Analogues of Capsaicin with Agonist Activity as Novel Analgesic Agents; Structure–Activity Studies. 3. The Hydrophobic Side-Chain "C-Region"

Christopher S. J. Walpole,* Roger Wrigglesworth,* Stuart Bevan, Elizabeth A. Campbell, Andy Dray, Iain F. James, Kay J. Masdin, Martin N. Perkins, and Janet Winter

Sandoz Institute for Medical Research, Gower Place, London WC1E 6BN, England

Received May 8, 1992

Structural variants of the hydrophobic side chain ("C region") of the capsaicin molecule have been incorporated into a series of vanillylamides and vanillylthioureas. These compounds have been tested in an *in vitro* assay for agonism ($^{45}Ca^{2+}$ influx into dorsal root ganglia neurones), previously shown to be predictive of analgesic activity. The results of this study have established the requirement for a hydrophobic substituent of limited size (molar refractivity, MR, <55) in order to obtain high potency. Combination of the information gained here about the "C-region" of the capsaicin molecule with the studies described in the preceding two papers provides a rational basis for the design of compounds of increased potency.

Introduction

The potential of analogues of capsaicin (1) as novel analgesic agents has been discussed in the preceding papers of this series.

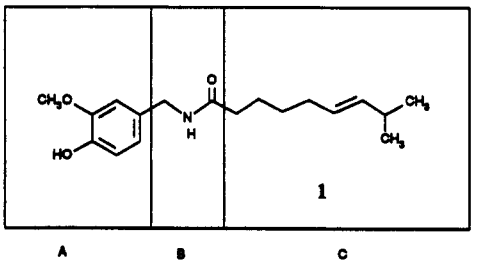
The data presented in this current paper completes the preliminary systematic structure–activity study of various regions of the capsaicin molecule. Herein we describe the consequences of structural variations of the hydrophobic side chain ("C-region", see Scheme I) on activity in *in vitro* bioassays which we have established are predictive of analgesic activity.

Chemistry

The majority of the C-region variants listed in Table I retain the structural features of capsaicin in the A- and B-regions; i.e. they are vanillylamides.

The common synthetic route to these molecules, namely the formation of the amide bond, was achieved by condensation of vanillylamines **3**, either as the parent amine or with the phenolic OH group protected as the 2-ethoxyethoxy ether,[1] with an acylating agent derived from an alkyl, aralkyl, or aralkenyl carboxylic acid. The carboxylic acid moiety was activated either as an acid chloride (method a), mixed anhydride (method b), with DCCI (method c), or as the *N*-hydroxysuccinimide ester (method d). These various coupling methods (see Table I) gave rise to the miscellaneous set of target structures, **4**, **6**, **8**, **10**, and **12**. In the cases where the phenolic OH group in the resulting amide was protected, treatment of the intermediate with dilute acid gave the free phenol in good yields. The details of the synthetic methods used are unexceptional and need no further description here. They are, however, given in the Experimental Section. Several of the target structures described above were subsequently transformed into other target compounds. Thus, treatment of **4b** with TFA removed the Boc protecting group to give the amine **4c** as the trifluoroacetate salt. The ester **4d** was saponified to the acid **4e**. Coupling of the amine **4h**, using the mixed anhydride activation method, with 3,6,9-trioxadecanoic acid, gave the product **4n**. Catalytic hydrogenation of the phenylethenyl compound **6b** gave the saturated analogue **8b**. Deprotection of the acetoxyphenyl derivative **8d** using sodium bicarbonate gave the phenol **8e**. The homovanillic acid amide

Scheme I



13 ("reverse" amide series) was prepared by the general method described in paper 2 of this series using 2-(*p*-chlorophenyl)ethylamine. The thioureas **15** were made by condensing the vanillylamines **3** with the appropriate isothiocyanate **14**. The vanillylamines were used either as the parent amine, following the method of Buckwalter and Lahann[1] for the synthesis of **15f**, or with the phenolic OH group protected as the ethoxyethyl ether,[1] as before. The isothiocyanates were commercially available except in the case of the target **15m**, where the isothiocyanate was made by a literature method.[2] The primary thiourea **15a** was made by treatment of the tritylthiourea **15p** with dilute acid.

Biological Results and Discussion

The contributions of the aromatic (A) region and the amide bond (B) region to the analgesic activity of capsaicin analogues have been described in the preceding papers. This paper describes a similar investigation of the hydrophobic side-chain (C) region.

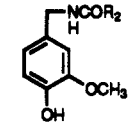
The data from the primary assay ($^{45}Ca^{2+}$ influx into dorsal root ganglia neurones in culture, induced by the capsaicin analogues) is presented in Table I. The close correspondence of activity in this assay compared with that from the guinea pig ileum assay is shown in Table II. The representative analgesia data presented reinforce the earlier derived conclusion that only potent capsaicin-like agonists are active in the mouse tail-flick assay. This data is included in Figure 1 of paper 1.

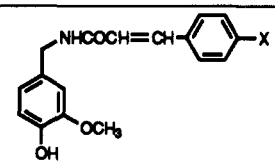
Several conclusions can be drawn from a consideration of the data presented in Table I.

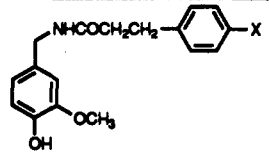
Capsaicin (1), dihydrocapsaicin (2), and the octylamide **4a** are approximately equipotent, suggesting that either

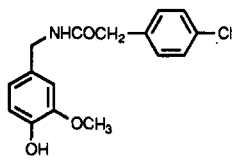
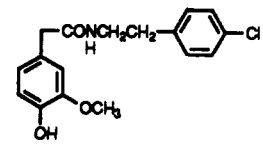
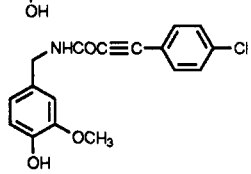
0022-2623/93/1836-2381$04.00/0

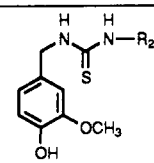
Table I. Coupling Method and $^{45}Ca^{2+}$ Influx Activity for a Series of C-Region Analogues

	R_2	coupling[a] method	Ca^{2+} influx EC_{50} (μM)		R_2	coupling[a] method	Ca^{2+} influx EC_{50} (μM)
							
1	$(CH_2)_4$(*E*)-CH=CH $CH(CH_3)_2$		0.30 ± 0.04	**4h**	$(CH_2)_{10}NH_2$	c	NT[i]
2[b]	$(CH_2)_6CH(CH_3)_2$		0.19 ± 0.02	**4i**[c]	$(CH_2)_{16}CH_3$	a	>100
4a	$(CH_2)_7CH_3$	a	0.55 ± 0.08	**4j**[c]	$(CH_2)_7$-(*E*)-CH=CH$(CH_2)_7CH_3$	a	0.36 ● 0.07
4b	$(CH_2)_5$NH Boc	d	79.80 ± 10.70	**4k**[d]	$(CH_2)_7$-(*Z*)-CH=CH$(CH_2)_7CH_3$	a	0.17 ● 0.03
4c	$(CH_2)_5NH_3^+TFA^-$		>100	**4l**[e]	CH_2Br	a	>100
4d	$(CH_2)_{10}CO_2CH_3$	a	NT[i]	**4m**[e]	CH_2Cl	a	>100
4e	$(CH_2)_{10}CO_2H$		>100	**4n**	$-(CH_2)_{10}NHCOCH_2O$ $\lvert$ $CH_3[O(CH_2)_2]_2$		>100
4f	$CH_2O(CH_2)_2OCH_3$	b	>100				
4g	$CH_2O(CH_2)_2O(CH_2)_2OCH_3$	b	>100				

	alkene	X	coupling[a] method	Ca^{2+} influx EC_{50} (μM)		alkene	X	coupling[a] method	Ca^{2+} influx EC_{50} (μM)
									
6a[e]	*E*	4-H	a	11.80 ± 1.90	**6g**	*E*	4-$N(CH_3)_2$	c	4.39 ± 0.67
6b	*E*	4-Cl	a	1.24 ± 0.11	**6h**	*E*	4-I	a	0.35 ± 0.05
6c	*Z*	4-Cl	a	50.10 ± 0.80	**6i**	*E*	4-NHCHO	b	1000
6d	*E*	4-NO_2	a	4.58 ± 0.29	**6j**	*E*	2,4-Cl_2	b	0.62 ± 0.25
6e	*E*	4-CN	a	26.50 ± 5.87	**6k**	*E*	3-Cl	a	2.58 ± 0.06
6f	*E*	4-Ph	a	0.24 ± 0.026[f]					

	X	coupling method	Ca^{2+} influx EC_{50} (μM)		X	coupling method	Ca^{2+} influx EC_{50} (μM)
							
8a[g]	H	a	45.26 ± 2.91	**8d**	4-$OCOCH_3$	b	NT[i]
8b	4-Cl		3.09 ± 0.07	**8e**	4-OH		>100
8c[e]	4-NO_2	a	21.0 ± 1.1	**8f**	4-N_3	d	4.20 ± 0.27

	structure	coupling[a] method	Ca^{2+} influx EC_{50} (μM)		structure	coupling[a] method	Ca^{2+} influx EC_{50} (μM)
10		a	7.77 ± 1.07	**13**			0.66 ± 0.07
12		a	4.10 ± 0.25				

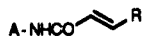
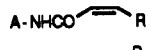
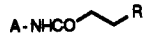
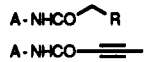
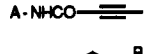
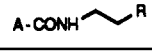
	R_2	Ca^{2+} influx EC_{50} (μM)		R_2	Ca^{2+} influx EC_{50} (μM)
					
15a	H	>100	**15i**	$(CH_2)_{11}CH_3$	0.16 ± 0.03
15b	$(CH_2)_3CH_3$	9.48 ± 1.05	**15j**	$(CH_2)_{15}CH_3$	>100
15c	$(CH_2)_4CH_3$	1.96 ± 0.51	**15k**	$(CH_2)_{17}CH_3$	8.1 ● 1.0
15d	$(CH_2)_5CH_3$	0.18 ± 0.02	**15l**	$(CH_2)_7$-(*Z*)-CH=CH$(CH_2)_7CH_3$	>100
15e	$(CH_2)_6CH_3$	0.29 ± 0.03	**15m**	adamantyl	1.08 ± 0.05
15f[h]	$(CH_2)_7CH_3$	0.06 ± 0.01	**15n**	$CH(Ph)_2$	0.27 ± 0.02
15g	$(CH_2)_8CH_3$	0.10 ± 0.01	**15p**	$C(Ph)_3$	>100
15h	$(CH_2)_9CH_3$	0.11 ± 0.01			

[a] See the text. [b] Reference 4. [c] Reference 5. [d] Reference 6. [e] Reference 3. [f] This value is an overestimate because of the limited aqueous solubility of **6f**. [g] Reference 7. [h] Reference 1. [i] Not tested.

Table II. $^{45}Ca^{2+}$ Influx Agonist Activity, Guinea Pig Ileum Contraction, and Analgesia (Mouse Tail Flick Latency) for a Series of C-Region Analogues

	EC_{50} (μM)		
compd	Ca^{2+} influx	guinea pig ileum contraction	analgesia ED_{50} (μmol Kg^{-1})
capsaicin	0.30 ± 0.04	0.26 ± 0.06	15.0
4a	0.55 ± 0.08	0.40 ± 0.10	5.0
15b	9.48 ± 1.05	3.40 ± 1.45	>50.0
15c	1.96 ± 0.51	1.80 ± 0.53	>50.0
15d	0.18 ± 0.02	0.18 ± 0.05	12.5
15e	0.29 ± 0.03	0.10 ± 0.03	15.0
15f	0.06 ± 0.01	0.06 ± 0.01	3.2

Table III. $^{45}Ca^{2+}$ Influx Activity of a Series of 4-Chlorophenyl Substituted Derivatives

	structure[a]	Ca^{2+} influx EC_{50} (μM)
6b		1.24 ± 0.11
6c		50.1 ± 0.1
8b		3.09 ± 0.07
10		7.77 ± 1.07
12		4.10 ± 0.25
13		0.66 ± 0.07

[a] A = 3-methoxy-4-hydroxybenzyl, R = 4-chlorophenyl.

the *overall* size or the hydrophobicity (or both) are more important than the double bond and the branched side chain. For simplicity the octyl side chain has been used as the prototype throughout this work. The importance of size and hydrophobicity is also emphasized by the lack of activity shown by compounds with short side chains (**4l, 4m, 15a, 15b**), with long *polar* side chains (**4f, 4g, 4n**), with polar functional groups attached to the end of hydrophobic chains (**4b, 4c, 4e**), and with longer hydrophobic chains (**4i, 15j, 15k**). However two compounds possessing long aliphatic monounsaturated side chains (**4j** and **4k**) are active in the *in vitro* and *in vivo* assays. We have no explanation for this apparent anomaly. One of these compounds, **4k** (Olvanil) has been extensively investigated as an analgesic agent for local application.[8]

The results discussed above support the existence of a hydrophobic binding site of a limited size which can accommodate the C-region of the capsaicin molecule. In an attempt to delineate this site more clearly, we have investigated the activity of compounds containing substituted aromatic rings in the C-region. In contrast to indications from the early literature,[3] it is clear from the data shown in Table I that aromatic substituents can be accommodated in this putative binding site, although the mode of attachment to the "B-region" unit is critical. This is exemplified by compounds **6–13**, shown in Table I. In particular, the subset of *p*-chlorophenyl-substituted compounds shown in Table III suggest that a constrained, linear, extended conformation of a two-carbon spacer unit is optimal (high potency of **6b** and **12**). Conformationally flexible analogues (**8b** and the bioequivalent "reverse" amide **13**; see paper 2 of this series) can be accommodated well by this model, whereas the shorter chain length analogue **10** is accepted less well, and the *cis*-constrained isomer **6c** is accepted poorly.

Comparison of the dehydro series exemplified by **6b** in Table III with the saturated series (**8b**) shows that the former is more potent (cf **6a** vs **8a**, **6b** vs **8b**, and **6d** vs **8c**)

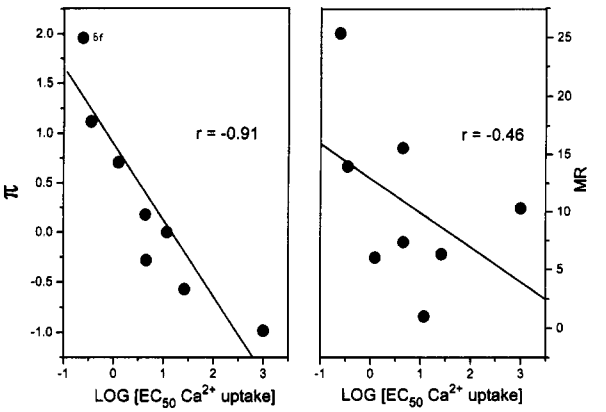
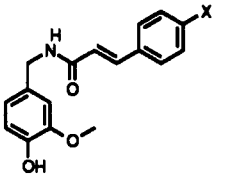


Figure 1. Graphs of data from Table IV: (1) hydrophobic substituent constant, π, values plotted against log EC_{50} values from the $^{45}Ca^{2+}$ influx assay and (2) molar refractivity (MR) values plotted against log EC_{50} values from the $^{45}Ca^{2+}$ influx assay.

Table IV. $^{45}Ca^{2+}$ Influx Activity, Hydrophobic Substituent Constants, and Molar Refractivity Values for a Series of *N*-(4-Hydroxy-3-methoxybenzyl)-(*E*)-3-(4-substituted phenyl)propenamides



compd	X	Ca^{2+} influx EC_{50} (μM)	π[a]	MR[a]
6a	H	11.8 ± 1.9	0	1.03
6b	Cl	1.24 ± 0.11	0.71	6.03
6d	NO_2	4.58 ± 0.29	−0.28	7.36
6e	CN	26.50 ± 5.87	−0.57	6.33
6f	C_6H_5	0.24 ± 0.03	1.96	25.36
6g	$N(CH_3)_2$	4.39 ± 0.67	0.18	15.55
6h	I	0.35 ± 0.05	1.12	13.94
6i	NHCHO	1000	−0.98	10.31

[a] Reference 9.

and consequently a more extensive study has been carried out on the *trans*-alkene analogues **6a,b,d-k**.

Variation of the para-substituent on the aromatic ring (in **6a**, **6b**, and **6d-i**) shows that a very good correlation exists ($r = 0.91$, $P < 0.01$) between potency in the $^{45}Ca^{2+}$ uptake assay and the value of the hydrophobic substituent constant π[9] (Figure 1). The substituents were chosen in an attempt to remove any covariance between the hydrophobic parameter (π) and steric parameter (exemplified here by the molar refractivity MR[9]). It appears from the poor correlation of MR with agonist activity ($r = 0.46$, $P > 0.1$; see Table IV and Figure 1) that the steric bulk of these relatively small functional groups is not an important controlling factor *in this series*.

Compounds **6f** (X = *p*-Ph) and **6h** (X = *p*-I) were synthesized to test the hypothesis that increasing the hydrophobicity of the para-substituent would increase activity. While **6h** falls well onto the correlation line, the *p*-phenyl-substituted compound **6f** is less active than the hypothesis would predict (see Figure 1). However, this compound is poorly soluble in water and it is likely that the measured EC_{50} value is an overestimate, as the material at this nominal concentration is not completely in solution.

These data further support the existence of a hydrophobic binding site. More information about the *size* of this site has been obtained from the thiourea series (**15**). It has been established (from data in paper 2 of this series

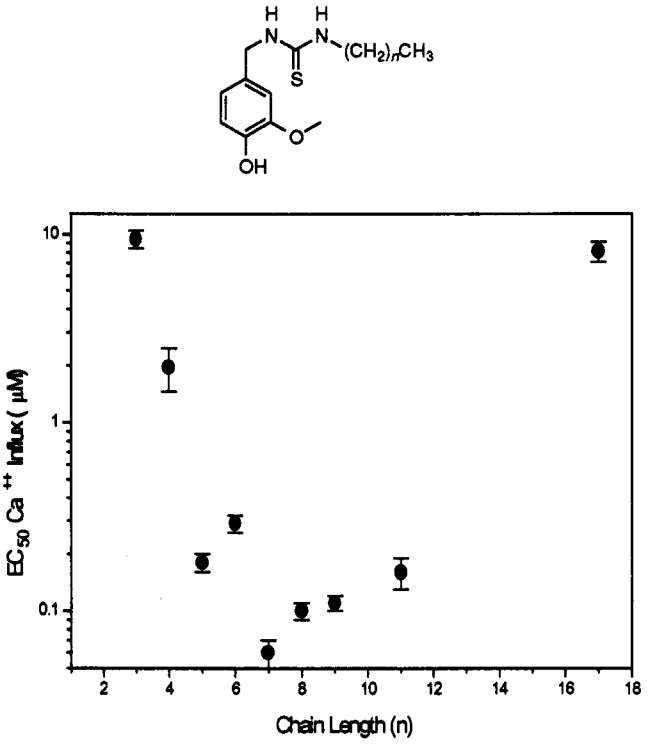


Figure 2. Graph of log EC_{50} values from the $^{45}Ca^{2+}$ influx assay against side-chain length (n) in a series of thioureas (**15**).

and in a forthcoming publication) that the thiourea moiety is the most potent B-region recognition function and we have used this series also to investigate the binding requirements in the C-region.

From the data provided in Table I and plotted in Figure 2 it is clear that potency increases with increasing chain length for the series **15a–k** to a plateau at a chain length of 8–12 carbon atoms. Compounds with longer chain lengths are poorly active or inactive.

Because there are no convenient hydrophobic substituent parameters for these polymethylene alkyl side chains, we have attempted to use reverse-phase HPLC[10,11] to obtain a measure of the contribution of these alkyl substituents to the overall hydrophobicity of the molecule. By the use of the classical shake-flask technique,[12] the measurement of log P values of a subset of the thioureas (**15b–g**) has enabled calibration of the HPLC method for assessing hydrophobicity. From the data plotted in Figure 3 it appears that HPLC retention time is a good linear indicator of hydrophobicity (as measured by log P) of this series of molecules and that the hydrophobicity of the whole molecule increases in a linear manner with increasing side-chain length. At side-chain lengths of greater than C_9 the shake-flask method becomes impracticable because of very low aqueous solubility. However, the correlation between chain length and retention time remains linear (data not shown).

From the data reported above (Figure 1) on the substituted phenylpropenamides **6** we have established that there is a correlation of activity with hydrophobicity (π) but not with molecular size (MR). If the assumption is made that the propenamides **6** and the aliphatic thioureas **15** bind at the same site (C-region) it appears that the molecular size of the side-chain substituent is not a controlling factor on activity up to a certain size (i.e., not unreasonably, the binding site has a finite size). This is illustrated by the data presented in Figure 2, where the potency of the thioureas increases with increasing chain

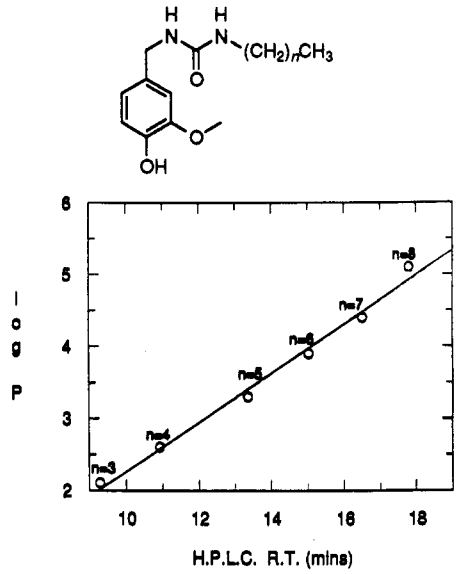


Figure 3. Graph of partition coefficients (log P) against HPLC retention times for a series of thioureas (**15**).

length up to approximately 12 carbon atoms but then decreases with even longer (n = 15, 17) side chains. The fact that the activities of the compounds which are smaller than this size appear to asymptote to this limit may simply reflect the increasing difficulty of fitting a substituent approaching the size limit. A more meaningful estimate of the "size" of this hydrophobic binding site can be presented in terms of molar refractivity, MR. The dodecyl side chain has a MR of 57.[9] In this context it is of interest that the relatively potent benzhydrylthiourea **15n**, which has a nominal aliphatic polymethylene "chain length" of 6.5 from its HPLC retention time (from Figure 3), fits well onto the curve in Figure 2. The molar refractivity of the benzhydryl substituent is 54, i.e., just below the size limit for the binding site. From these considerations it is possible to make an estimate of the properties of a substituent which should bind optimally to the C-region binding site. It is expected that small, hydrophobic substituents will confer high potency.

Exploitation of these findings will be the subject of a publication in preparation which attempts to combine the information gained from these systematic studies of the three (A, B, C) regions of the prototype capsaicin molecule, in order to produce compounds which exhibit higher *in vitro* potencies. It is anticipated that this approach will lead to novel analgesic agents.

Experimental Section

General Information. Melting points were determined using a Reichert hot-stage microscope and are uncorrected. Routine NMR spectra were recorded using a Hitachi Perkin-Elmer R12B machine. High-field spectra were recorded using Varian VX400 400 MHz (University College London Chemistry Department) and Bruker AM 360 360-MHz (Sandoz, Basle, Switzerland) instruments. All spectra were recorded using tetramethylsilane (TMS) as an internal standard and chemical shifts are reported in parts per million (δ) downfield from TMS. Coupling constants are reported in hertz. A Perkin-Elmer 781 machine was used to record IR spectra. Elemental analyses were performed by the Analytical Department of University College London and were within 0.4% of the theoretical values unless otherwise indicated. Mass spectra were recorded by the Mass Spectrometry Department of University College London, using a VG 7070F/H spectrometer, and FAB spectra were recorded in Sandoz (Basle, Switzerland), using a VG 70-SE spectrometer. TLC was per-

formed using Merck Kieselgel 60 F_{254} silica plates or Merck aluminium oxide 60 F_{254} plates and components were visualized using UV light and iodine vapor. HPLC was performed using a Waters 600 system (μ-Bondapak C-18 column (RP_{18}), using CH_3CN/0.1% aqueous TFA gradients of compositions stated in the text). Compounds were purified by flash column chromatography[13] using Merck Kieselgel 60 (230–400 mesh) or Merck neutral aluminium oxide (70–230 mesh) unless otherwise indicated. Solvents were HPLC grade and were used without further purification. Solvents were dried according to the standard procedures.[14] Test compounds were homogeneous by TLC or HPLC unless otherwise stated. Chemical yields were not optimized.

N-(4-Hydroxy-3-methoxybenzyl)-6-(*tert*-butoxycarboxamido)hexanamide (4b). Boc-ϵ-Aminocaproic acid *N*-hydroxysuccinimide ester (1 g, 3.05 mmol) was dissolved in dry DMF (5 mL) and stirred on ice, under N_2.

4-(2-ethoxyethoxy)-3-methoxybenzylamine[1] (0.7 g, 3.1 mmol), as a solution in DMF (3 mL), was slowly added. The reaction was stirred overnight before the removal of solvent *in vacuo*. The residue was redissolved in CH_2Cl_2 and washed with H_2O. The organic layer was evaporated *in vacuo* to leave a colorless oil, which was redissolved in THF (10 mL). 2 N HCl (1 mL) was added to the stirred solution. After 10 min of stirring, the solvent was again removed *in vacuo* and the residue partitioned between CH_2Cl and water. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a colorless solid which was recrystallized from petroleum ether (bp 100–120 °C)/EtOAc to give white crystals (0.8 g, 72%); mp 52–56 °C; TLC (silica, CH_2Cl_2/MeOH 5:1) R_f 0.7; ^{1}H NMR [$CDCl_3$, 60 MHz] δ 1–1.6 (15H, env, alkyl CH_2 and BOC CH_3), 2.2 (2H, t, $COCH_2CH_2$), 3.1 (2H, d of t, CH_2CH_2NH), 3.85 (3H, s, $ArOCH_3$), 4.35 (2H, d, $ArCH_2NH$), 4.6 (1H, br s, NH), 5.9 (1H, br s NH), 6.8 (3H, m, ArH); MS *m/e* 366 (M^+). Anal. ($C_{19}H_{30}N_2O_5$) C, H, N.

N-(4-Hydroxy-3-methoxybenzyl)-6-aminohexanamide Trifluoroacetate (4c). *N*-(4-Hydroxy-3-methoxybenzyl)-6-(*tert*-butoxycarboxamido)hexanamide (0.55 g, 1.5 mmol) was dissolved in distilled trifluoroacetic acid (1 mL) and stirred at room temperature for 1 h. After this time, the TFA was removed *in vacuo* to leave a colorless oil which was left under high vacuum overnight to remove traces of TFA (0.38 g, 98%): TLC (silica, CH_2Cl_2/MeOH 5:1) R_f 0.13 (ninhydrin); ^{1}H NMR (D_2O, 60 MHz) δ 1–1.7 (6H, env, alkyl CH_2), 2.1 (2H, t, $COCH_2$), 2.8 (2H, t, $CH_2CH_2ND_3^+$), 3.6 (3H, s, $ArOCH_3$), 4.03 (2H, s, $ArCH_2NDCO$), 4.95 (1H, s, ArOH), 6.7 (3H, m, ArH); MS *m/e* 266 (M^+); HRMS *m/e* calcd for $C_{14}H_{22}N_2O_3$ 266.1631, found 266.1608; HPLC RP_{18} (gradient 10–50% MeCN/0.1% aqueous TFA) 98% pure.

N-(4-Hydroxy-3-methoxybenzyl)-11-carbomethoxyundecanamide. This compound was prepared by the method described for **8a**[7] (see supplementary material). 11-carbomethoxyundecanoyl chloride (100% unpurified) and *N*-[4-(2-ethoxyethoxy)-3-methoxybenzyl]-11-carbomethoxyundecanamide were intermediates. The product from the final deprotection reaction was an oil which crystallized on standing (58% yield): TLC (silica, CH_2Cl_2/MeOH 10:1) R_f 0.33; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.2 (16H, env, alkyl CH_2), 2.2 (4H, 2 × overlapping t, CH_2CH_2CONH, $CH_2CH_2COOCH_3$), 3.7 (3H, s, ester OCH_3), 3.9 (3H, s, $ArOCH_3$), 4.2 (2H, d, $ArCH_2NH$), 5.3 (1H, br s, ArOH), 5.4 (1H, br t, NH), 6.8 (3H, m, ArH).

N-(4-Hydroxy-3-methoxybenzyl)-11-carboxyundecanamide (4e). *N*-(4-Hydroxy-3-methoxybenzyl)-11-carbomethoxyundecanamide (40 mg, 0.11 mmol) was dissolved in MeOH (2 mL) and to this was added 5N NaOH (0.5 mL, 2.5 mmol). The solution was stirred at room temperature for 2 h, after which time no starting material was present by TLC. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and water (20 mL). The aqueous layer was separated and acidified to approximately pH 1, precipitating a white solid. The solid was collected by filtration and dried *in vacuo* to give colorless crystals (30 mg, 78%): mp 103–105 °C; TLC (silica, CH_2Cl_2/MeOH 10:1) R_f 0.09; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.3 (16 H, env, alkyl CH_2), 2.25, 2.35 (4H, 2 × overlapping t, CH_2CH_2CONH, CH_2CH_2COOH), 3.9 (3H, s, $ArOCH_3$), 4.35 (2H, d, $ArCH_2NH$), 6.0 (1H, br t, NH), 6.7–7.0 (3H, m, ArH); MS *m/e* 365 (M^+). Anal. ($C_{20}H_{31}NO_5 \cdot 0.3H_2O$) C, H, N.

N-(4-Hydroxy-3-methoxybenzyl)-3,6-dioxaheptanamide (4f). 3,6-Dioxaheptanoic acid (2 g, 14.9 mmol) was dissolved in dry DMF (20 mL), *N*-methylmorpholine (1.5 g, 14.9 mmol) was added, and the mixture was stirred, under N_2 at −15 °C. Isobutyl chloroformate (2.2 g, 16.1 mmol) was slowly added such that the temperature did not exceed −10 °C. The mixture was stirred for 5 min before the slow addition of 4-(2-ethoxyethoxy)-3-methoxybenzylamine[1] (3.35 g, 14.9 mmol) in solution in DMF (5 mL). The reaction was stirred at room temperature overnight before removal of the solvent *in vacuo*. The residue was redissolved in THF (100 mL), 1 N HCl (5 mL) was added, and the reaction was stirred for 5 min. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica, EtOAc) to give a colorless oil on removal of the solvent (1.9 g, 47%): TLC (silica, CH_2Cl_2/MeOH 25:1) R_f 0.14; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.25 (3H, s, $CH_2CH_2OCH_3$), 3.48–3.8 (4H, m, OCH_2CH_2O), 3.82 (3H, s, $ArOCH_3$)4.05 (2H, s, $COCH_2O$), 4.4 (2H, d, $ArCH_2NH$), 6.8–6.85 (3H, m, ArH), 7.05 (1H, br s, ArOH), 7.5 (1H, br t, amide NH); MS *m/e* 269 (M^+); HRMS, *m/e* calcd for $C_{13}H_{19}NO_5$ 269.1263, found 269.1279; HPLC RP_{18} (gradient 10–50% MeCN/0.1% aqueous TFA) >99% pure.

N-(4-Hydroxy-3-methoxybenzyl)-3,6-9-trioxadecanamide (4g). This compound was prepared by the method described for **4f** and was purified by flash column chromatography (silica, CH_2Cl_2/MeOH 35:1) to give a colorless oil on removal of the solvent *in vacuo*: 54% yield; TLC (silica, CH_2Cl_2/MeOH 25:1) R_f 0.17; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.3 (3H, s, $CH_2CH_2OCH_3$), 3.5–3.75 (8H, m, 2 × OCH_2CH_2O), 3.86 (3H, s, $ArOCH_3$), 4.05 (2H, s, $COCH_2O$), 4.4 (2H, d, $ArCH_2NH$), 5.95 (1H, br s, ArOH), 6.9–7.0 (3H, m, ArH), 7.3 (1H, br t, amide NH); MS *m/e* 313 (M^+); HRMS, *m/e* calcd for $C_{15}H_{23}NO_6$ 313.1525, found 313.1515; HPLC RP_{18} (gradient 10–50% MeCN/0.1% aqueous TFA) >99% pure.

N-[4-(2-ethoxyethoxy)-3-methoxybenzyl]-11-(*tert*-butoxycarboxamido)undecanamide. 11-(*tert*-butoxycarboxamido)undecanoic acid[15] (4 g, 13 mmol) and 4-(2-ethoxyethoxy)-3-methoxybenzylamine (3 g, 13 mmol) were dissolved in dry CH_2Cl_2 (50 mL), and the solution was stirred on ice, under N_2. DCCI (2.95 g, 14.3 mmol), in CH_2Cl_2 (10 mL), was added and the mixture stirred overnight. After this time the precipitate was removed by filtration and the solvent was removed *in vacuo*. The residual oil was redissolved in diethyl ether and the precipitate again removed by filtration. The ether solution was cooled to 0 °C, causing a white compound to crystallize. The crystals were collected by filtration and air-dried: yield 5.1 g (75%); TLC (silica, cyclohexane/EtOAc 1:1) R_f 0.19; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 1.15 (3H, t, OCH_2CH_3), 1.3 (16H, env, alkyl CH_2), 1.4 (3H, d, $CH_3CH(OC_2H_5)$) overlapping 1.45 (9H, s, Boc 3 × CH_3), 2.2 (2H, t, CH_2CH_2CO), 3.2 (2H, d of t, CH_2CH_2NH), 3.7 (2H, q, OCH_2CH_3), 3.9 (3H, s, $ArOCH_3$), 4.4 (2H, d, $ArCH_2NH$), 4.5 (1H, br s, NH), 5.5 (1H, q, $CH_3CH(OR)OC_2H_5$), 6.0 (1H, br s, NH), 6.9 (3H, m, ArH).

N-(4-Hydroxy-3-methoxybenzyl)-11-aminoundecanamide Trifluoroacetate (4h). *N*-[4-(2-ethoxyethoxy)-3-methoxybenzyl]-11-(*tert*-butoxycarboxamido)undecanamide (1 g, 2 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and stirred on ice, under N_2. TFA (5 mL, 66 mmol) was added and the mixture was stirred for 30 min, after which time no starting material remained by TLC. The solvent was removed *in vacuo*, leaving a colorless oil which was purified by flash column chromatography (silica, CH_2Cl_2/MeOH 10:1, then MeOH). The pure fractions were evaporated *in vacuo* to give a colorless oil: 0.85 g (97%); TLC (silica, CH_2Cl_2/MeOH 5:1, ninhydrin) R_f 0.11.

N-(4-Hydroxy-3-methoxybenzyl)-11-(3,6,9-trioxadecanamido)undecanamide (4n). 3,6,9-Trioxadecanoic acid (0.4 g, 2.2 mmol) was dissolved in dry DMF (10 mL) and *N*-methylmorpholine (0.22 g, 2.2 mmol) was added. The solution was stirred, under N_2, at −15 °C while isobutyl chloroformate (0.3 g, 2.4 mmol) in DMF was slowly added. After 5 min of stirring, **4h** (1 g, 2.2 mmol) was added, in DMF (1 mL), together with *N*-methylmorpholine (0.25 g, 2.5 mmol). The reaction mixture was stirred overnight before removal of the solvent *in vacuo*. The crude product was purified by flash column chromatography (silica, CH_2Cl_2/MeOH 25:1) to give a colorless oil: yield 0.3 g (27%); TLC (silica, CH_2Cl_2/MeOH 10:1) R_f 0.42; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (12H, env, alkyl CH_3), 1.5 (2H, m, $COCH_2CH_2$), 1.65 (2H, m, $NHCH_2CH_2$), 2.2 (2H, t, $COCH_2CH_2$), 3.28 (2H, d

of t, CH_2CH_2NH), 3.39 (3H, s, OCH_3), 3.57–3.66 (8H, m, 2 × OCH_2CH_2O), 3.87 (3H, s, $ArOCH_3$), 3.98 (2H, s, $COCH_2O$), 4.36 (2H, d, $ArCH_2NH$), 5.31 (1H, s, ArOH), 5.86 (1H, br t, amide NH), 6.75 (1H, d of d, J = 2 Hz, J′ = 8 Hz, ArH_6), 6.80 (1H, d, J = 2 Hz, ArH_2), 6.86 (1H, d, J′ = 8 Hz, ArH_5), 7.05 (1H, br t, amide NH); MS *m/e* 496 (M^+); HRMS *m/e* calcd for $C_{26}H_{44}N_2O_7$ 496.3150, found 496.3207; HPLC RP_{18} (gradient 10–50% MeCN/0.1% aqueous TFA) >95% pure.

***N*-(4-Hydroxy-3-methoxybenzyl)-(*E*)-3-(4-chlorophenyl)-propenamide (6b).** This compound was prepared from 4-chlorocinnamic acid in three steps by a method similar to that described for **8a**[7] (see supplementary material). 4-Chlorocinnamoyl chloride (98% without purification) and *N*-[4-(2-ethoxyethoxy)-3-methoxybenzyl]-(*E*)-3-(4-chlorophenyl)propenamide (33% after recrystallization from EtOAc) were intermediates. The crude product from the final deprotection step was recrystallized from EtOAc to yield fine, colorless needles (400 mg, 97%): mp 151–153 °C; TLC (silica, $CHCl_3$/MeOH 5:1) R_f 0.58; ^1H NMR (DMSO-d_6, 60 MHz) δ 3.75 (3H, s, $ArOCH_3$), 4.3 (2H, d, CH_2NH), 6.6 (1H, d, J = 15 Hz, *trans* $COCH$=CH), 6.7–6.9 (3H, m, vanillyl ArH), 7.45 (1H, d, J = 15 Hz, *trans* COCH=CH), 7.5–7.6 (4H, m, 4-Cl-phenyl ArH), 8.2–8.6 (1H, broad t, NH), 8.8 (1H, s, ArOH); MS *m/e* 317 (M^+). Anal. ($C_{17}H_{16}NO_3Cl·H_2O$) C, H, N, Cl.

***N*-(4-Hydroxy-3-methoxybenzyl)-(*Z*)-3-(4-chlorophenyl)-propenamide (6c).** A solution of 4-chlorocinnamic acid (400 mg) in MeOH (25 mL) was irradiated for 24 h with UV light (λ = 254 nm). Removal of the solvent *in vacuo* yielded a white crystalline material consisting of a mixture of *Z* and *E* isomers in a 1:3 ratio (by NMR). The mixed (*Z*)- and (*E*)-cinnamic acids (0.39 g, 2.14 mmol) were dissolved in dry DMF (15 mL) and cooled to −15 °C. *N*-Methylmorpholine (0.22 g, 2.1 mmol) was added, followed by the slow addition of isobutyl chloroformate (0.32 g, 2.3 mmol), the temperature being kept below −10 °C. The mixture was stirred for 10 min, after which time 4-(2-ethoxyethoxy)-3-methoxybenzylamine (0.48 g, 2.1 mmol) in dry DMF (1 mL) was slowly added and the mixture stirred for 2 h. Removal of the solvent *in vacuo* left a yellow oil, which was dissolved in EtOAc and washed with 1 M Na_2CO_3 and then dried over $MgSO_4$. The solvent was removed *in vacuo* to leave a pale yellow oil (0.8 g, 2 mmol) which was dissolved in THF (20 mL) and cooled on ice. 1 N HCl (3 mL) was then added and the mixture stirred under N_2 for 1 h, after which time the solution was neutralized with 1 N NaOH and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (silica, cyclohexane/EtOAc 2:3) to give a colorless oil: yield 150 mg (22%); TLC (silica, cyclohexane/EtOAc 2:3) R_f 0.26; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.83 (3H, s, $ArOCH_3$), 4.34 (2H, d, CH_2NH), 5.62–5.8 (2H, br s, NH, ArOH), 6.0 (1H, d, J = 12 Hz, *cis* $COCH$=CH), 6.65–6.72 (3H, m, vanillyl ArH), 6.83 (1H, d, J = 12 Hz, *cis* COCH=CH), 7.2–7.4 (4H, m, 4-Cl-Ph ArH); MS *m/e* 317 (M^+); HRMS, *m/e* calcd for $C_{17}H_{16}NO_3Cl$ 317.0819, found 317.0835; HPLC RP_{18} (gradient 10–50% MeCN/0.1% aqueous TFA) >99% pure.

***N*-(4-Hydroxy-3-methoxybenzyl)-(*E*)-3-(4-nitrophenyl)-propenamide (6d).** This compound was prepared from 4-nitrocinnamic acid in three steps by a method similar to that described for **8a**[7] (see supplementary material). 4-Nitrocinnamoyl chloride (83%) and N-[4-(2-ethoxyethoxy)-3-methoxybenzyl)-(*E*)-3-(4-nitrophenyl)propenamide (69% after recrystallization from EtOAc) were intermediates. The crude product from the subsequent deprotection step was crystallized from MeOH/petroleum ether (bp 100–120 °C) to give yellow crystals, 90% yield: mp 170–173 °C; TLC ($CHCl_3$/MeOH 5:1) R_f 0.55; ^1H NMR (DMSO-d_6, 60 MHz) δ 3.8 (3H, s, $ArOCH_3$), 4.35 (2H, d, CH_2NH), 6.8–7.0 (3H, m, vanillyl ArH), 6.9 (1H, d, J = 15 Hz, *trans* CH=CHPh), 7.65 (1H, d, J = 15 Hz, *trans* CH=CHPh), 7.8–8.4 (4H, m, ArH), 8.7 (1H, br t, NH), 8.9 (1H, br s, ArOH); MS *m/e* 328 (M^+). Anal. ($C_{17}H_{16}N_2O_5$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-(*E*)-3-(4-cyanophenyl)-propenamide (6e).** This compound was prepared from 4-cyanocinnamic acid by a method similar to that described for **8a**[7] (see supplementary material): yield 76% overall; mp 179–179 °C; TLC (silica, cyclohexane/EtOAc 1:1) R_f 0.08; ^1H NMR [DMSO-d_6, 60 MHz] δ 3.83 (3H, s, $ArOCH_3$), 4.35 (2H, d, J = 6 Hz, CH_2NH), 6.8–6.98 (3H, m, vanillyl ArH) overlapping (1H, d, J = 15 Hz, *trans* CH=CHPh) 7.65 (1H, d, J = 15 Hz, *trans* CH=CHPh), 7.8 (4H, s, ArH), 8.1 (1H, br s, amide NH); FAB MS *m/e* 309 (M + 1$^+$). Anal. ($C_{18}H_{16}N_2O_3$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-(*E*)-3-(4-phenylphenyl)-propenamide (6f).** This compound was prepared by the method described for **8a**[7] (see supplementary material). 4-Phenylcinnamoyl chloride (98% unpurified) and N-[4-(2-ethoxyethoxy)-3-methoxybenzyl)-(*E*)-3-(4-phenylphenyl)propenamide (94%) were intermediates. The final deprotection step gave a white solid which was recrystallized from MeOH to give colorless crystals (43% yield): mp 200–203 °C; TLC (cyclohexane/EtOAc 1:1) R_f 0.2; ^1H NMR (DMSO-d_6, 60 MHz) δ 3.8 (3H, s, $ArOCH_3$), 4.35 (2H, d, J = 6 Hz, CH_2NH), 6.8 (1H, d, J = 15 Hz, *trans* CH=CHPh), 6.8–7.8 (12H, m, ArH), 7.65 (1H, d, J = 15 Hz, *trans* CH=CHPh), 8.5 (1H, t, J = 6 Hz, NH), 8.85 (1H, s, ArOH); MS *m/e* 359 (M^+). Anal. ($C_{23}H_{21}NO_3$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-(*E*)-3-[4-(dimethylamino)phenyl]propenamide (6g).** A solution of DCCI (3.55 g, 17 mmol) in CH_2Cl_2 (20 mL) was slowly added to an ice-cooled mixture of 4-(2-ethoxyethoxy)-3-methoxybenzylamine[1] (3.53 g, 16 mmol) and 4-(dimethylamino)cinnamic acid (3.0 g, 16 mmol) in CH_2Cl_2 (20 mL) and the mixture stirred overnight under N_2. The resulting precipitate of DCU was filtered off and washed with acetone and the filtrate evaporated *in vacuo* to yield a yellow solid (3.2 g, 47%). The solid (2 g, 5 mmol), in THF (10 mL), was deprotected without further purification by the addition of 1 N HCl (5 mL) with stirring on ice for 2 h. The solvent was removed *in vacuo* to yield a yellow solid which was dried and recrystallized from $CHCl_3$/petroleum ether (bp 80–100 °C) to give pale yellow crystals (0.3 g, 5% overall): mp 168–171 °C; TLC (silica, cyclohexane/EtOAc 1:2) R_f 0.3; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.0 (6H, s, $N(CH_3)_2$), 3.85 (3H, $ArOCH_3$), 4.45 (2H, d, $ArCH_2NH$), 5.2 (1H, br s, ArOH), 5.95 (1H, d, J = 15 Hz, $COCH$=CHAr), 6.45 (1H, d, J = 15 Hz, CH=CHAr), 6.55–7.75 (7H, m, ArH), 7.3 (1H, br t, CH_2NH); MS *m/e* 326 (M^+). Anal. ($C_{19}H_{22}N_2O_3$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-(*E*)-3-(4-iodophenyl)-propenamide (6h).** This compound was prepared by the method described for **8a**[7] (see supplementary material). 4-Iodocinnamoyl chloride (100% unpurified) and *N*-[4-(2-ethoxyethoxy)-3-methoxybenzyl]-(*E*)-3-(4-iodophenyl)propenamide (95%) were intermediates. The final deprotection step gave an off-white solid which was recrystallized from EtOAc to give colorless crystals (90% yield): mp 171–173 °C; TLC (silica, $CHCl_3$/MeOH 5:1) R_f 0.57; ^1H NMR (DMSO-d_6, 60 MHz) δ 3.75 (3H, s, $ArOCH_3$), 4.3 (2H, d, J = 6 Hz, CH_2NH), 6.7 (1H, d, J = 15 Hz, *trans* CH=CHPh), 6.75–6.95 (3H, m, ArH), 7.35–7.75 (4H, m, Ar(I)-H), 7.45 (1H, d, J = 15 Hz, *trans* CH=CHPh), 8.45 (1H, br t, NH), 8.8 (1H, s, ArOH); MS *m/e* 409 (M^+). Anal. ($C_{17}H_{16}NO_3$) C, H, N.

***N*-(4-hydroxy-3-methoxybenzyl)-(*E*)-3-(4-formamidophenyl)propenamide (6i).** This compound was prepared as described for **4f** and the crude product from the final deprotection reaction was purified by recrystallization from MeOH/H_2O to give a cream-colored, crystalline product (0.1 g, 8%): mp 180 °C dec; TLC ($CHCl_3$/MeOH 5:1) R_f 0.46; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.75 (3H, s, $ArOCH_3$), 4.28 (2H, d, $ArCH_2NHCO$), 6.6 (1H, d, J = 16 Hz, *trans* CO-CH=CH-Ph), 6.7–6.9 (3H, m, vanillyl-ArH), 7.2–7.7 (4H, m, ArH), 7.4 (1H, d, J = 16 Hz, *trans* CO-CH=CH-Ph), 8.3 (1H, d, ArNHCHO), 8.45 (1H, t, CONHCH_2), 8.85 (1H, s, ArOH), 10.35 (1H, br s, ArNHCHO); MS *m/e* 326 (M^+). Anal. ($C_{18}H_{18}N_2O_4$) C, H, N.

N-(4-Hydroxy-3-methoxybenzyl)-(*E*)-3-(2,4-dichlorophenyl)propenamide (6j). This compound was prepared as described for **4f** and the crude product from the final deprotection reaction recrystallized from EtOAc/petroleum ether to give colorless crystals (45%): mp 163–166 °C; TLC (cyclohexane/EtOAc 1:1) R_f 0.18; ^1H NMR (DMSO-d_6, 60 MHz) δ 3.85 (3H, s, $ArOCH_3$), 4.4 (2H, d, $ArCH_2NHCO$), 6.75–7.9 (6H, m, ArH), 6.85 (1H, d, J = 16.8 Hz, *trans* CO-CH=CH-Ph), 7.85 (1H, d, J = 16.8 Hz, *trans* CO-CH=CH-Ph), 8.7 (1H, t, NH), 8.95 (1H, s, ArOH); MS *m/e* 351 (M^+). Anal. ($C_{17}H_{15}NO_3Cl_2$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-(*E*)-3-(3-chlorophenyl)-propenamide (6k).** This compound was prepared as described for **8a**[7] (see supplementary material) and the crude product from the deprotection step was recrystallized from EtOAc/petroleum ether (100–120 °C) to give colorless crystals (82%); mp 171–173

°C; TLC (cyclohexane/EtOAc 1:1) R_f 0.23; ^{1}H NMR (DMSO-d_6, 60 MHz) δ 3.8 (3H, s, $ArOCH_3$), 4.35 (2H, d, CH_2NH), 6.8 (1H, d, J = 16 Hz, *trans* COCH=CHPh) 6.8–7.0 (3H, m, vanillyl ArH), 7.35–7.75 (3H, m, ArH), 7.55 (1H, d, J = 16 Hz, *trans* COCH=CHPh), 8.55 (1H, t, NH), 8.9 (1H, s, ArOH); MS *m/e* 317 (M^+). Anal. ($C_{17}H_{16}NO_3Cl$) C, H, N.

N-(4-Hydroxy-3-methoxybenzyl)-3-(4-chlorophenyl)propanamide (8b). *N*-(4-hydroxy-3-methoxybenzyl)-(*E*)-3-(4-chlorophenyl)propenamide (0.1 g, 0.3 mmol) was dissolved in dry MeOH (10 mL) and added to a suspension of 10% Pd/C (10 mg) in dry MeOH (10 mL), under a H_2 atmosphere, and stirred overnight at room temperature. The catalyst was removed by filtration and the solvent removed *in vacuo* to leave a clear oil which was recrystallized from EtOAc/petroleum ether and dried to give colorless needles: yield 0.065 g (68%); mp 97–99 °C; TLC ($CHCl_3$/MeOH 5:1) R_f 0.58; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 2.5 (2H, t, $COCH_2CH_2$), 2.95 (2H, t, $COCH_2CH_2Ar$), 3.82 (3H, s, $ArOCH_3$), 4.28 (2H, d, $ArCH_2NH$), 5.6–6.3 (2H, broad, ArOH, NH), 6.65–6.8 (3H, m, vanillyl ArH), 7.1–7.3 (4H, m, 4-Cl phenyl ArH); MS *m/e* 319 (M^+). Anal. ($C_{17}H_{18}NO_3Cl$) C, H, N.

***N*-(3-Methoxy-4-hydroxybenzyl)-3-(4-acetoxyphenyl)propanamide.** 4-Acetoxyphenylpropanoic acid and 4-(2-ethoxyethoxy)-3-methoxybenzylamine[1] were condensed using the isobutyl chloroformate method (38% yield) and deprotected using 1 N HCl in THF (98%) as described for **4f**: TLC (alumina, CH_2Cl_2/MeOH 5:1) R_f 0.72; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 2.25 (3H, s, $COCH_3$), 2.48 (2H, t, $COCH_2CH_2$), 2.98 (2H, t, CH_2CH_2Ar), 3.8 (3H, s, $ArOCH_3$), 4.3 (2H, d, CH_2NH), 5.75–6.05 (1H, br s, NH), 6.65–7.3 (7H, m, ArH).

***N*-(3-Methoxy-4-hydroxybenzyl)-3-(4-hydroxyphenyl)propionamide (8e).** *N*-(3-Methoxy-4-hydroxybenzyl)-3-(4-acetoxyphenyl)propionamide (2.6 g, 7.6 mmol) was dissolved in MeOH (100 mL) and added to a suspension of $NaHCO_3$ (6.5 g, 77 mmol) in 50% MeOH/H_2O (30 mL) and the reaction stirred under N_2 overnight. 1 N HCl was added until no more frothing occurred and the product came out of solution as a white precipitate. This was collected by filtration, and the filtrate and reaction mixture were extracted with CH_2Cl_2, the phases were separated, and the organic phase was washed with 1 N HCl and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the precipitate and the extracts were combined and recrystallized from EtOAc/petroleum ether (bp 100–120 °C) to give colorless crystals (2.1 g, 92%): mp 125–127 °C; TLC (alumina, CH_2Cl_2/MeOH 5:1) R_f 0.58; ^{1}H NMR (DMSO-d_6, 60 MHz) δ 2.45 (2H, t, $COCH_2CH_2$) 2.62 (2H, t, $COCH_2CH_2$), 3.72 (3H, s, $ArOCH_3$), 4.15 (2H, d, CH_2NH), 6.55–7.15 (7H, m, ArH), 8.15 (1H, broad t, NH), 8.95 (2H, broad, 2 × ArOH); MS *m/e* 301 (M^+). Anal. ($C_{17}H_{19}NO_4$) C, H, N.

3-(4-Azidophenyl)propanoic Acid. 3-(4-Aminophenyl)propanoic acid (3 g, 18 mmol) was dissolved in 6 N H_2SO_4 (18 mL) and stirred on ice. A solution of sodium nitrite (1.24 g, 18 mmol) in water (10 mL) was slowly added, the temperature not being allowed to exceed 5 °C. A solution of sodium azide (1.6 g, 24 mmol) in water (10 mL) was then added, dropwise. The frothy suspension gradually precipitated a cream-colored solid which was collected by filtration and washed with cold water and then diethyl ether. The solid was dried *in vacuo* to give a cream solid (2.9 g, 86%); IR (Nujol) ν 2600–2900 (br, CO_2H), 2100 (m, N_3), 1700 (s, CO) cm^{-1}.

4-Azidophenylpropanoic Acid *N*-Hydroxysuccinimide Ester. 3-(4-Azidophenyl)propanoic acid (2 g, 10.5 mmol) was dissolved in dry CH_2Cl_2 (100 mL), and N-hydroxysuccinimide (1.2 g, 10.5 mmol) was added and the solution was stirred, on ice, under N_2. DCCI (2.3 g, 11.5 mmol) in CH_2Cl_2 (30 mL) was added and the solution stirred overnight. After this time the precipitate which had formed was removed by filtration and the solvent was removed *in vacuo*. The residue was dissolved in acetone and filtered again, the solvent was removed, and the residue was recrystallized from petroleum ether (bp 80–100 °C)/EtOAc to give beige crystals (2.2 g, 72%): TLC (silica, cyclohehane/EtOAc 1:1) R_f 0.4 (streaks); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 2.83 (4H, s, NHS ester 2 × CH_2), 2.85 (2H, t, $COCH_2CH_2$) 2.95 (2H, t, $COCH_2CH_2$), 7.1 (4H, m, ArH).

***N*-(3-Methoxy-4-hydroxybenzyl)-3-(4-azidophenyl)propanamide(8f).** 3-(4-Azidophenyl)propanoic acid *N*-hydroxysuccinimide ester (0.5 g, 1.7 mmol) was dissolved in dry DMF and stirred at room temperature, under N_2. 4-(2-Ethoxyethoxy)-3-methoxybenzylamine, in DMF (1 mL), was added and the reaction left stirring overnight. After this time water (100 mL) was added, the solution was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried over Na_2SO_4. The solvent was removed *in vacuo* to leave an oil which was deprotected without purification by dissolving the oil in THF (10 mL) and treatment with 1 N HCl (10 mL). The reaction mixture was stirred for 10 min before removal of the solvent *in vacuo* to leave a cream solid which was recrystallized from petroleum ether (bp 100–120 °C)/dioxane to give cream-colored needles (0.15 g, 25%): mp 105–110 °C; TLC (silica, cyclohexane/EtOAc 1:3) R_f 0.18 ^{1}H NMR ($CDCl_3$, 60 MHz) δ 2.55 (2H, t, $COCH_2CH_2$), 2.95 (2H, t, CH_2CH_2Ar), 3.85 (3H, s, $ArOCH_3$), 4.35 (2H, d, CH_2NH), 5.6 (2H, br s, ArOH, NH), 6.7–7.1 (7H, m, ArH); MS *m/e* 326 (M^+). Anal. ($C_{17}H_{18}N_4O_3$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-4-chlorophenylacetamide (10).** This compound was prepared as described for **8a**[7] (see supplementary material) and the crude product from the deprotection step was recrystallized from EtOAc/petroleum ether (bp 100–120 C) to give colorless crystals (10% overall): mp 128–130 °C; TLC ($CHCl_3$/MeOH 5:1) R_f 0.58; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.55 (2H, s, $COCH_2Ar$), 3.8 (3H, s, $ArOCH_3$), 4.3 (2H, d, CH_2NH), 5.7–6.2 (2H, br s, NH, ArOH), 6.7–6.8 (3H, m, vanillyl ArH), 7.25 (4H, m, ArH); MS *m/e* 305 (M^+). Anal. ($C_{16}H_{16}NO_3Cl$) C, H. N.

***N*-(4-Hydroxy-3-methoxybenzyl)-2-(4-chlorophenyl)ethynamide (12).** This compound was prepared as described for **8a**[7] (see supplementary material) and the crude product from the deprotection step was purified by flash column chromatography (silica, cyclohexane/EtOAc 1:1) and recrystallized twice from EtOAc/petroleum ether (100–120 °C) to give colorless crystals (11% overall yield): mp 117–119 °C; TLC (silica, cyclohexane/EtOAc 1:1) R_f 0.3; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.85 (3H, s, $ArOCH_3$), 4.45 (2H, d, CH_2NH), 6.0 (1H, br s, ArOH), 6.75 (1H, br t, NH), 6.85–7.0 (3H, m, vanillyl ArH), 7.2–7.6 (4H, m, ArH); MS *m/e* 315 (M^+). Anal. ($C_{17}H_{14}NO_3Cl$) C, H, N.

***N*-[2-(4-Chlorophenyl)ethyl]-4-hydroxy-3-methoxyphenylacetamide (13).** Acetylhomovanilloyl chloride was prepared from acetylhomovanillic acid and thionyl chloride as described for **8a**[7] (see supplementary material) and was obtained as a yellow oil (99% yield), which was dissolved in EtOAc and added to an ice-cooled solution of 2-(4-chlorophenyl)ethylamine (0.7 g, 4.5 mmol) and triethylamine (4.8 mmol) in EtOAc, with stirring. The mixture was stirred overnight under N_2 before addition of water and separation of the phases. The organic layer was washed with water, 0.2 N HCl, and saturated NaCl and dried over $MgSO_4$ before removal of the solvent *in vacuo*. A pale orange oil was obtained which was used without further purification. The compound (1.4 g, 4 mmol) was dissolved in MeOH (5 mL) and deprotected by stirring overnight with a suspension of K_2CO_3 (6 g, 40 mmol) in 50% MeOH/H_2O (25 mL). 2 N HCl was added until frothing no longer occurred, $CHCl_3$ was added and the phases were separated. The organic phase was washed with water and saturated NaCl and dried over Na_2SO_4. Removal of the solvent *in vacuo* and crystallization of the resulting oil from EtOAc/petroleum ether (bp 80–100 °C) yielded buff-colored crystals (0.35 g, 27%): mp 124–127 °C; TLC (EtOAc) R_f 0.3; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 2.65 (2H, t, J = 6 Hz, CH_2CH_2Ph), 3.3 (2H, t, J = 6 Hz, CH_2CH_2Ph), 3.4 (2H, s CH_2CO), 3.72 (3H, s, $ArOCH_3$), 5.9 (1H, br s, ArOH), 6.2 (1H, br s, NH), 6.65–7.3 (7H, m, ArH); MS *m/e* 319 (M^+). Anal. ($C_{17}H_{18}NO_3Cl$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)thiourea (15a).** 4-[(2-Ethoxy)ethoxy]-3-methoxybenzylamine[1] (1.5 g, 6.6 mmol) was stirred, on ice, in EtOAc during the addition of trityl isothiocyanate (2 g, 6.6 mmol) in EtOAc. The solution was stirred at room temperature for 18 h, after which time no starting materials remained by TLC, which showed one product spot (silica, CH_2Cl_2/MeOH, R_f 0.8). The solvent was removed *in vacuo* and the reaction mixture was redissolved in THF (50 mL). 1 N HCl (10 mL) was added to the stirred solution, on ice, and the mixture allowed to stir for 30 min before the removal of the solvents *in vacuo*. The cream-colored residue was recrystallized from EtOAc/MeOH to give white crystals (1.15, 81%): mp 138–142 °C; TLC (silica, CH_2Cl_2/MeOH 25:1) R_f 0.12: ^{1}H NMR (CD_3OD, 60 MHz)

δ 3.85 (3H, s, $ArOCH_3$), 4.55 (2H, s, $ArCH_2NH$), 6.8–6.9 (3H, m, ArH); MS *m/e* 212 (M^+). Anal. ($C_9H_{12}N_2O_2S \cdot 0.5H_2O$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-butylthiourea (15b).** This compound was prepared as described for **15f**[1] (see supplementary material) and was recrystallized from diisopropyl ether/EtOAc to give white crystals: 21% yield; mp 87–89 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.39; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.9 (3H, t, alkyl CH_3), 1.25 (4H, env, alkyl CH_2), 3.35 (2H, d of t, $NHCH_2CH_2$), 3.86 (3H, s, $ArOCH_3$), 4.54 (2H, d, $ArCH_2NH$), 5.70–6.2 (3H, br s, ArOH, 2 × thiourea NH), 6.85 (3H, m, ArH); MS *m/e* 268 (M^+). Anal. ($C_{13}H_{20}N_2O_2S$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-pentylthiourea (15c).** This compound was prepared as described for **15f**[1] and was purified by flash column chromatography (silica, cyclohexane/EtOAc 2:1) and then recrystallized from petroleum ether (bp 100–120 °C)/diisopropyl ether to give white crystals: 20% yield; mp 85–87 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.40; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.88 (3H, t, alkyl CH_3), 0.95–1.25 (6H, env, alkyl CH_2), 3.33 (2H, d of t, $NHCH_2CH_2$), 3.9 (3H, s, $ArOCH_3$), 4.55 (2H, d, $ArCH_2NH$), 5.60–6.6 (3H, br s, ArOH, 2 × thiourea NH), 6.88 (3H, m, ArH); MS *m/e* 282 (M^+). Anal. ($C_{14}H_{22}N_2O_2S$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-hexylthiourea (15d).** This compound was prepared as described for **15f**[1] (see supplementary material) and was recrystallized from petroleum ether (bp 100–120 °C)/diisopropyl ether to give white crystals: 52% yield; mp 87–89 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.41; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.9 (3H, t, alkyl CH_3), 1.24 (8H, env, alkyl CH_2), 3.33 (2H, d of t, $NHCH_2CH_2$), 3.90 (3H, s, $ArOCH_3$), 4.54 (2H, d, $ArCH_2NH$), 5.70–6.2 (3H, br s, ArOH, 2 × thiourea NH), 6.85 (3H, m, ArH); MS *m/e* 296 (M^+). Anal. ($C_{15}H_{24}N_2O_2S$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-heptylthiourea (15e).** This compound was prepared as described for **15f**[1] (see supplementary material) and was purified by flash column chromatography (silica, cyclohexane/EtOAc 2:1) and then recrystallized from petroleum ether (bp 100–120 °C)/diisopropyl ether to give white crystals: 3% yield; mp 92–94 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.42; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.88 (3H, t, alkyl CH_3), 1.25 (10H, env, alkyl CH_2), 3.36 (2H, d of t, $NHCH_2CH_2$), 3.88 (3H, s, $ArOCH_3$), 4.55 (2H, d, $ArCH_2NH$), 5.5–6.3 (3H, br s, ArOH, 2 × thiourea NH), 6.88 (3H, m, ArH); MS *m/e* 310 (M^+). Anal. ($C_{16}H_{26}N_2O_2S \cdot 0.15H_2O$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-nonylthiourea (15g).** This compound was prepared by the method described for **15f**[1] (see supplementary material) and was recrystallized from petroleum ether (bp 80–100 °C)/diisopropyl ether to give white crystals: 54% yield; mp 85–89 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) 0.44; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.9 (3H, t, alkyl CH_3), 1.25 (14H, env, alkyl CH_2), 3.35 (2H, m, $NHCH_2CH_2$), 3.87 (3H, s, $ArOCH_3$), 4.55 (2H, d, $ArCH_2NH$), 5.7 (1H, s, ArOH), 5.9 (1H, br s, thiourea NH), 6.1 (1H, br s, thiourea NH), 6.85 (3H, m, ArH); MS *m/e* 338 (M^+). Anal. ($C_{18}H_{30}N_2O_2S$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-decylthiourea (15h).** This compound was prepared as described for **15f**[1] (see supplementary material) and was recrystallized from petroleum ether (bp 80–100 °C)/diethyl ether to give white crystals: 27% yield; mp 81–82 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.45; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.9 (3H, t, alkyl CH_3), 1.25 (16H, env, alkyl CH_2), 3.35 (2H, d of t, $NHCH_2CH_2$), 3.90 (3H, s, $ArOCH_3$), 4.55 (2H, d, $ArCH_2NH$), 5.70 (1H, s, ArOH), 5.90 (1H, br s, thiourea NH), 6.20 (1H, br s, thiourea NH), 6.85 (3H, m, ArH); MS *m/e* 352 (M^+). Anal. ($C_{19}H_{32}N_2O_2S$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-dodecylthiourea (15i).** This compound was prepared as described for **15f**[1] (see supplementary material) and was recrystallized from petroleum ether (bp 80–100 °C) to give white crystals: 48% yield; mp 86–88 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.47; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.88 (3H, t, alkyl CH_3), 1.25 (20H, env, alkyl CH_2), 3.35 (2H, m, $NHCH_2CH_2$), 3.85 (3H, s, $ArOCH_3$), 4.50 (2H, d, $ArCH_2NH$), 5.5–6.2 (3H, br s, ArOH, 2 × thiourea NH), 6.81 (3H, m, ArH); MS *m/e* 380 (M^+). Anal. ($C_{21}H_{36}N_2O_2S$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-hexadecylthiourea (15j).** This compound was prepared as described for **15f**[1] (see supplementary material) and was recrystallized from petroleum ether (bp 100–120 °C)/diisopropyl ether to give white crystals: 54% yield; mp 97.5–98.5 C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.50; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.9 (3H, t, alkyl CH_3), 1.25 (28H, env, alkyl CH_2), 3.4 (2H, d of t, $NHCH_2CH_2$), 3.9 (3H, s, $ArOCH_3$), 4.57 (2H, d, $ArCH_2NH$), 5.7–6.3 (3H, br s, ArOH, 2 × thiourea NH), 6.88 (3H, m, ArH); MS *m/e* 436 (M^+). Anal. ($C_{25}H_{44}N_2O_2S$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-octadecylthiourea (15k).** This compound was prepared as described for **15f**[1] (see supplementary material) and was recrystallized from petroleum ether (bp 100–120 °C)/diisopropyl ether to give white crystals: 12% yield; mp 98–99 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.52; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.9 (3H, t, alkyl CH_3), 1.25 (32H, env, alkyl CH_2), 3.33 (2H, d of t, $NHCH_2CH_2$), 3.88 (3H, s, $ArOCH_3$), 4.54 (2H, d, $ArCH_2NH$), 5.60–6.3 (3H, br s, ArOH, 2 × thiourea NH), 6.85 (3H, m, ArH); MS *m/e* 464 (M^+). Anal. ($C_{27}H_{48}N_2O_2S$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-oleylthiourea (15l).** This compound was prepared by the method described for **15f**[1] from oleyl isothiocyanate[2] and was purified by flash column chromatography (silica, CH_2Cl_2/MeOH 100:1). Recrystallization from petroleum ether (bp 100–120 °C) gave a white crystalline solid: yield (45% yield); mp 94–97 °C; TLC (silica, CH_2Cl_2/MeOH 25:1) R_f 0.56; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (3H, t, alkyl CH_3), 1.3 (22H, env, alkyl CH_2), 1.55 (2H, m, $NHCH_2CH_2CH_2$), 2.0 (4H, m, $CH_2CH_2CH{=}CHCH_2CH_2$), 3.38 (2H, br s, $NHCH_2CH_2$), 3.7 (3H, s, $ArOCH_3$), 4.5 (2H, br s, $ArCH_2NH$), 5.33 (2H, m, $CH_2CH{=}CHCH_2$), 6.0 (1H, thiourea NH), 6.15 (1H, br s, thiourea NH), 6.62–6.8 (3H, m, ArH); MS *m/e* 462 (M^+); HPLC RP_{18} (gradient 10–70% CH_3CN/0.1% aqueous TFA) >95% pure.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-adamantylthiourea (15m).** This compound was prepared as described for **15f**[1] (see supplementary material) and was purified by flash column chromatography (silica, CH_2Cl_2) and then recrystallized from petroleum ether (bp 80–100 °C)/diethyl ether to give white crystals: 49% yield; mp 140–144 °C; TLC (silica, CH_2Cl_2/MeOH 25:1) R_f 0.6; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.7–2.05 (15H, m, adamantyl CH_2 and CH) 3.9 (3H, s, $ArOCH_3$), 4.7 (2H, d, $ArCH_2NH$), 5.7–6.1 (3H, br s, 2 × thiourea NH, ArOH), 6.9 (3H, m, ArH); MS *m/e* 364 (M^+). Anal. ($C_{19}H_{28}N_2O_2S$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-benzhydrylthiourea (15n).** This compound was prepared by the same method as that described for **15a** and the residue after removing the THF/1 N HCl *in vacuo* was recrystallized from petroleum ether (bp 100–120 °C)/EtOAc to give white crystals: yield 91%; mp 62–64 °C; TLC (silica, CH_2Cl_2/MeOH) R_f 0.59; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.78 (3H, s, $ArOCH_3$), 4.52 (2H, d, $ArCH_2NH$), 5.62 (1H, br s, ArOH), 5.95 (1H, br s, thiourea NH), 6.06 (1H, br s, thiourea NH), 6.46 (1H, br d, $NHCHAr_2$), 6.56 (1H, d of d, J = 2 Hz, J' = 8 Hz, ArH_6), 6.67 (1H, d, J = 2 Hz, ArH_2), 6.78 (1H, d, J' = 8 Hz, ArH_5), 7.15–7.38 (10H, m, benzhydryl ArH); MS *m/e* 378 (M^+). Anal. ($C_{22}H_{22}N_2O_2S \cdot 0.25H_2O$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-tritylthiourea (15p).** This compound was prepared as described for **15f**[1] (see supplementary material) and was purified by flash column chromatography (silica, CH_2Cl_2) and then recrystallized from petroleum ether (bp 80–100 °C) to give white crystals: 26% yield; mp 72–77 °C; TLC (silica, CH_2Cl_2/MeOH 25:1) R_f 0.7; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.75 (3H, s, $ArOCH_3$), 4.42 (2H, d, $ArCH_2NH$), 5.35 (1H, br s, thiourea NH), 6.15 (1H, d of d, J = 2 Hz, J' = 8 Hz, ArH_6), 6.45 (1H, d, J = 2 Hz, ArH_2), 6.68 (1H, d, J' = 8 Hz, ArH_5), 7.3 (15H, s, trityl ArH), 7.3–7.5 (2H, br s, ArOH, thiourea NH); MS *m/e* 454 (M^+). Anal. ($C_{28}H_{26}N_2O_2S$) C, H, N.

Biology. The *in vitro* and *in vivo* assays used in this paper are described in paper 1 of this series.

Supplementary Material Available: Experimental protocols for the synthesis of compounds previously described in the literature where the methods described herein may differ from the published procedures (6 pages). Ordering information is given on any current masthead page.

References

(1) Buckwalter, B. L.; Lahann, T. R. Novel Urea Derivatives. Eur. Pat. 0068590, 1982.
(2) Schmidt, E.; Fehr, L. Preparation of higher N-alkylisothiocyanates. *Liebigs Ann. Chem.* **1959**, *621*, 1–7.

(3) Jones, E. C. S.; Pyman, F. L. The Relation between Chemical Constitution and Pungency in Acid Amides. *J. Chem. Soc.* **1925**, *127*, 2588–2598.
(4) Gannett, P. M.; Nagel, D. L.; Reilly, P. J.; Lawson, T.; Sharpe, J.; Toth, B. The Capsaicinoids: Their Separation, Synthesis, and Mutagenicity. *J. Org. Chem.* **1988**, *53*, 1064–1071.
(5) Brand, L. M., Capsaicinoid Nonsteroid Analgesics, Eur. Pat. Application 14945, 1985.
(6) Lahann, T. R.; Buckwalter, B. L. Analgesic Compositions. U.S. Pat. US 4493848 A, 1985.
(7) Janusz, J. M.; Loomans, M. E. Aralkylaralkanamides and Compositions Thereof Having Antiinflammatory and Analgesic Activity. UK Pat. Application 2168975, 1986.
(8) (a) Sietsema, W. K.; Berman, E. F.; Farmer, R. W.; Maddin, C. S. The Antinociceptive Effect and Pharmacokinetics of Olvanil following Oral and Subcutaneous Dosing in the Mouse. *Life Sci.* **1988**, *43*, 1385–1391. (b) Brand, L.; Berman, E.; Schwen, R.; Loomans, M.; Janusz, J.; Bohne, R.; Maddin, C.; Gardner, J.; Lahann, T.; Farmer, R.; Jones, L.; Chiabrando, C.; Fanelli, R. NE-19550: A Novel, Orally Active Anti-inflammatory Analgesic. *Drug Exp. Clin. Res.* **1987**, *13*, 259–265.
(9) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; John Wiley and Sons: New York, 1979.
(10) Mirlees, M. S.; Moulton, S. J.; Murphy, C. T.; Taylor, P. J. Direct Measurement of Octanol-Water Partition Coefficients by High Pressure Liquid Chromatography. *J. Med. Chem.* **1976**, *19*, 615–619.
(11) Minick, D. J.; Frenz, J. H.; Patrick, M. A.; Brent, D. A. A Comprehensive Method for Determining Hydrophobicity Constants by Reversed-Phase High-Performance Liquid Chromatography. *J. Med. Chem.* **1988**, *31*, 1923–1929.
(12) Leo, A.; Hansch, C.; Elkins, D. Partition Coefficients and Their Uses. *Chem. Rev.* **1971**, *71*, 525–616.
(13) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(14) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1980.
(15) Ruys, L.; Schacht, E. Synthesis of some low molecular weight derivatives of procainamide. *Bul. Soc. Chim. Belg.* **1984**, *93*, 483–438.