C(75.46 MHz; $CDCl_3$) 6.8, 18.3, 25.3, 25.9, 26.3, 31.6, 32.6, 46.6, 51.7, 63.1, 116.9, 122.0, 128.9, 134.8, 160.9 and 180.8; *m*/*z* (ESI) 368 $[M + H]^+$, 352 $[M - 15]^+$ {Found (HRMS): *m*/*z* 368.2259. Calc. $[M + H]^+$ for $C_{19}H_{34}NO_4Si$: 368.2257}.

Methyl 5-formyl-1-(6-hydroxyhexyl)pyrrole-2-carboxylate 4

To a solution of **3** (2.1 g, 4.2 mmol) in 5 ml of THF was added TBAF (1 M in THF, 8.4 mmol) under N_2 at room temp. with stirring. The reaction mixture was poured into saturated aqueous NH_4Cl after stirring for 2 h. The ethyl acetate extract was washed with water and with brine, dried ($MgSO_4$) and concentrated. Chromatography on silica gel column, eluting with ethyl acetate–hexanes (3 : 2, R_f = 0.45), gave **4** (1.0 g, 94%) as a colorless oil; ν_{max}(neat)/cm^{-1} 3430, 1725, 1674 and 1231; δ_H(300 MHz; $CDCl_3$) 1.35–1.48 (4 H, m, 3-H_2 + 4-H_2), 1.51–1.65 (2 H, m, 5-H_2), 1.68–1.85 (2 H, m, 2-H_2), 1.90 (1 H, s, OH), 3.63 (2 H, t, *J* 6.5, 6-H_2), 3.87 (3 H, s, OCH_3), 4.78 (2 H, t, *J* 7.7, NCH_2), 6.88 (1 H, d, *J* 4.3, 3-ArH), 6.93 (1 H, d, *J* 4.2, 4-ArH) and 9.70 (1 H, s, CHO); δ_C(75.46 MHz; $CDCl_3$) 25.1, 26.2, 31.4, 32.5, 46.5, 51.8, 62.6, 117.0, 122.2, 134.9, 161.0 and 180.9; *m*/*z* (ESI) 254 $[M + H]^+$ {Found (HRMS): *m*/*z* 254.1392. Calc. $[M + H]^+$ for $C_{13}H_{20}NO_4$: 254.1392}.

Methyl 5-formyl-1-(6-azidohexyl)pyrrole-2-carboxylate 5

To a solution of **4** (1.0 g, 3.95 mmol) and PPh_3 (1.25 g, 4.77 mmol) in CH_2Cl_2 (15 ml) were added sequentially HN_3 (1.2 M in CH_2Cl_2, 10 mmol) and DEAD (0.9 ml, 5.5 mmol) at 0 °C under N_2 with stirring. The reaction was quenched with water after 1 h stirring at 0 °C. The CH_2Cl_2 extract was washed with brine, dried ($MgSO_4$) and concentrated. Chromatography on silica gel, eluting with ethyl acetate–hexanes (1 : 19, R_f = 0.32), afforded **5** (0.98 g, 89%) as a light yellow oil; ν_{max}(neat)/cm^{-1} 2097, 1725, 1674 and 1231; δ_H(300 MHz; $CDCl_3$) 1.35–1.48 (4 H, m, 3-H_2 + 4-H_2), 1.55–1.68 (2 H, m, 5-H_2), 1.70–1.83 (2 H, m, 2-H_2), 3.25 (2 H, t, *J* 6.9, 6-H_2), 3.87 (3 H, s, OCH_3), 4.78 (2 H, t, *J* 7.7, NCH_2), 6.87 (1 H, d, *J* 4.2, 3-ArH), 6.93 (1 H, d, *J* 4.4, 4-ArH) and 9.70 (1 H, s, CHO); δ_C(75.46 MHz; $CDCl_3$) 26.0, 26.2, 28.6, 31.3, 46.5, 51.3, 51.8, 117.0, 122.2, 129.0, 134.9, 161.0 and 180.9; *m*/*z* (ESI) 279 $[M + H]^+$ {Found (HRMS): *m*/*z* 279.1462. Calc. $[M + H]^+$ for $C_{13}H_{19}N_4O_3$: 279.1457}.

5-Formyl-1-(6-azidohexyl)pyrrole-2-carboxylic acid 6

A solution of compound **5** (0.39 g, 1.4 mmol) in MeOH (6 ml), THF (4 ml) and KOH (2 M, 5 ml) was refluxed for 3 h. After cooling to room temp., the reaction mixture was acidified to pH 3 with 20% aqueous HCl. The ethyl acetate extract was washed with water and with brine, dried (Na_2SO_4) and concentrated to give pure **6** [R_f = 0.26 in ethyl acetate–hexanes (1 : 1)] (0.37 g, 99%) as a yellow oil; ν_{max}(neat)/cm^{-1} 3131, 2097, 1715, 1669 and 1250; δ_H(300 MHz; $CDCl_3$) 1.36–1.52 (4 H, m, 3-H_2 + 4-H_2), 1.56–1.72 (2 H, m, 5-H_2), 1.73–1.85 (2 H, m, 2-H_2), 3.26 (2 H, t, *J* 6.9, 6-H_2), 4.80 (2 H, t, *J* 7.6, NCH_2), 6.93 (1 H, d, *J* 4.2, 3-ArH), 7.10 (1 H, d, *J* 4.4, 4-ArH) and 9.74 (1 H, s, CHO); δ_C(75.46 MHz; $CDCl_3$) 26.0, 26.2, 28.7, 31.3, 46.7, 51.4, 119.0, 122.3, 128.2, 135.7, 165.5 and 181.3; *m*/*z* (ESI) 287 $[M + Na]^+$ {Found (HRMS): *m*/*z* 287.1130. Calc. $[M + Na]^+$ for $C_{12}H_{16}N_4O_3Na$: 287.1120}.

5-Azidopentyl 5-formyl-1-(6-azidohexyl)pyrrole-2-carboxylate 7

To a solution of **6** (180 mg, 0.68 mmol), DCC (168 mg, 0.82 mmol) and DMAP (100 mg, 0.82 mmol) in CH_2Cl_2 (10 ml) was added 5-azidopentan-1-ol (100 mg, 0.75 mmol) at room temp.

under N_2 with stirring. The solution was concentrated after 1 h stirring at room temp. Chromatography on a silica gel column, eluting with ethyl acetate–hexanes (1:4, $R_f = 0.60$), afforded **7** (210 mg, 82%) as a colorless oil; ν_{max}(neat)/cm^{-1} 2097, 1723, 1676 and 1227; δ_H(300 MHz; $CDCl_3$) 1.35–1.50 (4 H, m, 3-H_2 + 4-H_2), 1.50–1.88 (10 H, m, 5 CH_2), 3.26 (2 H, t, *J* 6.9, 6-H_2), 3.31 (2 H, t, *J* 6.7, 5′-H_2), 4.29 (2 H, t, *J* 6.5, OCH_2), 4.78 (2 H, t, *J* 7.7, NCH_2), 6.89 (1 H, d, *J* 4.1, 3-ArH), 6.94 (1 H, d, *J* 4.3, 4-ArH) and 9.71 (1 H, s, CHO); δ_C(75.46 MHz; $CDCl_3$) 23.3, 26.0, 26.2, 28.2, 28.5, 28.6, 31.3, 46.5, 51.2, 51.3, 64.5, 117.0, 122.2, 129.2, 134.9, 160.6 and 180.9; *m*/*z* (ESI) 376 $[M + H]^+$ {Found (HRMS): *m*/*z* 376.2086. Calc. $[M + H]^+$ for $C_{17}H_{26}N_7O_3$: 376.2097}.

5-(5-Azidopentyloxycarbonyl)-1-(6-azidohexyl)pyrrole-2-carboxylic acid 8

To a solution of **7** (210 mg, 0.56 mmol), Bu^{t}OH (5 ml) and 5% aqueous KH_2PO_4 (2 ml) was added $KMnO_4$ (0.7 M, 3 ml) at room temp. with stirring. After 30 min stirring at room temp., the reaction mixture was washed with cooled saturated aqueous Na_2SO_3 and acidified to pH 4 with 20% aqueous HCl. The ethyl acetate extract was washed with water and with brine, dried ($MgSO_4$) and filtered through a very short silica gel column to remove the inorganic salts. Concentration of the eluate gave **8** (210 mg, 96%) [$R_f = 0.30$ in ethyl acetate–hexanes (1:1)] as a colorless oil without further purification; ν_{max}(neat)/cm^{-1} 3137, 2097, 1725, 1678 and 1252; δ_H(300 MHz; $CDCl_3$) 1.30–1.86 (14 H, m, 7 CH_2), 3.22–3.34 (4 H, m, CH_2N_3), 4.26 (2 H, t, *J* 6.5, OCH_2), 4.80 (2 H, t, *J* 7.7, NCH_2), 6.90 (1 H, d, *J* 4.2, 3-ArH), 7.04 (1 H, d, *J* 4.3, 4-ArH) and 11.50 (1 H, s, CO_2H); δ_C(75.46 MHz; $CDCl_3$) 23.2, 26.0, 26.1, 28.1, 28.4, 28.6, 31.3, 46.4, 51.1, 51.2, 64.2, 116.5, 118.4, 126.1, 128.3, 160.4 and 165.4.

***N*-[(2*S*)-1-Adamantylamino-3-(4-*tert*-butoxyphenyl)-1-oxopropan-2-yl]-1-(6-azidohexyl)-5-(5-azidopentyloxycarbonyl)pyrrole-2-carboxamide 9**

A solution of **8** (147 mg, 0.37 mmol), *N*-adamantyl-2-amino-3-(4-*tert*-butoxyphenyl)propanamide (O-Bu^t-Tyr-NH-Ada) **16a** (183 mg, 0.45 mmol), DCC (93 mg, 0.45 mmol) and hydroxybenzotriazole (HOBT) (61 mg, 0.45 mmol) in DMF (10 ml) was stirred at 40 °C under N_2 for 12 h. The reaction was then quenched with saturated aqueous NH_4Cl. The ethyl acetate extract was washed with water and with brine, dried ($MgSO_4$) and concentrated. Chromatography on silica gel column, eluting with ethyl acetate–hexanes (1:4, $R_f = 0.42$), afforded **9** (242 mg, 84%) as a white solid; mp 94.4–94.8 °C; ν_{max}(neat)/cm^{-1} 3295, 2095, 1713, 1630 and 1235; δ_H(300 MHz; $CDCl_3$) 1.32–1.48 (13 H, m, 2 CH_2 + 3 CH_3), 1.48–1.90 [22 H, m, 6 CH_2(Ada) + 5 CH_2], 2.02 [3 H, s, CH(Ada)], 2.88 (1 H, dd, *J* 9.5, 13.4, φCH), 3.15–3.35 (5 H, m, 2 CH_2N_3 + φCH), 4.25 (2 H, t, *J* 6.5, OCH_2), 4.46–4.55 (1 H, m, COCH), 4.68–4.81 (2 H, m, NCH_2), 4.98 (1 H, s, CONHAda), 6.45 (1 H, d, *J* 4.2, 3-ArH), 6.79 (1 H, d, *J* 7.4, ArCONH), 6.86 (1 H, d, *J* 4.2, 4-ArH), 6.96 (2 H, d, *J* 8.3, φH) and 7.19 (2 H, d, *J* 8.3, φH); δ_C(75.46 MHz; $CDCl_3$) 23.2, 26.1, 26.2, 28.2, 28.4, 28.59, 28.64, 29.2, 31.5, 36.1, 38.3, 41.2, 46.1, 51.1, 51.2, 52.0, 55.1, 63.8, 78.2, 111.2, 116.5, 124.2, 125.7, 129.8, 130.8, 131.6, 154.2, 160.4, 160.7 and 169.3; *m*/*z* (ESI) 744 $[M + H]^+$ {Found (HRMS): *m*/*z* 744.4591. Calc. $[M + H]^+$ for $C_{40}H_{58}N_9O_5$: 744.4560}.

***N*-[(2*S*)-1-Adamantylamino-3-(4-hydroxyphenyl)-1-oxopropan-2-yl]-1-(6-aminohexyl)-5-(5-aminopentyloxycarbonyl)pyrrole-2-carboxamide bis(trifluoroacetate) salt (mimic-4)**

A solution of compound **9** (140 mg, 0.18 mmol), conc. HCl (0.1 ml) and 10% Pd–C (20 mg) in MeOH (4 ml) and EtOAc (8 ml) was stirred under H_2 atmosphere at room temp. for 12 h. The Pd–C was removed by filtration through Celite. Concentration of the filtrate and the MeOH used to wash the Celite gave a light yellow residue. The residue was dissolved in 0.1% TFA (1 ml) and CH_3CN (0.5 ml) and purified by reversed-phase HPLC on a Vydak C_8 (15–20 μm particle size, 250 mm length × 22 mm id) column using gradient elution. Starting with 90% buffer A (0.1% TFA in H_2O) and then linearly increasing the concentration of buffer B (prepared from 20% buffer A in CH_3CN) from 10% to 90% over 30 min at a flow rate of 8 cm^3 min^{-1} with the detector wavelength set at 220 nm gave mimic-**4** as its bis(trifluoroacetate) salt (>95% pure). The retention time (t_r) of mimic-**4** was 25.94 min. After lyophilization, a white powder was isolated; mp 105.2–107.1 °C (structural characterizations were performed with the HPLC-purified product); ν_{max}(KBr)/cm^{-1} 3295, 1678, 1632 and 1204; δ_H(300 MHz; [$^2H_6$]DMSO) 1.11–1.32 (4 H, m, CH_2), 1.36–1.75 [16 H, m, 3 CH_2(Ada) + 5 CH_2], 1.92 [6 H, s, 3 CH_2(Ada)], 2.01 [3 H, s, CH(Ada)], 2.71–2.95 (6 H, m, 2 CH_2N^+ + φCH_2), 4.17 (2 H, t, *J* 6.2, OCH_2), 4.45–4.64 (3 H, m, NCH_2 + COCH), 6.63 (2 H, d, *J* 8.4, φH), 6.66 (1 H, d, *J* 4.2, 3-ArH), 6.85 (1 H, d, *J* 4.2, 4-ArH), 7.10 (2 H, d, *J* 8.4, φH), 7.43 (1 H, s, CONHAda), 7.50–7.99 (6 H, m, NH_3^+) and 8.27 (1 H, d, *J* 8.5, ArCONH); δ_C(75.46 MHz; [$^2H_6$]DMSO) 22.4, 25.4, 25.6, 26.6, 26.9, 27.6, 28.8, 31.2, 36.0, 36.7, 40.9, 45.3, 50.8, 55.0, 63.5, 111.7, 114.7, 116.2, 124.4, 128.1, 130.1, 131.7, 155.7, 160.1, 160.4 and 170.3; *m*/*z* (ESI) 636 $[M + H]^+$ {Found (HRMS): *m*/*z* 636.4105. Calc. $[M + H]^+$ for $C_{36}H_{54}N_5O_5$: 636.4124}.

Methyl 1-[6-(*tert*-butyldimethylsilyloxy)hexyl]-5-[(*E*/*Z*)-7-(*tert*-butyldimethylsilyloxy)hept-1-enyl]pyrrole-2-carboxylate 10

To a solution of [6-(*tert*-butyldimethylsilyloxy)hexyl]triphenylphosphonium iodide (1.97 g, 3.26 mmol) in THF (5 ml) was added dropwise Bu^{n}Li (2.5 M, 3.26 mmol) at −10 °C under N_2 with stirring. After 30 min stirring at the same temperature, a solution of **3** (900 mg, 2.45 mmol) in 5 ml of THF was added to the mixture at 0 °C with stirring. The reaction was quenched with saturated aqueous $NaHCO_3$ after 1 h stirring at room temp. The ethyl acetate extract was washed with brine, dried ($MgSO_4$) and condensed. Chromatography on silica gel, eluting with ethyl acetate–hexanes (1:19, $R_f = 0.53$ and 0.55), afforded **10** (1.36 g, 95%) as a colorless oil; ν_{max}(neat)/cm^{-1} 3032, 1707 and 1252; δ_H(300 MHz; $CDCl_3$) 0.04–0.10 (12 H, m, $SiCH_3$), 0.9 [18 H, s, $C(CH_3)_3$], 1.30–1.58 (12 H, m, CH_2), 1.60–1.73 (2 H, m, CH_2), 2.18–2.40 (2 H, m, CH_2), 3.55–3.62 (4 H, m, OCH_2), 3.76–3.83 (3 H, m, OCH_3), 4.28–4.35 (2 H, m, NCH_2) and 5.25–7.0 (4 H, m, ArH + Alkenyl-H); δ_C(75.46 MHz; $CDCl_3$) 6.4, 18.3, 25.4, 25.5, 25.6, 25.9, 26.5, 29.0, 29.2, 29.3, 31.3, 31.5, 32.66, 32.7, 33.3, 44.8, 45.0, 50.8, 50.9, 63.1, 105.5, 109.4, 117.2, 117.6, 118.1, 118.2, 121.06, 121.1, 134.2, 135.5, 136.3, 138.6 and 161.5; *m*/*z* (ESI) 566 $[M + H]^+$ {Found (HRMS): *m*/*z* 566.4042. Calc. $[M + H]^+$ for $C_{31}H_{60}NO_4Si_2$: 566.4060}.

Methyl 1-[6-(*tert*-butyldimethylsilyloxy)hexyl]-5-[7-(*tert*-butyldimethylsilyloxy)heptyl]pyrrole-2-carboxylate 11

A mixture of **10** (1.36 g, 2.0 mmol) and 10% Pd–C (50 mg) in MeOH (5 ml) and EtOAc (10 ml) was stirred under H_2 atmosphere for 12 h. The mixture was filtered through Celite. Concentration of the filtrate and the MeOH used to wash the Celite gave pure **11** [$R_f = 0.53$ in ethyl acetate–hexanes (1:19)] (1.32 g, 98%) as a light yellow oil; ν_{max}(neat)/cm^{-1} 1705 and 1252; δ_H(300 MHz; $CDCl_3$) 0.02–0.06 (12 H, m, $SiCH_3$), 0.85–0.92 [18 H, m, $C(CH_3)_3$], 1.28–1.45 (10 H, m, CH_2), 1.45–1.58 (4 H, m, CH_2), 1.60–1.72 (4 H, m, CH_2), 2.54 (2 H, t, *J* 7.7, $ArCH_2$), 3.50–3.61 (4 H, m, OCH_2), 3.78 (3 H, s, OCH_3), 4.22 (2 H, t, *J* 7.7, NCH_2), 5.91 (1 H, d, *J* 3.8, 4-ArH) and 6.91 (1 H, d, *J* 4.0, 3-ArH); δ_C(75.46 MHz; $CDCl_3$) 6.9, 18.3, 25.6, 25.7, 26.0, 26.4, 26.7, 28.5, 29.2, 29.4, 31.5, 32.8, 44.9, 50.7, 63.1, 63.2, 106.5, 117.7, 120.6, 141.0 and 161.4; *m*/*z* (ESI) 568 $[M + H]^+$ {Found (HRMS): *m*/*z* 568.4208. Calc. $[M + H]^+$ for $C_{31}H_{62}NO_4Si_2$: 568.4217}.

Methyl 1-(6-hydroxyhexyl)-5-(7-hydroxyheptyl)pyrrole-2-carboxylate 12

A similar procedure to that used to prepare **4** was followed to afford **12** (87%) as a yellowish oil [$R_f = 0.30$ in ethyl acetate–hexanes (2:1)]; ν_{max}(neat)/cm^{-1} 3391, 1701 and 1246; δ_H(300 MHz; $CDCl_3$) 1.35–1.70 (20 H, m, 9 CH_2 + 2 OH), 2.54 (2 H, t, *J* 7.9, $ArCH_2$), 3.55–3.65 (4 H, m, OCH_2), 3.77 (3 H, s, OCH_3), 4.22 (2 H, t, *J* 7.8, NCH_2), 5.90 (1 H, d, *J* 4.0, 4-ArH) and 6.90 (1 H, d, *J* 3.9, 3-ArH); δ_C(75.46 MHz; $CDCl_3$) 25.2, 25.5, 26.2, 26.4, 28.3, 29.0, 29.2, 31.2, 32.4, 32.5, 44.7, 50.7, 62.4, 62.5, 106.5, 117.7, 120.4, 141.0 and 161.4; *m*/*z* (ESI) 340 $[M + H]^+$ {Found (HRMS): *m*/*z* 340.2477. Calc. $[M + H]^+$ for $C_{19}H_{34}NO_4$: 340.2487}.

Methyl 1-(6-azidohexyl)-5-(7-azidoheptyl)pyrrole-2-carboxylate 13

A similar procedure to that used to prepare **5** was followed to afford **13** (99%) as a yellowish oil [$R_f = 0.30$, ethyl acetate–hexanes (1:19)]; ν_{max}(neat)/cm^{-1} 2095, 1701 and 1244; δ_H(300 MHz; $CDCl_3$) 1.15–1.30 (10 H, m, CH_2), 1.38–1.58 (8 H, m, CH_2), 2.39 (2 H, t, *J* 7.8, $ArCH_2$), 3.05–3.15 (4 H, m, CH_2N_3), 3.62 (3 H, s, OCH_3), 4.07 (2 H, t, *J* 7.8, NCH_2), 5.75 (1 H, d, *J* 4.0, 4-ArH) and 6.75 (1 H, d, *J* 3.9, 3-ArH); δ_C(75.46 MHz; $CDCl_3$) 26.3, 26.5, 28.3, 28.7, 28.9, 29.2, 31.1, 44.7, 50.7, 51.2, 51.3, 106.5, 117.6, 120.6, 140.8 and 161.4; *m*/*z* (ESI) 390 $[M + H]^+$ {Found (HRMS): *m*/*z* 390.2616. Calc. $[M + H]^+$ for $C_{19}H_{32}N_7O_2$: 390.2617}.

1-(6-Azidohexyl)-5-(7-azidoheptyl)pyrrole-2-carboxylic acid 14

A similar procedure to that used to prepare **6** was followed to afford **14** (100%) as a yellowish oil [$R_f = 0.25$ in ethyl acetate–hexanes (1:4)]; ν_{max}(neat)/cm^{-1} 2095, 1659 and 1260; δ_H(300 MHz; $CDCl_3$) 1.35–1.50 (10 H, m, CH_2), 1.55–1.75 (8 H, m, CH_2), 2.57 (2 H, t, *J* 7.8, $ArCH_2$), 3.27 (4 H, t, *J* 6.9, CH_2N_3), 4.23 (2 H, t, *J* 7.8, NCH_2), 5.96 (1 H, d, *J* 4.0, 4-ArH), 7.08 (1 H, d, *J* 4.0, 3-ArH) and 12.07 (1 H, s, CO_2H); δ_C(75.46 MHz; $CDCl_3$) 26.2, 26.4, 26.6, 28.3, 28.6, 28.7, 28.9, 29.2, 31.1, 44.8, 51.3, 51.34, 107.2, 119.9, 120.0, 142.2 and 165.8; *m*/*z* (ESI) 398 $[M + Na]^+$ {Found (HRMS): *m*/*z* 332.2557. Calc. $[M - CO_2 + H]^+$ for $C_{17}H_{30}N_7$: 332.2562}.

***N*-[(2*S*)-1-Adamantylamino-3-(4-*tert*-butoxyphenyl)-1-oxopropan-2-yl]-1-(6-azidohexyl)-5-(7-azidoheptyl)pyrrole-2-carboxamide 15a**

A similar procedure to that used to prepare **9** was followed to afford **15a** eluting with ethyl acetate–hexanes (1:4, $R_f = 0.30$) (77%) as a white solid; mp 92.1–93.5 °C; ν_{max}(neat)/cm^{-1} 3287, 2095, 1659, 1622 and 1262; δ_H(300 MHz; $CDCl_3$) 1.30–1.48 [19 H, m, 5 CH_2 + $C(CH_3)_3$], 1.54–1.72 [14 H, m, 3 CH_2(Ada) + 4 CH_2], 1.83 [6 H, s, CH_2(Ada)], 2.0 [3 H, s, CH(Ada)], 2.53 [2 H, t, *J* 7.5, $ArCH_2$), 2.89 (1 H, dd, *J* 8.9, 13.5, φCH), 3.17 (1 H, dd, *J* 5.3, 13.5, φCH), 3.24–3.33 (4 H, m, CH_2N_3), 4.15–4.25 (1 H, m, NCH), 4.28–4.38 (1 H, m, NCH), 4.50–4.55 (1 H, m, COCH), 5.19 (1 H, s, CONHAda), 5.85 (1 H, d, *J* 3.6, 4-ArH), 6.45–6.48 (2 H, m, 3-ArH + ArCONH), 6.95 (2 H, d, *J* 8.4, φH) and 7.19 (2 H, d, *J* 8.4, φH); δ_C(75.46 MHz; $CDCl_3$) 26.2, 26.28, 26.3, 26.5, 28.4, 28.7, 28.9, 29.2, 31.4, 36.1, 38.2, 41.3, 44.5 51.26, 51.3, 51.8, 54.7, 78.2, 105.8, 112.1, 123.9, 124.2, 129.9, 139.2, 154.1, 161.4 and 169.6; *m*/*z* (ESI) 728 $[M + H]^+$ {Found (HRMS): *m*/*z* 728.4955. Calc. $[M + H]^+$ for $C_{41}H_{62}N_9O_3$: 728.4975}.

***N*-[(2*S*)-1-Adamantylamino-3-(4-hydroxyphenyl)-1-oxopropan-2-yl]-1-(6-aminohexyl)-5-(7-aminoheptyl)pyrrole-2-carboxamide bis(trifluoroacetate) salt (mimic-5)**

A similar procedure to that used to prepare mimic-**4** was followed to afford mimic-**5** as a white solid (structural characterizations were performed with the HPLC-purified product). The retention time (t_r) of mimic-**5** was 26.44 min; mp 82.3–85.4 °C; ν_{max}(KBr)/cm^{-1} 3422, 3295, 1678, 1626 and 1204; δ_H(300 MHz; [$^2H_6$]DMSO) 1.16–1.39 (10 H, m, CH_2), 1.40–1.70 [14 H, m, 3 CH_2(Ada) + 4 CH_2], 1.90 [6 H, s, CH_2(Ada)], 2.0 [3 H, s, CH(Ada)], 2.45–2.55 (2 H, m, $ArCH_2$), 2.68–2.90 (6 H, m, 2 CH_2N^+ + φCH_2), 4.04–4.28 (2 H, m, NCH_2), 4.36–4.47 (1 H, m, COCH), 5.80 (1 H, d, *J* 3.7, 4-ArH), 6.57–6.65 (3 H, m, 3-ArH + 2 φH), 7.06 (2 H, d, *J* 8.3, φH), 7.28 (1 H, s, CONHAda) and 7.60–7.91 (8 H, m, 2 NH_3^+ + ArCONH + φOH); δ_C(75.46 MHz; [$^2H_6$]DMSO) 25.5, 25.7, 26.9, 28.1, 28.3, 28.5, 28.8, 31.1, 36.0, 36.7, 41.0, 43.7, 50.7, 54.7, 105.1, 112.3, 114.7, 124.1, 128.3, 130.1, 138.0, 155.6, 161.1 and 170.8; *m*/*z* (ESI) 620 $[M + H]^+$ {Found (HRMS): *m*/*z* 620.4544. Calc. $[M + H]^+$ for $C_{37}H_{58}N_5O_3$: 620.4539}.

***N*-[(2*S*)-1-Adamantylamino-3-(indol-3-yl)-1-oxopropan-2-yl]-1-(6-azidohexyl)-5-(7-azidoheptyl)pyrrole-2-carboxamide 15b**

A similar procedure to that used to prepare **9** was followed with O-Bu^t-Trp-NH-Ada **16b** to afford **15b** eluting with ethyl acetate–hexanes (3:7, $R_f = 0.40$) (91%) as a yellowish oil; ν_{max}(neat)/cm^{-1} 3405, 3306, 2096, 1651 and 1258; δ_H(300 MHz; $CDCl_3$) 1.34–1.48 (10 H, m, CH_2), 1.51–1.82 [20 H, m, 6 CH_2(Ada) + 4 CH_2], 1.96 [3 H, s, CH(Ada)], 2.52 (2 H, t, *J* 7.8, $ArCH_2$), 3.15 (1 H, dd, *J* 8.2, 14.5, φCH), 3.16–3.30 (4 H, m, CH_2N_3), 3.39 (1 H, dd, *J* 5.5, 14.5, φCH), 4.16–4.27 (1 H, m, NCH), 4.28–4.40 (1 H, m, NCH), 4.68–4.76 (1 H, m, COCH), 5.41 (1 H, s, CONHAda), 5.82 (1 H, d, *J* 3.9, 4-ArH), 6.40 (1 H, d, *J* 4.0, 3-ArH), 6.54 (1 H, d, *J* 7.6, ArCONH), 7.07 (1 H, d, *J* 2.1, 2-φ′-H), 7.10–7.23 (2 H, m, 5-φ′-H + 6-φ′-H), 7.35 (1 H, d, *J* 7.8, 7-φ′-H), 7.74 (1 H, d, *J* 7.6, 4-φ′-H) and 8.45 (1 H, s, 1-φ′-H); δ_C(75.46 MHz; $CDCl_3$) 26.2, 26.25, 26.3, 26.5, 28.2, 28.4, 28.6, 28.8, 29.2, 31.4, 33.8, 36.1, 41.1, 44.5, 51.2, 51.3, 51.6, 53.8, 105.8, 110.8, 111.2, 112.2, 118.9, 119.5, 122.0, 123.1, 123.9, 127.3, 136.2, 139.2, 161.6 and 170.2; *m*/*z* (ESI) 695 $[M + H]^+$ {Found (HRMS): *m*/*z* 695.4506. Calc. $[M + H]^+$ for $C_{39}H_{55}N_{10}O_2$: 695.4509}.

***N*-[(2*S*)-1-Adamantylamino-3-(indol-3-yl)-1-oxopropan-2-yl]-1-(6-aminohexyl)-5-(7-aminoheptyl)pyrrole-2-carboxamide bis-(trifluoroacetate) salt (mimic-6)**

A similar procedure to that used to prepare mimic-**4** was followed to afford mimic-**6** as a white powder (structural characterizations were performed with the HPLC-purified product). The retention time (t_r) of mimic-**6** was 28.96 min; mp 103.3–105.1 °C; ν_{max}(KBr)/cm^{-1} 3422, 1678, 1630 and 1204; δ_H(300 MHz; [$^2H_6$]DMSO) 1.15–1.39 (10 H, m, CH_2), 1.41–1.78 [14 H, m, 3 CH_2(Ada) + 4 CH_2], 1.91 [6 H, s, CH_2(Ada)], 2.0 [3 H, s, CH(Ada)], 2.47–2.55 (2 H, m, $ArCH_2$), 2.66–2.83 (4 H, m, CH_2N^+), 3.02–3.19 (2 H, m, φ′-CH_2), 4.02–4.15 (1 H, m, NCH), 4.18–4.32 (1 H, m, NCH), 4.48–4.58 (1 H, m, COCH), 5.79 (1 H, d, *J* 3.8, 4-ArH), 6.63 (1 H, d, *J* 3.9, 3-ArH), 6.96 (1 H, t, *J* 7.1, 5-φ′-H), 7.05 (1 H, t, *J* 7.1, 6-φ′-H), 7.16 (1 H, d, *J* 2, 2-φ′-H), 7.26–7.34 (2 H, m, 7-φ′-H + CONHAda), 7.55–7.86 (8 H, m, 2 NH_3^+ + 4-φ′-H + ArCONH) and 10.79 (1 H, s, 1-φ′-H); δ_C(75.46 MHz; [$^2H_6$]DMSO) 24.4, 25.3, 25.5, 25.7, 26.9, 27.5, 28.1, 28.3, 28.5, 28.8, 31.1, 33.3, 36.0, 41.0, 43.7, 47.5, 50.7, 53.9, 105.1, 110.5, 111.2, 112.3, 118.0, 118.5, 120.7, 123.5, 124.1, 127.4, 136.0, 138.0, 161.1 and 171.1; *m*/*z* (ESI) 643 $[M + H]^+$ {Found (HRMS): *m*/*z* 643.4694. Calc. $[M + H]^+$ for $C_{39}H_{59}N_6O_2$: 643.4699}.

***N*-Adamantyl-2-amino-3-(indol-3-yl)propanamide 16b**

A literature procedure[2] was followed to afford intermediate of *N*-adamantyl-2-(fluoren-9-ylmethoxycarbonylamino)-3-(indol-3-yl)propanamide (92%) [$R_f = 0.42$ in ethyl acetate–hexanes (2:3)] as a white solid contaminated with small amount of impurities which were removed in the subsequent reaction; mp 92.1–93.6 °C; ν_{max}(KBr)/cm^{-1} 3326, 1709, 1657 and 1246; δ_H(300 MHz; $CDCl_3$) 1.53 [6 H, s, CH_2(Ada)], 1.73 [6 H, s, CH_2(Ada)], 1.97 [3 H, s, CH(Ada)], 3.06 (1 H, dd, *J* 8.7, 14.3, φ′-CH), 3.31–3.45 (1 H, m, φ′-CH), 4.20 (1 H, t, *J* 7.0, 9-FnH), 4.32–4.48 (3 H, m, OCH_2 + COCH), 5.10 (1 H, s, NHAda),

5.64 (1 H, d, *J* 4.6, FmocNH), 7.02 (1 H, s, 2-φ′-H), 7.10–7.45 (8 H, m, 3 Indolyl-H + 4 Fn-H + impurity), 7.52–7.60 (2 H, m, Fn-H), 7.70–7.80 (3 H, 2 Fn-H + 4-φ′-H) and 8.20 (1 H, s, 1-φ′-H); δ_C(75.46 MHz; $CDCl_3$) 29.0, 29.2, 36.1, 41.1, 47.0, 51.8, 55.8, 66.9, 110.6, 111.2, 118.8, 119.6, 119.9, 122.1, 123.2, 125.0, 127.0, 127.2, 127.6, 136.2. 141.1, 143.7, 155.9 and 169.9; *m*/*z* 560 ($M + H^+$) {Found (HRMS) (ESI): *m*/*z* 560.2916. Calc. [$M + H^+$] for $C_{36}H_{38}N_3O_3$: 560.2913}. A literature procedure[2] was followed with the intermediate to afford **16b** (94%) (R_f = 0.40, methanol–ethyl acetate 1 : 4) as a white solid; mp 171.2–172.5 °C; ν_{max}(neat)/cm^{-1} 3283 and 1645; δ_H(300 MHz; $CDCl_3$) 1.44 (2 H, s, NH_2), 1.65–1.75 [6 H, m, CH_2(Ada)], 1.96–2.05 [6 H, m, CH_2(Ada)], 2.07 [3 H, s, CH(Ada)], 2.90 (1 H, dd, *J* 8.9, 14.5, φ′-CH), 3.35 (1 H, dd, *J* 4.8, 14.9, φ′-CH), 3.59 (1 H, dd, *J* 8.8, 4.2, COCH), 6.96 (1 H, s, CONHAda), 7.09 (1 H, d, *J* 2.3, 2-φ′-H), 7.16 (1 H, dt, *J* 8.0, 0.9, 5-φ′-H), 7.24 (1 H, dt, *J* 7.1, 1.1, 6-φ′-H), 7.38 (1 H, d, *J* 8.1, 7-φ′-H), 7.69 (1 H, d, *J* 7.9, 4-φ′-H) and 8.10 (1 H, s, 1-φ′-H); δ_C(75.46 MHz; $CDCl_3$) 29.4, 30.8, 36.4, 41.5, 51.0, 56.1, 111.2, 111.9, 118.9, 119.4, 122.1, 123.1, 127.6, 136.4 and 173.8; *m*/*z* (ESI) 338 $[M + H]^+$ {Found (HRMS): *m*/*z* 338.2238. Calc. $[M + H]^+$ for $C_{21}H_{28}N_3O$: 338.2232}.

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