Synthesis of partial nonpeptidic peptide mimetics as potential neurotensin agonists and antagonists

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The synthesis of partially nonpeptidic peptides as mimetics of neurotensin (8–13) [NT(8–13)] is described. The sequence $Arg^8Arg^9Pro^{10}$ of NT(8–13) was replaced by substituted indole-2-carboxylates as non-peptidic equivalents. For the NT(8–13) fragment, a range of dimensions was calculated with the aid of computer modelling of which a subset was translated synthetically into two structures (**1** and **2**) containing indole-2-carboxylates substituted with guanidines containing appendages at C-3/C-5 and C-3/C-7, respectively. Regioisomeric C-5 and C-7 substituted indole intermediates **4** and **5** were obtained from a single indole precursor **3** *via* thermally induced nitrene insertion. The readily separable indoles **4** and **5** were isolated as a ~ 1 : 1 mixture. In turn, these indoles were functionalized individually in seven steps to give the Pmc-protected bisguanidino indole-2-carboxylic acids **14a** and **14b**, respectively. The carboxylic acids were coupled to the resin-bound tripeptide fragment NT(11–13), and the resulting products were cleaved from the resin using a trifluoroacetic acid cocktail to give NT mimetics **1** and **2**. Functional evaluation of **1** and **2** on neuroblastoma N1E-115 cells showed mimetic **1** to be an NT antagonist, while mimetic **2** was found to be an NT antagonist at low concentrations and an NT agonist at higher concentrations in the 10–100 μmol dm^{-3} range.

Introduction

Neurotensin (NT)[1] is a tridecapeptide (pGluLeuTyrGluAsnLysProArgArgProTyrIleLeu) that acts as a neuromodulator in the central and peripheral nervous system and is associated with many physiological functions.[1–11] These include production of hypotension,[1] effects on the contractility of various nonvascular smooth muscles,[7] and growth stimulation of human colon cancers[8a] and human pancreatic cancer.[8b] More interestingly, NT has been found to be associated with reduction of pain sensation[9] and in the pathophysiology of schizophrenia.[10,11] As an analgesic,[9] NT has proven to be more potent than morphine when it is administered directly into the central nervous system (CNS). Treatment of schizophrenic patients with antipsychotic drugs causes the normally depressed NT levels in the cerebrospinal fluid (CSF) of these patients to return to normal levels.[10,11] In accord with these findings the possible use of NT agonists as therapeutic agents in the treatment of schizophrenia[11] and in the alleviation of acute and chronic pain would appear possible.[9a]

In view of the important role that NT plays in biology, we undertook a programme aimed at developing full or partial nonpeptidic NT mimetics. These mimetics would be organic molecules with improved stability and hydrophobicity, which can mimic the action of the native peptide and which may additionally possess improved selectivity, affinity, and degrees of agonism or antagonism.

Structure–activity relationship (SAR) studies on NT have shown that the full 13 amino acids are not necessary to elicit biological activity.[9,12] The *C*-terminal hexapeptide NT(8–13) has been found to be equipotent or better than the native NT(1–13) in binding to the NT receptor. The neuropeptide has intrigued many chemists from the standpoint of identifying its preferred conformation in the hope of developing nonpeptidic mimetics as NT agonists. Although a potent nonpeptidic NT antagonist has been developed by structural modification of a lead compound discovered from screening thousands of compounds,[13] no nonpeptidic NT agonist has been reported.

To develop such mimetics, a traditional approach or a hierarchical approach would require a deduction of NT's receptor-bound conformation so that a rigid organic molecule could be designed to mimic this specific conformation.[14,15] Unfortunately, various conformational studies on NT reveal that this peptide is too flexible to deduce its likely receptor-bound conformation.[16–22] The costly and time-consuming random screening of chemical libraries thus appeared to be the only feasible route to the discovery of NT mimetics.

Alternatively, we developed the Multiple Template Approach (MTA) for the design of such mimetics at a stage when information on the topography of the receptor is not available.[23] This approach converts a vast number of conformers of a peptide into a comparatively small number of partially flexible molecules which can individually mimic a unique portion of the conformations available to the native peptide. By testing all these flexible molecules, one should arrive at a molecule that covers the receptor-bound conformation of the native peptide and that fits to the receptor. According to the MTA, we converted, with the aid of computer modelling, all possible conformers of NT(8–13) into 12 partially flexible molecular archetypes by replacing the first three amino acids with a nonpeptidic equivalent (a non-peptidic template with functional groups appended to it) (Fig. 1).[23] The template is a structural counterpart of the spacer residues of the peptide, and the appendant functional groups are identical with the functional groups of the peptide (a functional group is defined as a residue in the peptide which interacts directly with the recognition site; a spacer residue is defined as a residue in the peptide which governs the conformation of the peptide and that can be replaced by an appropriate molecular unit without affecting the activity of the peptide). These 12 congeners differ only in the distances between the points of attachment (C^1, C^2 and C^3, see Fig. 1) of the side chains bearing the functional groups of NT(8–13). The intrinsic conformational accessibility of these congeners is governed by the size of the triangle of C^1, C^2 and C^3. We then translated synthetically two of these congeners into two structures (**1** and **2**) as shown in Fig. 2.

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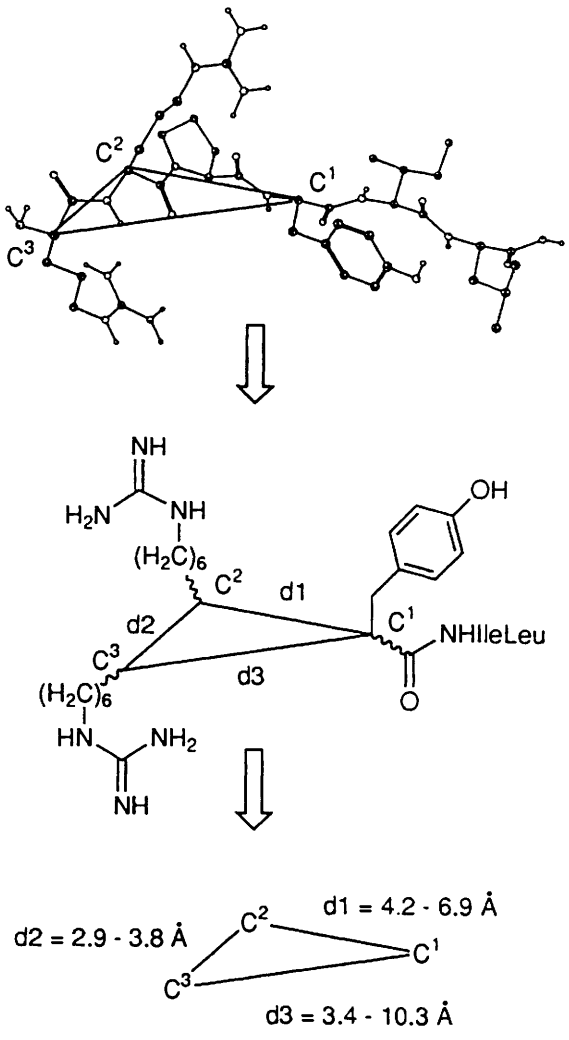
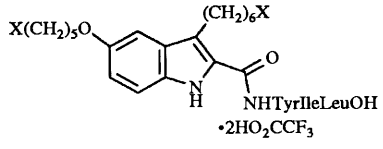
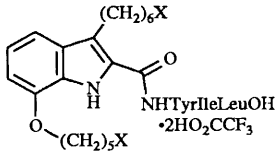


Fig. 1



1 X = NHC(NH$_2$)NH
17 X = NH$_2$



2 X = NHC(NH$_2$)NH
18 X = NH$_2$

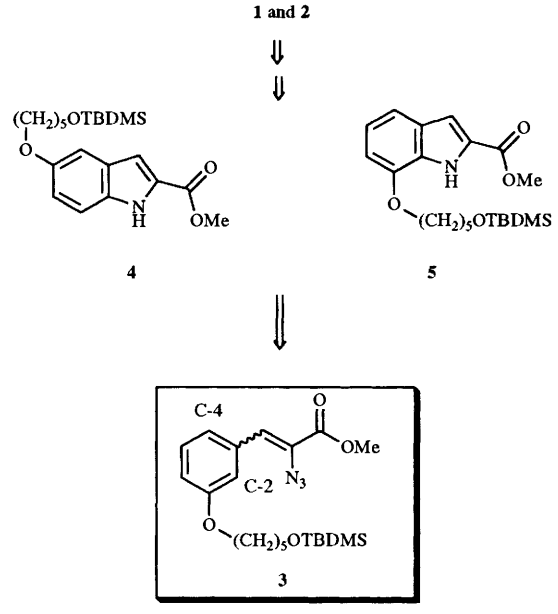
Fig. 2

The last three amino acids in these molecules were maintained for the purpose of introducing a minimum number of unknown parameters (*i.e.*, we assume that the two guanidine-bearing side chains of Arg^8 and Arg^9 are the functional groups of NT(8–13) and that Pro^{10} is a spacer which governs the conformation of the peptide and does not directly interact with the receptor). The chains bearing the guanidino groups at C^2 and C^3 of the imaginary triangle contain six linker atoms relative to the three carbon atoms that are found in the side chain of Arg itself. This modification was made in order to increase side chain flexibility, thus allowing the guanidino groups to achieve the proper interaction with the NT recognition site. It was hoped that these extra linker atoms would be tolerated by the NT recognition site, but in cases where they are not, the use of a smaller template would be required. For further details of the Multiple Template Approach, the reader is directed to the article cited in ref. 23.

We believed that synthesis of partially non-peptidic mimetics incorporating the tripeptide Tyr^{11}Ile^{12}Leu^{13} would be an ideal starting point. Recent SAR studies[24] have concluded that the side chains of Tyr^{11} and Leu^{13} of NT(8–13) contribute the most in binding to the NT receptor and, moreover, that Arg^8, Arg^9 and Pro^{10} of NT(8–13) can individually be replaced by Lys, Orn, or even Ala without significant loss in binding. Further studies also show that fragments consisting of the tripeptides Arg^{8}Arg^{9}Pro^{10} or Tyr^{11}Ile^{12}Leu^{13} fail to bind to the rat NT receptor. It was our plan to search first for the best non-peptidic equivalent of the first three amino acids of NT(8–13) to give optimum binding and then to search for equivalents of the last three amino acids.

Results and discussion

Selection of an indole-2-carboxylic acid as our molecular template was based on synthetic expediency in that both of the regioisomeric C-5 or C-7 substituted indole intermediates could be readily obtained from a single indole precursor **3** (Scheme 1).



Scheme 1

Thermally induced expulsion of nitrogen from the azide **3** was expected to generate a nitrene which should show no preference in its mode of insertion into C-4 or C-2 of the aromatic ring to give C-5 and C-7 substituted indoles **4** and **5**, respectively. To facilitate the synthesis, a methylene group was replaced by an oxygen atom (ether linkage) in the attachment of the guanidino appendage to the C-5 or C-7 position of the indole ring. Furthermore, it was decided that protected hydroxyl groups on the chains would serve as the precursor to the guanidino groups.

I. Synthesis

A. Synthesis of mimetics 1 and 2

The synthesis of **1** and **2** (Scheme 2) started from the reaction

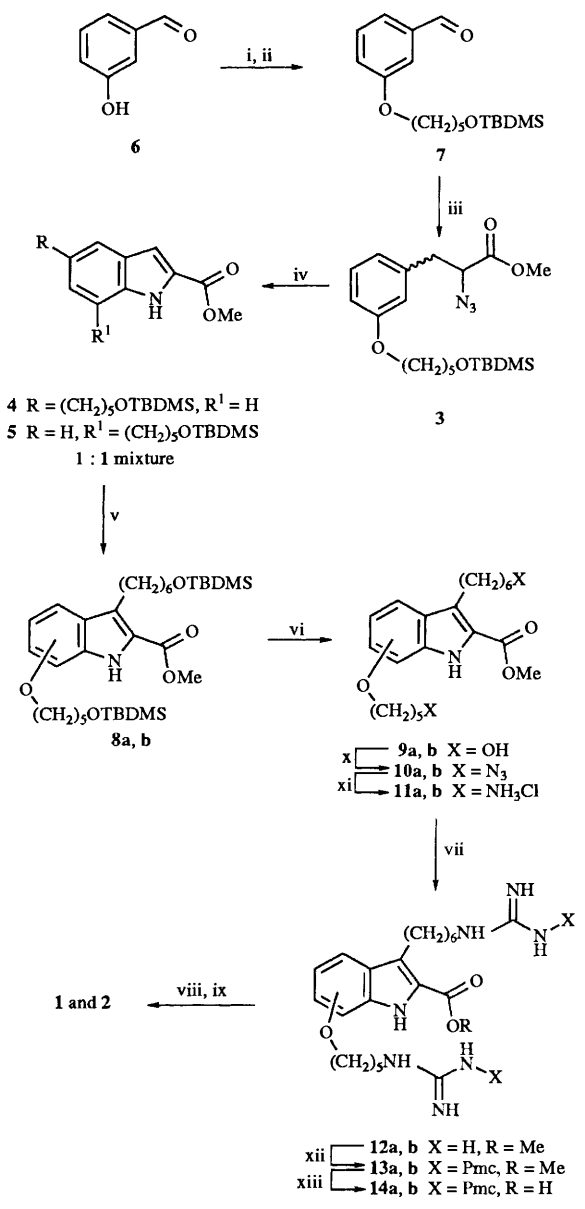
of *m*-hydroxybenzaldehyde **6** with 1-(*tert*-butyldimethylsilyloxy)-6-iodopentane† to give the alkoxybenzaldehyde **7** in 90–95% yield. Reaction of **7** with methyl azidoacetate (4 equiv.)[26] in the presence of NaOMe in MeOH at −15 °C gave the azide **3**, usually contaminated with 5–10% of the inseparable starting aldehyde which, however, presented no problem in the next step. When treated in refluxing toluene for 4 h, compound **3** underwent thermally induced nitrene insertion to give a mixture of the two indoles **4** and **5**[26] in a combined yield of ~ 50%. These indoles were easily separated on silica gel and subjected individually to further modifications. The assignment of structure to these two indoles was readily made on the basis of the ^{1}H NMR coupling patterns of their aromatic protons. The indoles **4** and **5** were alkylated[27] at the indole 3-position in 75–80% yield with 1-(tert-butyldimethylsilyloxy)-6-iodohexane† in refluxing MeCN in the presence of anhydrous K_2CO_3 to give **8a** and **8b**, respectively. Treatment of **8a** and **8b** with tetrabutylammonium fluoride generated the diols **9a** and **9b**, respectively, which were then converted into their respective diazides **10a** and **10b** using HN_3 as the source of the nucleophile under the Mitsunobu conditions.[28] Catalytic hydrogenation (10% Pd/C) of the azides at atmospheric pressure in the presence of concentrated HCl resulted in the bisamine hydrochlorides **11a** and **11b**, respectively, in 90–95% yield. These salts were then converted into the bisguanidine derivatives **12a** and **12b** by reaction with amino(imino)methanesulfonic acid.[29] The bisguanidines were found to be almost completely insoluble in all organic solvents and could only be characterized by mass and IR spectroscopy. Protection of the guanidino groups using 2,2,5,7,8-pentamethylchromane-6-sulfonyl chloride (pmc sulfonyl chloride)[30] gave the readily soluble derivatives **13a** and **13b**, but only in yields of 25–30%. Next, saponification with 2 mol dm^{-3} aqueous KOH gave the carboxylic acids **14a** and **14b**. HOBt/DCC mediated coupling of **14a** to the tripeptide TyrIleLeu bound to Wang resin[31] followed by treatment with a trifluoroacetic acid cocktail [consisting of TFA (10 cm^3), ethanedithiol (0.25 cm^3) of thioanisole (0.5 cm^3) and distilled water (0.5 cm^3)] and purification by reverse-phase HPLC provided the mimetic **1**. The same procedure utilizing the carboxylic acid **14b** gave the mimetic **2**. Both mimetics exhibited correct FAB MS data. Reagents and conditions are listed in Scheme 2.

B. Synthesis of mimetics 17 and 18

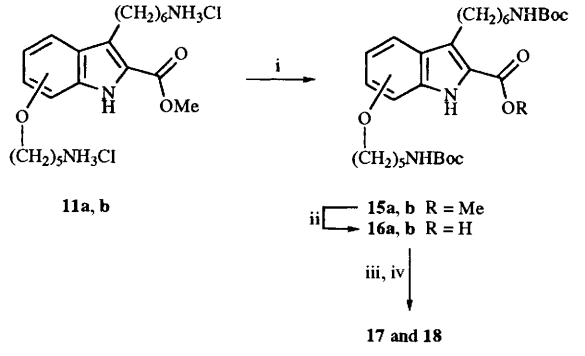
Based on structure–activity relationship studies of NT(8–13) and its lysine substituted analogues,[32] we reasoned that the guanidino group of Arg^8 and Arg^9 could be replaced by a simple amino group and, therefore, converted the bisamine hydrochlorides **11a** and **11b** into the diamine mimetics **17** and **18**, respectively (Scheme 3). The mimetics **17** and **18** could be used to test the suitability of indole-2-carboxylic acid as a partial NT template. If the indole-2-carboxylic acid unit in the mimetics **1** and **2** mimics its natural counterpart, **17** and **18** should show biological activities relative to mimetics **1** and **2** which are comparable to the difference in activity found between NT(8–13) and LysLysProTyrIleLeu.

This synthesis involved protecting the diamines **11a** and **11b** by reaction with Boc_2O to give **15a** and **15b**, respectively, in ~ 90% yield. Saponification of the ester functions using 2 mol dm^{-3} aqueous KOH resulted in the acids **16a** and **16b**, which were subsequently coupled with the resin-bound tripeptide using the DCC/HOBt conditions. Cleavage of the resin-bound peptide followed by purification using reverse-phase HPLC gave the mimetics **17** and **18**.

† The iodides were synthesized by reaction of PPh_3–I_2 and imidazole with 6-(*tert*-butyldimethylsilyloxy)pentan-1-ol and 6-(*tert*-butyldimethylsilyloxy)hexan-1-ol prepared by the method given in ref. 25.



Scheme 2 *Reagents and conditions:* i, NaH, DMF; ii, $I(CH_2)_5$ OTBDMS; iii, $N_3CH_2CO_2Me$, NaOMe, MeOH, 10 °C; iv, toluene reflux; v, $I(CH_2)_6$ OTBDMS, K_2CO_3, MeCN, reflux; vi, TBAF, THF; vii, $HN{=}C(SO_3H)NH_2$, K_2CO_3, H_2O; viii, H_2NTyrIleLeuCO_2-Resin, DCC, HOBT, *N*-methylpyrrolidone; ix, TFA; x, HN_3, PPh_3, DEAD; xi, H_2, 10% Pd–C, HCl, MeOH; xii, PmcCl, NaOH; xiii, KOH, MeOH



Scheme 3 *Reagents and conditions:* i, Boc_2O, Et_3N, CH_2Cl_2; ii, KOH, MeOH; iii, H_2NTyrIleLeuCO_2-Resin, DCC, HOBT, *N*-methylpyrrolidone; iv, TFA

C. Biological results

The deprotected synthetic intermediates **14a, b** and the final mimetics were tested for their ability to compete for [^{3}H]NT binding and for their action on intracellular cGMP production or on PI turnover in N1E-115 cells.‡ The deprotected intermediates **14a** and **14b** as mimetics of the ArgArgPro portion were found to be inactive in binding to the NT receptor, while mimetics **1** and **2** were active. The equilibrium dissociation constants (K_d) for **1** and **2** are 3.3 μmol dm^{-3} and 1.9 μmol dm^{-3}, respectively. Functionally, **1** and **2** antagonized NT-stimulated production of cGMP. Using the dose ratio method, the K_d can be determined from the EC_{50} values for NT with and without the addition of mimetics **1** and **2**. The corresponding K_d's for **1** and **2** are 4.2 and 2.4 μmol dm^{-3}, respectively. Interestingly, the mimetic **2** behaves as a full agonist in stimulating cGMP production at higher doses in the 10–100 μmol dm^{-3} range. The dualistic behaviour of the mimetic **2** is somewhat unexpected, and it would appear to provide a useful tool to further characterize the active domain of the NT receptor.‡ Importantly, the mimetics **17** and **18** were found to be active in binding experiments, but they are about 2- to 3-fold less potent than **1** and **2**, respectively. These results are consistent with the observation that the NT(8–13) analogues with Arg^8 and Arg^9 substituted by Lys are about 2-fold less potent in binding than NT(8–13), indicating that the template of the mimetics **1** and **2** may well mimic the active conformer of NT(8–13).

In summary, four partial nonpeptidic mimetics of NT designed by the MTA have been efficiently synthesized in eight steps as outlined in Schemes 2 and 3. These mimetics were found to be moderately active in both binding and functional experiments employing the NT receptor. Our success in identifying partial mimetics of the highly flexible NT peptide by the MTA provides an advance in rational drug design, especially when this approach is contrasted with the results of random screening methods, which led to the discovery of micromolar affinity NT antagonists only after random screening of a large chemical library.[13,32] Accordingly, the MTA approach may prove useful to the design of other peptide mimetics and it thus deserves further exploration. This approach is, of course, to be contrasted with other rigid-template approaches, in which, for example, a template is developed to mimic a particular structural motif.[34]

Experimental[34]

3-[5-(*tert*-Butyldimethylsilyloxy)pentyloxy]benzaldehyde 7

To a vigorously stirred suspension of NaH (60% dispersion in oil; 1.23 g, 30.7 mmol) in dry DMF (50 cm^3) at 0 °C under argon was added dropwise a solution of 3-hydroxybenzaldehyde **6** (3.12 g, 25.6 mmol) in DMF (25 cm^3). The mixture was warmed to room temperature and treated with 5-(*tert*-butyldimethylsilyloxy)pentyl iodide (7.0 g, 21.3 mmol). After 5 h, the reaction mixture was diluted with Et_2O (100 cm^3) and poured into ice-cold brine (100 cm^3). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 cm^3). The combined organic layer and extracts were washed successively with distilled water (2 × 50 cm^3) and brine (50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give **7** (6.5 g, 95%) as a clear oil, pure by TLC and ^{1}H NMR; ν_{max}(neat)/cm^{-1} 2930, 1703 and 1599; *m/z* (rel. intensity) 265 (M^+ − Bu^t, 100), 197 (50), 179 (85), 151 (85) and 69 (100); δ_H($CDCl_3$) 9.97 (s, 1 H), 7.50–7.45 (m, 2 H), 7.37 (s, 1 H), 7.20–7.14 (m, 1 H), 4.00 (t, 2 H, *J* 7.0), 3.64 (t, 2 H, *J* 7.0), 1.87–1.83 (m, 2H), 1.65–1.56 (m, 4 H), 0.87 (s, 9 H) and 0.12 (s, 6 H); δ_C($CDCl_3$) 191.8, 159.5, 137.7, 129.8, 122.9, 121.8, 112.7, 67.9, 62.7, 32.3, 28.8, 25.8 (3 C), 22.2, 18.2 and −5.4 (2 C) (Found: C, 67.05; H, 9.4. Calc. for $C_{18}H_{30}O_3Si$: C, 67.04; H, 9.38%).

Methyl 2-azido-3-{3[5-(*tert*-butyldimethylsilyloxy)pentyloxy]-phenyl}propenoate 3

To dry methanol (75 cm^3) cooled to 0 °C was added, in portions under argon, sodium metal (1.95 g, 84.6 mmol) over 45 min. The solution was cooled to −10 °C and a mixture of the aldehyde **7** (6.80 g, 21.1 mmol) and methyl azidoacetate (12.4 mL, 84.6 mmol) in methanol (10 cm^3) was added to it over 1.5 h. The mixture was stirred at −10 °C for an additional 1.5 h after which it was warmed to 15 °C over 30 min, poured into ice–water (100 cm^3) and extracted with Et_2O–ethyl acetate (1:1) (4 × 50 cm^3). The combined extracts were washed with brine (50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a light yellow oil. Flash chromatography of this on silica gel using ethyl acetate–hexanes (1:9) gave the title compound **3** (7.40 g, 84%) as a light yellow oil; ν_{max}(neat)/cm^{-1} 2930, 2124 and 1718; δ_H($CDCl_3$) 7.44 (m, 1 H), 7.31–7.30 (2 H, m), 6.89–6.86 (m, 2 H), 3.99 (t, 2 H, *J* 7.0), 3.91 (s, 3 H), 3.66 (t, 2 H, *J* 7.0), 1.84–1.79 (m, 2 H), 1.66–1.50 (m, 4 H), 0.90 (s, 9 H) and 0.06 (s, 6 H); δ_C($CDCl_3$) 164.1, 159.0, 134.4, 129.4, 125.6, 125.5, 123.3, 116.2, 116.0, 68.1, 63.3, 53.0, 32.9, 29.3, 26.0, 25.9, 18.4 and −5.2 (Found: *M*, 419.2230. Calc. for $C_{21}H_{33}N_3O_4Si$: *M*, 419.2240).

Methyl 5-[5-(*tert*-butyldimethylsilyloxy)pentyloxy]indole-2-carboxylate 4 and methyl 7-[5-(*tert*-butyldimethylsilyloxy)-pentyloxy]indole-2-carboxylate 5

Crude azido ester **3** (3.40 g, 8.11 mmol) was dissolved in dry, oxygen-free toluene (50 cm^3) under argon. The solution was refluxed for 4 h, after which it was evaporated under reduced pressure. The resulting oil was chromatographed on silica gel using ethyl acetate–hexane (1:9) as eluent to give compound **5** (0.88 g) eluted first as an oil followed by **4** (1.0 g) as an oil which crystallized with time. Compound **4**: mp 93 °C; ν_{max}(neat)/cm^{-1} 3335 and 1684; δ_H($CDCl_3$) 7.30 (d, 1 H, *J* 9.0), 7.12 (s, 1 H), 7.06 (s, 1 H), 6.99 (d, 1 H, *J* 9.0), 3.99 (t, 2 H, *J* 7.0), 3.93 (s, 3 H), 3.65 (t, 2 H, *J* 7.0), 1.85–1.80 (m, 2 H), 1.60–1.50 (m, 4 H) 0.89 (s, 9 H) and 0.05 (s, 6 H); δ_C($CDCl_3$) 162.3, 154.1, 132.4, 127.8, 127.3, 117.5, 112.8, 108.3, 103.5, 68.4, 63.0, 51.8, 32.5, 29.1, 25.9, 22.4, 18.3 and −5.3 (Found: C, 64.41; H, 8.27; N, 3.69%; M, 391.2178. Calc. for $C_{21}H_{33}NO_4Si$: C, 64.41; H, 8.49; N, 3.58%. *M*, 391.2168).

Compound **5**: ν_{max}(neat)/cm^{-1} 3949 and 1713; δ_H($CDCl_3$) 7.25 (d, 1 H, *J* 8.0), 7.18 (s, 1 H), 7.04 (t, 1 H, *J* 8.0), 6.70 (d, 1 H, *J* 8.0), 4.13 (t, 2 H, *J* 7.0), 3.94 (s, 3 H), 3.66 (t, 2 H, *J* 7.0), 1.94–1.85 (m, 2 H), 1.67–1.54 (m, 4 H), 0.90 (s, 9 H) and 0.05 (s, 6 H); δ_C($CDCl_3$) 162.4, 148.0, 128.7, 128.4, 126.8, 121.3, 114.6, 109.1, 104.9, 68.2, 63.0, 52.0, 32.6, 29.2, 26.0, 22.6, 18.4 and −5.2 (Found: M, 391.2153. Calc. for $C_{21}H_{33}NO_4Si$: *M*, 391.2178).

Methyl 3-[6-(*tert*-butyldimethylsilyloxy)hexyl]-5-[5-(*tert*-butyldimethylsilyloxy)pentyloxy]indole-2-carboxylate 8a and 3-[6-(*tert*-methylbutyldimethylsilyloxy)hexyl]-7-[5-(*tert*-butyl-dimethylsilyloxy)pentyloxy]indole-2-carboxylate 8b

To a solution of compound **4** (1.0 g, 2.52 mmol) in dry MeCN (35 cm^3) under argon were added 6-(*tert*-butyldimethylsilyloxy)-hexyl iodide (1.32 g, 3.84 mmol) and anhydrous K_2CO_3 (0.81 g, 5.88 mmol). The mixture was refluxed for 48 h, cooled, and filtered through a pad of Celite. The Celite was rinsed with Et_2O (100 cm^3) and the combined filtrate and washings were evaporated under reduced pressure. Flash chromatography of the residue on silica gel using ethyl acetate–hexanes (5:95) gave **8a** (1.20 g, 75%) as an oil: ν_{max}(neat)/cm^{-1} 2951, 2858 and 1714; δ_H($CDCl_3$) 7.33 (s, 1 H), 7.13–7.07 (m, 2 H), 4.59 (t, 2 H, *J* 7.0),

‡ For the details of the pharmacological studies on mimetics **1** and **2**, see Ref. 33.

3.99 (s, 3 H), 3.73 (t, 2 H, *J* 6.0), 3.66 (t, 2 H, *J* 6.0), 1.95–1.45 (m, 14 H), 0.97 (s, 18 H) and 0.03 (s, 12 H); $\delta_C(CDCl_3)$ 162.3, 155.9, 134.6, 127.1, 126.1, 117.0, 111.3, 109.8, 103.5, 68.5, 63.1, 63.0, 51.4, 44.7, 32.7, 32.6, 30.7, 29.2, 28.7, 25.9, 25.6, 22.4, 18.3 and −5.3 (Found: M, 605.3934. Calc. for $C_{33}H_{59}NO_5Si_2$: *M*, 605.3932).

Compound **8b** was prepared similarly starting from **5**: ν_{max}(neat)/cm^{-1} 2932, 2859 and 1719; $\delta_C(CDCl_3)$ 7.21 (d, 1 H, *J* 8.0), 6.98 (t, 1 H, *J* 8.0), 6.67 (d, 1 H, *J* 8.0), 4.97 (t, 2 H, *J* 8.0), 4.09 (t, 2 H, *J* 7.0), 3.88 (s, 3 H), 3.65 (t, 2 H, *J* 6.0), 3.57 (t, 2 H, *J* 7.0), 1.94–1.25 (m, 14 H), 0.89 (s, 18 H) and 0.04 (s, 12 H); $\delta_C(CDCl_3)$ 162.4, 147.5, 129.4, 128.2, 127.4, 120.8, 114.9, 111.1, 105.5, 68.2, 63.3, 63.0, 51.6, 47.1, 33.0, 32.7, 29.4, 26.7, 26.0, 25.8, 22.8, 18.4 and −5.2 (Found: M, 605.3938. Calc. for $C_{33}H_{59}NO_5Si_2$: *M*, 605.3932).

Methyl 3-(6-hydroxyhexyl)-5-(5-hydroxypentyloxy)indole-2-carboxylate 9a and Methyl 3-(6-hydroxyhexyl)-7-(5-hydroxypentyloxy)indole-2-carboxylate 9b

The indole **8a** (1.00 g, 1.65 mmol) was dissolved in 1.0 mol dm^{-3} tetrabutylammonium fluoride in THF (10 cm^3) and the solution stirred at room temperature for 3 h. The mixture was then poured into saturated brine and extracted with ethyl acetate (4 × 35 cm^3). The combined extracts were washed successively with distilled water (2 × 35 cm^3) and saturated brine (25 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow oil. Chromatography of this on silica gel using ethyl acetate–hexanes (4 : 1) gave **9a** (0.53 g, 85%) as an oil; ν_{max}(neat)/cm^{-1} 3368 br, 2934 and 1711; $\delta_H(CDCl_3)$ 7.18 (s, 1 H), 7.05–6.98 (m, 2 H), 4.52 (t, 2 H, *J* 7.0), 4.00 (t, 2 H, *J* 7.0), 3.89 (s, 3 H), 3.68 (t, 2 H, *J* 6.0), 3.61 (t, 2 H, *J* 6.0) and 1.85–1.26 (m, 14 H); $\delta_C(CDCl_3)$ 162.0, 153.5, 134.3, 126.7, 125.7, 116.7, 110.9, 109.5, 103.1, 76.3, 68.0, 62.1, 51.2, 44.3, 32.2, 32.0, 30.2, 28.8, 26.2, 25.0 and 22.1 (Found: M, 377.2189. Calc. for $C_{21}H_{31}NO_5$: M, 377.2202).

Compound **9b** was prepared similarly in 90% yield starting from **8b**: mp 100–101 °C; ν_{max}(neat)/cm^{-1} 3293 br, 2930, 2853 and 1713; $\delta_H(CDCl_3)$ 7.21 (d, 1 H, *J* 8.0), 6.98 (t, 1 H, *J* 8.0), 6.67 (d, 1 H, *J* 8.0), 4.87 (t, 2 H, *J* 8.0), 4.10 (t, 2 H, *J* 6.0), 3.88 (s, 3 H), 3.68 (t, 2 H, *J* 6.0), 3.62 (t, 2 H, *J* 6.0) and 1.96–1.38 (m, 14 H); $\delta(CDCl_3)$ 162.3, 147.3, 129.2, 128.0, 127.1, 120.0, 114.8, 111.0, 105.4, 103.3, 67.9, 62.5, 62.4, 51.5, 46.9, 32.6, 32.4, 32.3, 29.2, 26.6, 25.5 and 22.7 (Found: C, 66.4; H, 8.7; N, 3.8%; *M*, 377.2200. $C_{21}H_{31}NO_5$: C, 66.80; H, 8.28; N, 3.71%; *M*, 377.2202).

Methyl 3-(6-azidohexyl)-5-(5-azidopentyloxy)indole-2-carboxylate 10a and 3-(6-azidohexyl)-7-(5-azidopentyloxy)-indole-2-carboxylate 10b

The diol **9a** (0.67 g, 1.78 mmol) and PPh_3 (1.02 g, 3.91 mmol) were dissolved in dry THF (25 cm^3) under argon and the solution cooled to 0 °C. To this solution was added dropwise a 1.78 mol dm^{-3} solution of HN_3 in CH_2Cl_2 (6.00 cm^3, 10.7 mmol) followed by diethyl azodicarboxylate (DEAD) (0.68 cm^3, 4.30 mmol) over 10 min. The mixture was warmed to room temperature and stirred for 4 h after which distilled water (0.5 cm^3) was added to it. The mixture was then concentrated under reduced pressure to provide an oil. Flash chromatography of this on silica gel using ethyl acetate–hexanes (1 : 9) gave **10a** (0.68 g, 90%) as a clear oil: ν_{max}(neat)/cm^{-1} 2940, 2863, 2097 and 1711 cm^{-1}; $\delta_H(CDCl_3)$ 7.18 (s, 1 H), 7.05–6.99 (m, 2 H), 4.52 (t, 2 H, *J* 7.0), 4.00 (t, 2 H, *J* 6.0), 3.89 (s, 3 H), 3.32 (t, 2 H, *J* 7.0), 3.23 (t, 2 H, *J* 7.0) and 1.87–1.36 (m, 14H); $\delta_C(CDCl_3)$ 162.2, 153.8, 134.5, 127.0, 126.0, 116.9, 111.2, 109.8, 103.4, 66.0, 51.4, 51.2, 44.5, 30.4, 28.8, 28.6, 26.3 and 23.4 (Found: M, 427.2323. Calc. for $C_{21}H_{29}N_7O_3$: *M*, 427.2331).

Compound **10b** was prepared similarly in >90% yield starting from **9b** as an oil: ν_{max}(neat)/cm^{-1} 2940, 2095 and 1715; $\delta_H(CDCl_3)$ 7.23 (d, 1H, *J* 8.0), 6.99 (t, 1H, *J* 8.0), 6.68 (d, 1 H, *J* 8.0), 4.88 (t, 2 H, *J* 8.0), 4.11 (t, 2 H, *J* 6.0), 3.89 (s, 3 H), 3.34 (t, 2 H, *J* 6.0), 3.24 (t, 2 H, *J* 7.0) and 1.94–1.45 (m, 14 H); $\delta_C(CDCl_3)$ 162.2, 147.2, 129.1, 128.1, 127.2, 120.7, 114.9, 111.1, 105.5, 67.7, 51.5, 51.3, 51.2, 46.7, 32.2, 28.9, 28.8, 28.6, 26.5, 26.2 and 23.5 (Found: M, 427.2323. Calc. for $C_{21}H_{29}N_7O_3$: *M*, 427.2331).

Methyl 3-(6-aminohexyl)-5-(5-aminopentyloxy)indole-2-carboxylate bishydrochloride 11a and 3-(6-aminohexyl)-7-(5-aminopentyloxy)indole-2-carboxylate bishydrochloride 11b

To a methanol solution (25 cm^3) of **10a** (0.68 g, 1.60 mmol) was added 10% Pd-on-charcoal (0.20 g) followed by concentrated HCl (0.50 cm^3). The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 12 h and then filtered through a pad of Celite. The Celite was washed with methanol (30 cm^3) after which the combined filtrate and washing were evaporated under reduced pressure. The resulting solid was dissolved in ethanol and the solution was diluted with Et_2O to give **11a** (0.68 g, 95%) as a white solid: mp 205 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3410 br, 2928, 2369 and 1718; $\delta_H(D_2O)$ 7.36 (s, 1 H), 7.11–7.07 (m, 2 H), 4.01 (t, 2 H, *J* 7.0), 3.95 (t, 2 H, *J* 7.0), 3.81 (s, 3 H), 2.95 (t, 2 H, *J* 7.0), 2.82 (t, 2 H, *J* 7.0) and 1.72–1.22 (m, 14 H); $\delta_C(CD_3OD)$ 163.5, 154.9, 135.8, 127.9, 127.2, 117.9, 112.2, 110.9, 104.4, 100.4, 68.8, 51.9, 45.1, 40.4, 31.2, 29.6, 28.1, 28.0, 27.0, 26.9 and 23.9 [Found (FAB, glycerol/CsI): 376.2561. Calc. for $C_{21}H_{34}N_3O_3$: (M + H^+ − 2 HCl), 376.2516].

Compound **11b** was prepared similarly from **10b** in 95% yield as a white solid: mp 135 °C (decomp); ν_{max}(KBr)/cm^{-1} 3422 br, 2965, 2369 and 1735; $\delta_H(D_2O)$ 7.24 (d, 1 H, *J* 8.0), 7.03 (t, 1 H, *J* 8.0), 6.79 (d, 1 H, *J* 8.0), 4.50 (t, 2 H, *J* 7.0), 4.04 (t, 2 H, *J* 6.0), 3.84 (s, 3 H), 2.98 (t, 2 H, *J* 8.0), 2.86 (t, 2 H, *J* 8.0) and 1.83–1.12 (m, 14 H); $\delta_C(D_2O)$ 165.8, 149.5, 131.7, 130.3, 129.3, 123.7, 117.4, 114.0, 108.9, 70.6, 54.5, 48.9, 42.0, 33.6, 30.9, 29.4, 29.3, 28.0, 27.9 and 25.3 [Found: *m*/*z* 375.2516. Calc. for $C_{21}H_{33}N_3O_3$: (M^+ − 2 HCl), 375.2522].

Methyl 3-(6-guanidinohexyl)-5-(5-guanidinopentyloxy)indole-2-carboxylate 12a and 3-(6-guanidinohexyl)-7-(5-guanidinopentyloxy)indole-2-carboxylate 12b

The diamine hydrochloride **11a** (0.68 g, 1.36 mmol) and amino(imino)methanesulfonic acid (0.34 g, 2.72 mmol) were dissolved in distilled water (10 cm^3) with the assistance of an ultrasonic bath. While the sonication was in progress, a solution of anhydrous K_2CO_3 (0.75 g, 5.45 mmol) in distilled water (5 cm^3) was added dropwise to the solution. The resulting cloudy mixture was sonicated for 30 min at room temperature and then left for 24 h. The water was decanted, and the gummy precipitate was triturated with water followed by ethyl acetate, and then rinsed several times with ethyl acetate. Finally it was dried *in vacuo* to give **12a** (0.56 g, 90%) as a solid which is insoluble in all solvents: mp 105–108 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3391 br, 2934, 1718, 1687, 1520, 1466, 1439 and 1377; *m*/*z* 460.

Compound **12b** was prepared similarly in >90% yield starting from **11b**: mp 118–120 °C (decomp); ν_{max}(KBr)/cm^{-1} 3358 br, 2938, 1711, 1686, 1638, 1574, 1487, 1406 and 1346; *m*/*z* 460.

Methyl 3-{6-[*N*-(2,2,5,7,8-pentamethylchroman-6-ylsulfonyl)-guanidino]hexyl}-5-{5-[*N*-(2,2,5,7,8-pentamethylchroman-6-ylsulfonyl)guanidino]pentyloxy}indole-2-carboxylate 13a and 3-{6-[*N*-(2,2,5,7,8-pentamethylchroman-6-ylsulfonyl)-guanidino]hexyl}-7-[5-[*N*-(2,2,5,7,8-pentamethylchroman-6-ylsulfonyl)guanidinopentyl]oxy}indole-2-carboxyate 13b

The bisguanidinoindole **12a** (0.50 g, 1.09 mmol) was stirred in a mixture of acetone (5 cm^3) and water (1.4 cm^3) and the solution

was cooled to 0 °C. Sufficient aqueous NaOH (4 mol dm^{-3}) was added to the solution to adjust it to pH 12–13 after which, as a heterogeneous mixture, it was stirred at 0 °C for 2 h. A solution of 2,2,5,7,8-pentamethylchromane-6-sulfonyl chloride (pmc sulfonyl chloride) (1.6 g, 5.3 mmol) in acetone (5 cm^3) was then added dropwise to the mixture after what it was maintained at pH 12–13 by the addition of aqueous NaOH (4 mol dm^{-3}) whilst being stirred at 0 °C for 3 h. The mixture was acidified to pH 3 by the addition of 6 mol dm^{-3} HCl. Acetone was removed from the mixture by evaporation under reduced pressure, and the residue was diluted with distilled water (10 cm^3) and extracted with ethyl acetate (3 × 25 cm^3). The combined extracts were dried ($MgSO_4$), and evaporated under reduced pressure and flash chromatography of the residue on silica gel using ethyl acetate–hexanes (4:1) gave **13a** (0.25 g, 24%) as a off-white solid: mp 90 °C; ν_{max}(film)/cm ^{1} 2934, 1711, 1622 and 1551; δ_H($CDCl_3$) 7.25 (d, 1 H, *J* 8.0), 7.18 (s, 1 H), 6.99 (m, 2 H), 6.10–5.70 (br m, 6 H), 4.47 (t, 2 H, *J* 6.5), 3.99 (t, 3 H, *J* 6.5), 3.88 (s, 3 H), 3.15 (br m, 2 H), 2.89 (br s, 2 H), 2.52–2.49 (m, 16 H), 2.06–2.04 (m, 6 H), 1.77–1.27 (m, 18 H) and 1.21 (s, 12 H); δ_C($CDCl_3$/CD_3OD) 162.3, 156.1, 153.8, 153.5, 135.3, 134.6, 133.3, 126.0, 123.9, 117.9, 117.1, 111.4, 109.9, 103.6, 75.5, 68.1, 60.3, 54.9, 51.5, 44.5, 41.0, 32.7, 30.4, 29.3, 28.9, 28.8, 26.7, 26.3, 23.9, 21.3, 18.4, 17.4, 14.1 and 12.1 [Found (FAB, glycerol/CsI): *m/z* 992.4951. Calc. for $C_{51}H_{74}N_7S_2O_9$: (M + H^+) 992.4989]. (Found: C, 61.5; H, 7.3; N, 9.1%. Calc. for $C_{51}H_{73}N_7O_9S_2$: C, 61.73; H, 7.42; N, 8.89).

Compound **13b** was prepared similarly in ~25% yield starting from **12b** as a white solid: mp 158–160 °C; ν_{max}(film)/cm^{-1} 2930, 1719, 1624 and 1557; δ_H($CDCl_3$/CD_3OD) 7.20 (d, 1 H, *J* 8.0), 6.98 (t, 1 H, *J* 8.0), 6.65 (d, 1 H, *J* 8.0), 4.81 (t, 2 H, *J* 8.0), 4.05 (t, 2 H, *J* 6.0), 3.87 (s, 3 H), 3.23 (m, 2 H), 3.15 (m, 2 H), 2.60–2.52 (m, 16 H), 2.08–2.05 (m, 6 H), 1.79–1.28 (m, 18 H) and 1.26 (s, 12 H); δ_C($CDCl_3$/CD_3OD) 162.2, 156.3, 153.4, 147.3, 135.3, 134.6, 133.7, 129.1, 128.0, 127.0, 124.1, 120.7, 117.9, 114.8, 111.0, 105.4, 73.6, 67.9, 60.4, 51.5, 47.1, 41.2, 41.0, 32.7, 32.4, 31.5, 29.4, 29.2, 26.7, 23.7, 21.4, 18.5, 17.4 and 12.1 [Found (FAB, glycerol/CsI): *m/z* 992.4976 [Found: *m/z* 992.4976. Calc. for $C_{51}H_{74}N_7O_9S_2$: (*M* + H^+), 992.4989].

3-{6-[*N*-(2,2,5,7,8-Pentamethylchroman-6-sulfonyl)-guanidino]hexyl}-5-{5-[*N*-(2,2,5,7,8-pentamethylchroman-6-ylsulfonyl)guanidino]pentyloxy}indole-2-carboxylic acid 14a and 3-{6-[*N*-(2,2,5,7,8-pentamethylchroman-6-ylsulfonyl)-guanidino]hexyl}-7-{5-[*N*-(2,2,5,7,8-pentamethylchroman-6-ylsulfonyl)guanidino]pentyloxyl}indole-2-carboxylic acid 14b

Compound **13a** (0.29 g, 0.29 mmol) was dissolved in a mixture of MeOH (14 cm^3) and THF (5 cm^3) and to this solution was added aqueous KOH (2 mol dm^{-3}; 7 cm^3). The mixture was stirred overnight at room temperature after which it was acidified to pH 3 by the dropwise addition of 6 mol dm^{-3} HCl and extracted with CH_2Cl_2 (4 × 25 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and flash chromatography of the residue using $CHCl_3$–MeOH (95:5) gave **14a** (0.25 g, 74%) as a white powder: mp 125–127 °C; ν_{max}(film)/cm^{-1} 3445 br, 2932 and 1710 cm^{-1}; δ_H($CDCl_3$/CD_3OD) 7.27 (d, 1 H, *J* 9.0), 7.04 (s, 1 H), 6.98 (d, 1 H, *J* 9.0), 4.50 (t, 2 H, *J* 7.0), 3.97 (t, 2 H, *J* 6.0), 3.19 (t, 2 H, *J* 6.0), 3.11 (t, 2 H, *J* 6.0), 2.64–2.55 (m, 16 H), 2.10 (s, 6 H), 1.81–1.43 (m, 18 H) and 1.29 (s, 12 H); δ_C($CDCl_3$/CD_3OD) 156.0, 153.4, 153.3, 135.1, 134.5, 134.5, 125.9, 123.7, 117.7, 111.0, 103.4, 73.4, 68.0, 32.4, 28.6, 26.2, 25.9, 23.0, 21.1, 18.0, 16.9 and 11.6 [Found (FAB, glycerol/CsI): *m/z* 978.4868. Calc. for $C_{50}H_{72}N_7O_9S_2$: (M + H^+), 978.4833].

Compound **14b** was prepared similarly starting from **13b** in 90% yield as a white solid: mp 145–147 °C; ν_{max}(film)/cm^{-1} 3450 br, 1716, 1624 and 1557; δ_H($CDCl_3$/CD_3OD) 7.17 (d, 1 H, *J* 8.0), 6.94 (t, 1 H, *J* 8.0), 6.61 (d, 1 H, *J* 8.0), 4.78 (br s, 2 H), 3.98 (br s, 2 H) 3.19 (br s, 4 H), 2.55–2.50 (m, 16 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 1.75–1.34 (m, 18 H) and 1.25 (s, 12 H); δ_C($CDCl_3$/CD_3OD) 165.7, 156.4, 153.6, 147.2, 135.3, 134.7, 129.5, 127.9, 126.8, 124.0, 117.9, 103.2, 73.6, 41.0, 32.6, 32.2, 29.1, 26.7, 26.3, 23.6, 21.3, 18.5, 17.4 and 12.1 [Found (FAB, glycerol/CsI): *m/z* 978.4828. Calc. for $C_{50}H_{72}N_7O_9S_2$: (M + H^+), 978.4833].

Methyl 3-[6-(*N*-*tert*-butoxycarbonylamino)hexyl]-5-[5-(*N*-*tert*-butyloxycarbonylamino)pentyl]indole-2-carboxylate 15a and methyl 3-[6-(*N*-*tert*-butoxycarbonylamino)hexyl]-7-[5-(*N*-*tert*-butoxycarbonylamino)pentyloxy]indole-2-carboxylate 15b

To a slurry of the bishydrochloride **11a** (0.25 g, 0.56 mmol) in CH_2Cl_2 (10 cm^3) was added at 0 °C Et_3N (0.42 cm^3, 3.20 mmol) followed by *tert*-butoxycarbonic anhydride (Boc_2O) (0.47 g, 2.15 mmol). The mixture was stirred for 4 h, diluted with water and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and chromatography on silica gel using ethyl acetate–hexanes (3:7) as the eluent gave **15a** (0.29 g, 89%) as an oil: ν_{max}(film)/cm^{-1} 3357, 2862 and 1710; δ_H($CDCl_3$) 7.29 (m, 1 H), 7.19 (d, 1 H, *J* 2.3), 7.03 (m, 2 H), 4.52 (m, 4 H), 3.99 (t, 2 H, *J* 6.3), 3.90 (s, 3 H), 3.13 (m, 4 H), 1.80 (m, 4 H) and 1.65–1.30 (m, 28 H); δ_C 162.1, 155.8, 153.7, 134.4, 126.9, 125.9, 116.9, 111.1, 103.3, 78.7, 68.0, 51.3, 44.4, 40.2, 30.3, 29.7, 28.8, 28.2, 26.3, 26.2 and 23.2 (Found: M, 575.3585. Calc. for $C_{31}H_{49}N_3O_7$: *M*, 575.3570).

Compound **15b** was prepared similarly starting from **11b** as a solid: mp 64 °C; ν_{max}(film)/cm^{-1} 3388, 2933 and 1625; δ_H($CDCl_3$) 7.24 (s, 1 H), 7.23 (d, 1 H, *J* 8.4), 6.99 (t, 1 H, *J* 8.0), 6.69 (d, 1 H, *J* 7.6), 4.86 (t, 2 H, *J* 7.5), 4.77 (br s, 1 H), 4.66 (br s, 1 H), 4.09 (t, 2 H, *J* 6.3), 3.89 (s, 3 H), 3.10 (m, 4 H), 1.85 (m, 4 H) and 1.15–1.35 (m, 28 H); δ_C($CDCl_3$) 162.2, 156.0, 147.3, 146.7, 129.2, 128.0, 127.2, 120.6, 114.8, 111.0, 105.4, 85.1, 79.0, 67.9, 51.5, 46.8, 40.5, 32.3, 29.9, 29.1, 28.4, 27.4, 26.6, 26.4 and 23.6 (Found: M 575.3554. Calc. for $C_{31}H_{49}N_3O_7$: *M*, 575.3570).

3-[6-(*N*-*tert*-Butoxycarbonylamino)hexyl]-5-[5-[*N*-*tert*-butoxycarbonylamino)pentyloxy]indole-2-carboxylic acid 16a and 3-(6-*N*-*tert*-Butoxycarbonylamino)hexyl]-7-[5-[*N*-*tert*-butoxycarbonylaminopentyl)oxy]indole-2-carboxylic acid 16b

To a solution of **15a** (0.17 g, 0.29 mmol) in MeOH (3 cm^3) and THF (2 cm^3) was added 2 mol dm^{-3} aqueous KOH (2 cm^3, excess). The mixture was stirred for 10 h and then poured into 5% aqueous $KHSO_4$ (25 cm^3) and extracted with CH_2Cl_2 (4 × 25 cm^3). The extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a solid, chromatography of which on silica gel using CH_2Cl_2/MeOH (95/5) afforded **16a** (0.145 g, 87%) as a solid: mp 44–46 °C; ν_{max}(KBr)/cm^{-1} 3388, 2939 and 1695; δ_H($CDCl_3$) 7.31 (m, 2 H), 7.06 (d, 1 H, *J* 2.0) 7.02 (d, 1 H, *J* 9.0), 4.54 (m, 4 H), 3.98 (t, 2 H, *J* 6.5), 3.10 (m, 4 H), 1.80 (m, 4 H) and 1.65–1.30 (m, 28 H); δ_C($CDCl_3$) 164.6, 155.3, 126.4, 125.3, 116.5, 110.5, 110.3, 102.7, 78.3, 67.5, 43.8, 39.7, 29.7, 29.0, 28.2, 27.7, 25.7, 25.6 and 22.6 (Found: M, 561.3447. Calc. for $C_{30}H_{47}N_3O_7$: *M*, 561.3414).

Compound **16b** was prepared similarly starting from **15b**: mp 53–54 °C; ν_{max}(film)/cm^{-1} 3336, 2976 and 1695; δ_H($CDCl_3$) 7.37 (s, 1 H), 7.24 (d, 1 H, *J* 8.0), 6.98 (t, 1 H, *J* 7.8), 6.68 (d, 1 H, *J* 7.7), 4.89 (m, 2 H), 4.70 (br s, 2 H), 4.09 (t, 2 H, *J* 6.3), 3.15 (m, 4 H), 1.85 (m, 4 H) and 1.65–1.30 (br m, 28 H); δ_C($CDCl_3$) 165.6, 156.0, 147.2, 129.5, 128.0, 126.9, 120.6, 114.9, 112.4, 105.5, 79.0, 67.8, 46.7, 41.5, 40.5, 32.1, 29.8, 29.0, 28.4, 26.5, 26.3 and 23.5 (Found: C, 63.7; H, 8.4; N, 7.35%; M, 561.3405. Calc. for $C_{30}H_{47}N_3O_7$: C, 64.13; H, 8.44; N, 7.48%; *M*, 561.3414).

Neurotensin mimetics 1, 2, 17 and 18

Indolecarboxylic acid **14a** (0.200 g, 0.205 mmol), tripeptide

(H_2N-Tyr-Ile-Leu-COO-Wang resin, 0.94 mmol g^{-1}; 0.109 g, 0.058 mmol), HOBt (0.027 g, 0.204 mmol) and DCC (0.042 g, 0.204 mmol) were charged into a round-bottom flask under argon. *N*-Methylpyrrolidone (5 cm^3) was added to the mixture which was then stirred at room temperature for 24 h. The resin beads were filtered off, washed several times with $CHCl_3$ and MeOH, dried and then treated with the cleavage mixture [consisting of TFA (10 cm^3) ethanedithiol (0.25 cm^3) thioanisole (0.5 cm^3) and distilled water (0.5 cm^3)] for 2 h at room temperature. The resin was separated from the peptide by filtration. The filtrate was concentrated under reduced pressure and then treated with cold Et_2O (15 cm^3). The precipitated peptide was filtered off, washed with Et_2O and purified by reverse-phase HPLC on a Vydak C18 (15–20 μm particle size, 250 mm L × 22 mm ID) column using gradient elution, starting with 0.1% TFA in H_2O (buffer A) and then linearly increasing the concentration of buffer B (prepared from 20% buffer A in MeCN) at t = 2 min from 10% to 70% B over 50 min at a flow rate of 14 cm^3 min^{-1} and the detector wavelength set at 220 nm, to give 14 mg (>95% pure) of **1** as its bis(trifluoroacetate) salt. Mimetic **1** displayed a retention time of 53 min. It was characterized by MS (FAB, glycerol/CsI) *m/z* 836 ($M + H^+ - 2\ HO_2CCF_3$).

Mimic **2** was similarly prepared from indole acid **14b** and purified using reverse-phase HPLC on a Vydak C4 (15–20 μm particle size, 250 mm L × 22 mm ID) column under the above elution conditions. Mimic **2** displayed a HPLC retention time of 55 min [Found (FAB, glycerol/CsI): *m/z* 835.518. Calc. for $C_{43}H_{67}N_{10}O_7$: ($M + H^+$), 835.5194].

Neurotensin mimics **17** and **18** were prepared from their corresponding bis-Boc protected diaminoindolecarboxylic acids, **16a** and **16b**, respectively, by a procedure similar to the one described for the synthesis of the mimetics **1** and **2**. They were both purified by reverse-phase HPLC on a Waters μBondapak C18 column (10 μm particle size, 125 Å pore size, 300 mm L × 19 mm ID) using a gradient elution starting at t = 0 with 100% of buffer A (0.1% TFA in H_2O) and then linearly increasing the concentration of buffer B (consisting of 20% buffer A in MeCN) over 45 min, at a flow rate of 9.0 cm^3 min^{-1}, and the detector wavelength set at 220 nm, from 0 to 82%. Mimetic **17** had a retention time of 34 min; mimic **18** displayed a retention time of 38 min [Found (FAB, glycerol/CsI): *m/z* 751.4740 (**17**), 751.4729 (**18**). Calc. for $C_{41}H_{63}N_6O_7$ ($M + H^+$) 751.4758].

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