Analogues of Capsaicin with Agonist Activity as Novel Analgesic Agents; Structure-Activity Studies. 2. The Amide Bond "B-Region"

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A series of compounds incorporating replacements for the amide bond "B-region" moiety of capsaicin have been synthesized, including vanillylamides and esters, homovanillic acid amides and esters, ureas, and thioureas. These have been tested in an *in vitro* assay for agonism ($^{45}Ca^{2+}$ influx into dorsal root ganglia neurones), which is predictive of analgesic activity, to investigate the requirements in this region of capsaicin for activity. *N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-octylthiourea (**14a**) emerged as the most potent analogue (EC_{50} = 0.06 μM). An operational model based on multiple hydrogen-bonding interactions is proposed to explain the structure-activity profile observed. In combination with studies on the other regions of the capsaicin molecule these results describe a picture of the molecular interactions of capsaicin with its putative receptor.

Introduction

In paper 1 of this series, an approach to the systematic investigation of the structure-activity profile of capsaicin as a potential analgesic agent has been outlined. This involved dissecting the capsaicin molecule into arbitrary but convenient molecular segments (see Scheme I) and then altering one component while the others remained structurally constant. Evaluation of the activity of these analogues was then carried out in an *in vitro* assay for agonism which we have established is predictive of analgesia in animal models for this class of compounds. Paper 1 of this series described our attempts to explore the aromatic ring ("A-region") of the molecule and this describes variations made in the connecting amide bond region ("B-region").

Chemistry

Structural variations to the B-region fall into the four categories listed below. In each of these the aromatic region (A-region) and the aliphatic side chain (C-region) have been held constant as 3-methoxy-4-hydroxyphenyl- and *n*-octyl, respectively.

(1) Vanillylamides, Esters and Related Compounds. The amides **3b-d** and the ester **3f** were made by acylation of the relevant vanillylamines **1b-d** and the alcohol **1f**, respectively. Protection of the phenolic OH proved unnecessary if the *N*-hydroxysuccinimide ester (NHS) was used as the acylating agent, but when the acid chloride was used, protective acylation at the 4-position was required. Subsequent removal of the acyl protecting groups from the intermediates **2b** and **2f** was achieved using sodium bicarbonate in the case of the amide **2b** and pyrrolidine[1] in the case of the ester **2f**. Thioamide **4**[2] was made from the commercially available amide **3a** using Lawesson's reagent. The sulfonamide **5**[3] was obtained by acylation of the protected vanillylamine **9**[4] with octanesulfonyl chloride, followed by deprotection of the phenol group using dilute acid.

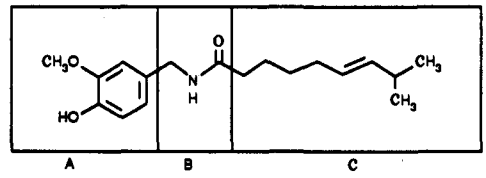
(2) Homovanillic Acid Amides, Esters and Related Compounds. The amides and esters **8a-h** were made by coupling of suitably activated *O*-acetyl aryl carboxylic acids **6a-h**, e.g. the *O*-acetylhomovanilloyl chloride,[5,6] with the appropriate *n*-octyl-substituted nucleophile. Removal of the acetyl protecting groups from the intermediates **7a-h** was carried out with aqueous sodium bicarbonate or pyrrolidine as before. The *Z* isomer **8i** was made by photolysis of the (*E*)-cinnamate derivative **8h** at 254 nm.

(3) Ureas and Thioureas. The urea **11**[7] was made from the protected amine **9**[4] via the intermediate **10**. Deprotection of the *O*-ethoxyethyl group to the phenol was achieved with dilute acid (see Scheme II).

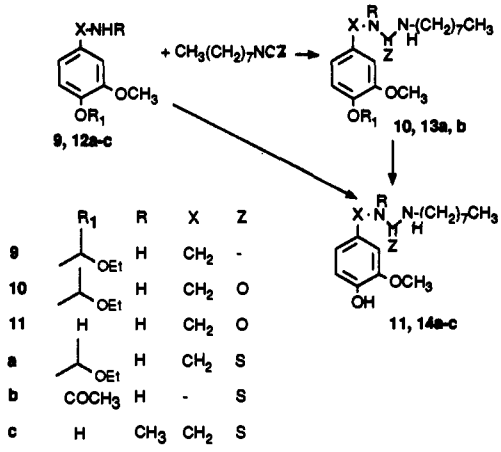
The thioureas **14a**[7]-**c** were made by the route illustrated in Scheme II. **14c** was made without protection of the phenol group in the precursor amine, but the syntheses of **14a** and **14b** required the use of protected amines and subsequent deprotection of the intermediates **13a** and **13b**.

The regioisomer **14d** of the *N*-methylthiourea **14c** was made from *N*-methyloctylamine by formation of the alternative C-N bond of the thiourea, by reaction with the protected benzyl isothiocyanate derived from amine **9**.[4]

Scheme I



Scheme II



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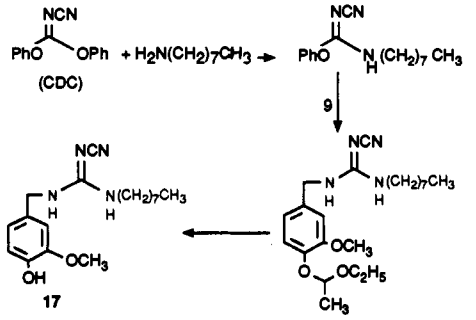
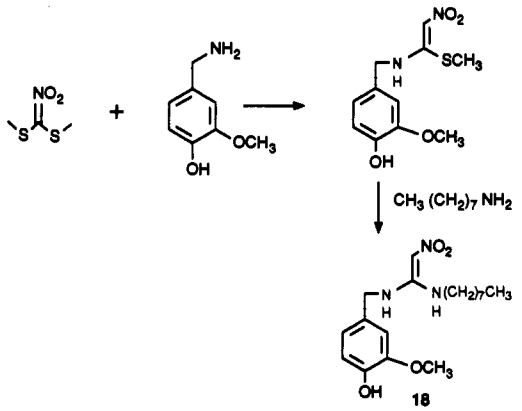
Scheme III



Scheme IV



Preparation of the acylthiourea **15** followed the pathway of Scheme II by reacting nonanoyl isothiocyanate[8] with **9**,[4] followed by removal of the acetal protecting group. Methylation of the parent thiourea **14a** with methyl iodide and potassium carbonate gave the thiouronium salt **16**. Two compounds, **17** and **18**, incorporating isosteric replacements of the thiourea[9] were also made. From a comparison of physical and chemical properties the N-cyanoguanidine and the nitroethene moieties have been reported as isosteric and bioisosteric with the thiourea. The latter property has been exemplified in the histamine H_2 antagonists cimetidine and ranitidine in comparison to the prototype thiourea metiamide.[9] The *N*-cyanoguanidine **17** was made by sequential nucleophilic displacement reactions on diphenyl cyanocarbonimidate (CDC),[10] firstly with octylamine and then with **9**, followed by deprotection (see Scheme III).

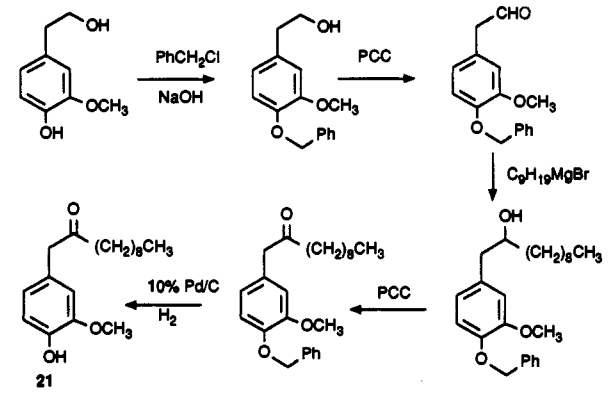
The nitroethene **18** was made using a similar principle to **17** from 1,1-bis(methylthio)-2-nitroethene.[11] In this instance protection of the vanillylamine unit did not prove necessary because of the reversed order of the nucleophilic displacements with respect to the preparation of **17**, whereby the first step is carried out under mild conditions (Scheme IV).

(4) Others. The ketone analogue **20** (cf. amide **3a**) was made following the procedure of Locksley[12] via the intermediate α,β-unsaturated ketone **19**, which was also evaluated biologically.

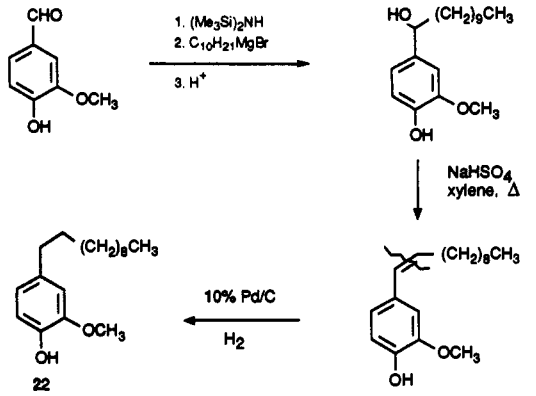
The novel ketone **21**, which is isomeric with **20**, can be considered as the ketone analogue of the "reverse" homovanillic acid amide **8a**. This undecan-2-one was assembled using Grignard chemistry from the commercially available homovanillyl alcohol illustrated in Scheme V.

The substituted phenylundecane **22** exemplifies a structure devoid of functionality in the B-region of the parent molecule. This compound was synthesized from

Scheme V



Scheme VI



vanillin. Transient protection of the phenol function as the trimethylsilyl ether permitted the Grignard reaction to incorporate the side chain. Subsequent dehydration of the secondary alcohol and catalytic reduction of the corresponding alkene provided the target compound **22** (Scheme VI).

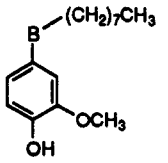
Biological Results and Discussion

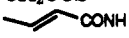
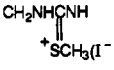
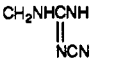
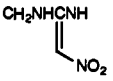
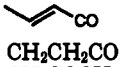
The contribution of the "B-region" (see Scheme I) to the overall structure–activity profile of the prototype capsaicin molecule has been evaluated using the testing principle outlined in the previous paper ("A-region"). *In vitro* assays have been used to provide a measure of capsaicin-like agonist activity, and analgesic activity has been measured in the tail flick latency model in the mouse. The data are presented in Tables I and II and further support the observations, made in paper 1 of this series, that analgesia is only observed with potent agonists in the $^{45}Ca^{2+}$ flux assay ($EC_{50} < 1\ \mu M$) and that the results of this assay show a good correlation with the results obtained with an ileum contraction assay. Representative data from Table I have been included in the graphical representation of these observations given in Figure 1 of paper 1.

Several points of detail emerge from structure–activity considerations of the $^{45}Ca^{2+}$ flux data in Tables I and II. These are as follows.

(1) The amide **3a** and the "reverse" amide **8a** are equipotent. In other such comparable pairs, the higher homologues **3c** and **8c**, the *N*-methylamides **3d** and **8d**, and the esters **3f** and **8f**, the "reverse" analogue is clearly more potent in each case (although all are significantly less active than the parent amides). An exception to this is shown by the lower homologue amides **3b** and **8b**, where the former is more active (however, see point 4 below).

Table I. $^{45}Ca^{2+}$ Influx Activity of a Series of "B-Region" Analogues



compd	B	Ca^{2+} influx EC_{50} (μM)
	capsaicin	0.30 ± 0.01
3a	CH_2NHCO	0.55 ± 0.08
3b	NHCO	4.48 ± 0.26
3c	$(CH_2)_2NHCO$	18.30 ± 2.80
3d	$CH_2N(CH_3)CO$	>100
3f	CH_2OCO	14.20 ± 0.06
4[a]	CH_2NHCS	0.28 ± 0.02
5[b]	CH_2NHSO_2	1.32 ± 0.03
8a[c]	CH_2CONH	0.30 ± 0.01
8b	CONH	>100
8c	$(CH_2)_2CONH$	2.32 ± 0.21
8d	$CH_2CON(CH_3)$	6.29 ± 0.25
8e	CH(OH)CONH	1.16 ± 0.03
8f[a]	CH_2COO	0.67 ± 0.11
8g	CH_2COS	1.17 ± 0.10
8h		>100
8i		17.90 ± 1.08
11[d]	$CH_2NHCONH$	0.36 ± 0.04
14a[d]	$CH_2NHCSNH$	0.06 ± 0.01
14b	NHCSNH	2.57 ± 0.90
14c	$CH_2N(CH_3)CSNH$	>100
14d	$CH_2NHCSN(CH_3)$	0.53 ± 0.08
15	$CH_2NHCSNHCO$	>100
16		>100
17		3.28 ± 0.63
18		>100
19		>100
20	CH_2CH_2CO	2.13 ± 0.24
21	CH_2COCH_2	3.78 ± 0.45
22	$CH_2CH_2CH_2$	>100

[a] Reference 2. [b] Reference 3. [c] Reference 6. [d] Reference 7.

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

	EC_{50} (μM)		
compd	Ca^{2+} influx	guinea pig ileum contraction	analgesia ED_{50} (μmol kg^{-1})
capsaicin	0.30 ± 0.01	0.26 ± 0.06	15.0
3a	0.55 ± 0.08	0.40 ± 0.10	5.0
3b	4.48 ± 0.26	1.17 ± 0.09	>50
4	0.28 ± 0.02	1.23 ± 0.59	38.0
5	1.32 ± 0.03	2.90 ± 0.40	>50
8a	0.30 ± 0.13	0.33 ± 0.08	9.2
14a	0.06 ± 0.01	0.06 ± 0.01	3.2
14b	2.57 ± 0.90	2.56 ± 0.55	>50
17	3.28 ± 0.63	6.35 ± 0.66	>50

(2) There appears to be an optimum length requirement of one carbon atom for the group "bridging" the A-region and the dipolar B-region moiety; e.g. **3a** is more potent than **3b** and **3c**, and **8a** is more potent than **8b** and **8c**.

(3) N-Methylation in all cases leads to a reduction or loss of activity, e.g. amides, cf. **3a** with **3d** and **8a** with **8d**; thioureas, cf. **14a** with **14c** and **14d**. This constraint is more severe on the vicinal (to the A-region) than on the distal nitrogen atom.

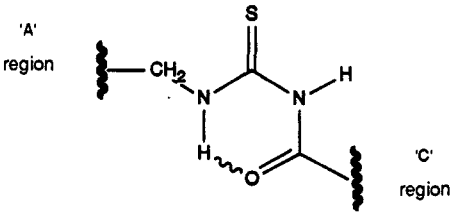


Figure 1. The pseudocyclic conformation of **15**.

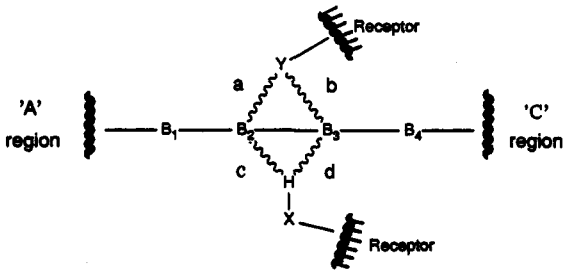


Figure 2. Potential dipolar interactions of "B-region" moieties with the receptor model.

(4) There appears to be a requirement for sp^3 hybridization at the bridging group. Compounds where the atom next to the aromatic ring is sp^2 hybridized are all weakly active or inactive (e.g. **3b**, **8b**, **8h**, **8i**, **14b**, **19**). However, substitution on the bridging methylene group, in the one case, **8e**, leads only to a small loss of activity (this compound was synthesized and tested as the racemate).

(5) The thiourea moiety (in **14a**) emerges as the structural group conferring highest potency in this series of analogues (further supporting data in other series where the superior potency of thioureas is more marked is the subject of another publication, currently in preparation).

The urea **11** is significantly less effective as are the conventional bioisosteres, the *N*-cyanoguanidine **17** and the *C*-nitroethenoamidine **18**. Introduction of positive charge by making the thiouronium salt **16** also removes activity, although a contribution to this loss by increasing steric bulk cannot be ruled out. The acylthiourea **15** is also completely inactive. This may be a consequence of the conformation of **15**. Evidence for the existence of a pseudocyclic B-region conformation of **15** in solution has been obtained from the NMR spectrum, which supports the existence of the hydrogen bond shown in Figure 1 (low-field broad singlet, δ 10.75).

(6) All other attempts to reduce or remove the dipolar functions of the B-region lead to reduction or loss in potency (see compounds **20**–**22**).

In an attempt to rationalize the structure–activity data discussed above and presented in Table I, we have developed an operational schematic model based on multiple hydrogen-bonding (dipolar) interactions (Figure 2), where B_1–B_4 are component structural units of the B-region e.g. NH, CO, SO_2, CH_2 and a–d represent *potential* dipolar interactions.

This model is derived solely from consideration of the $^{45}Ca^{2+}$ flux assay data presented in Table I and requires qualification to be all-embracing. This is discussed below. However, we feel that it presents a coherent picture with predictive value.

For activity in this model, compounds must possess some component of a hydrogen-bond-donor–acceptor pair at positions B_2 and B_3, which ideally (i.e. for compounds of

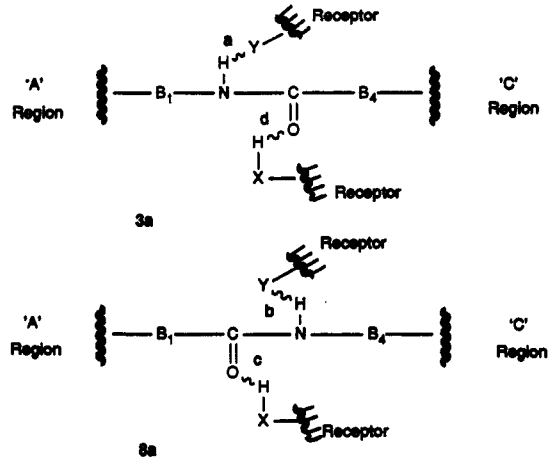


Figure 3. Potential dipolar interactions between the receptor and **3a** and **8a**.

high potency) assume an extended *trans* coplanar configuration (see below). The model is illustrated above for the amide **3a** and the "reverse" amide **8a** (Figure 3).

A larger number of H-bonding interactions results in higher activity. Thus for compounds having activities $EC_{50} < 1\ \mu M$ two interactions are necessary (see Figure 3) whereas less potent compounds ($1\ \mu M < EC_{50} < 10\ \mu M$) make only one interaction in the model.

The interactive "dyslexia" of the receptor with the isomeric amides **3a** and **8a** is thereby explained. The "frameshift" which occurs on the deletion or addition of a methylene group (e.g. cf. **3a** with **3b** and **3c**) is also accommodated, since only one H-bond can now be formed.

A caveat, that there is a steric constraint on the nitrogen atom at position B_2, is necessary to explain the inactivity of **3d** and **14c**, as they would be predicted to be weakly active from the model.

The high potency of the thiourea **14a** is ascribed not only to multiple H-bond interactions but also to the increased conformational restriction this moiety imparts on the B- and C-regions (relative to related amides and ureas).[9] Thioureas are known to assume three stable configurations in solution, arising from restricted rotation about the C–N bonds. In the 400-MHz $^1H^{13}$ and ^{13}C NMR spectra[14] of thiourea **14a**, line broadening of the methylene groups adjacent to the thiourea moiety was observed. This is a general property of such thioureas and is further discussed in a forthcoming publication.

At lower temperatures (−60 °C) these signals were resolved to three separate families and were assigned (by NOE experiments) to *Z,E*, *Z,Z*, and *E,Z* configurations of the thiourea moiety (see Figure 4). Such line broadening is absent in other B-region analogues, including the urea **11** and the N-methylthiourea **14d**.

The only other compound which shows similar line broadening is the nitroethene **18**. Since, however, this functional group cannot act as an H-bond acceptor at B_3, its inactivity is unremarkable. In low-temperature NMR spectra of **14d**[15] only two conformers, *Z,Z* and *Z,E*, in which the B_2–B_3 and B_3–B_4 bonds are *trans–trans* and *trans–cis*, respectively, were observed. Since this compound is active, it is unlikely that the *E,Z* species is important for activity. As there is no evidence for the existence of the *E,E* species in any of the thioureas studied it seems reasonable to suggest that a transoid coplanar disposition of the structural units B_2 and B_3 is necessary in the above model for activity, $EC_{50} < 1\ \mu M$.

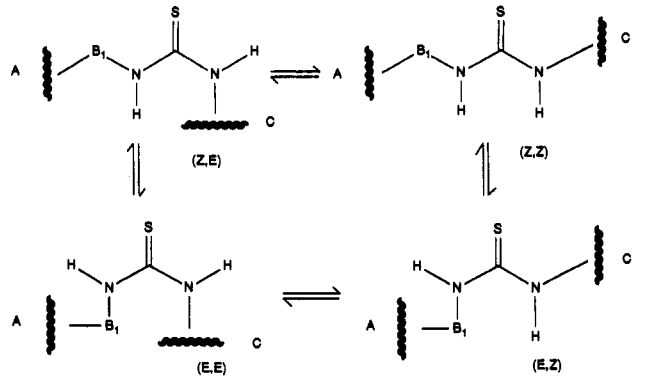


Figure 4. The four possible configurations of the thiourea moiety in analogues such as **14a**.

B-region functionality which permits this B_2–B_3 *trans* configuration and in which the B_2–B_3–B_4 unit is further conformationally constrained have still further enhanced potency.

The reduced activity of the conventional bioisosteres **17** and **18** is explained by the lower number of available H-bonding interactions (notably the absence of interaction "d" in the model). This is an important restatement of the principle that bioisosterism should not be regarded as *generally* applicable in environments where interactions may differ.[16]

One further important qualification to this model must be made. There is evidence that the binding site on the capsaicin receptor[17] is on the *inside* of the cell membrane. If this is so, then the Ca^{2+}-flux assay which has been used as the basis of the above model may be subject to access constraints (i.e. cell membrane penetration) which would have different and independent structure–activity correlations from "receptor interactions" for the compounds. Thus a charged species such as the thiouronium salt **16** may be inactive simply because it cannot reach the target binding site.

We are currently involved in testing this evolving model by the synthesis of conformationally restricted analogues.

Combination of the information gained from the interaction of the B-region of the capsaicin molecule with our reported studies of the adjacent regions, A and C (see accompanying papers 1 and 3, respectively), is enabling a molecular picture of the capsaicin "receptor" to be built.

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 AM360 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 at Sandoz, (Basle, Switzerland), using a VG 70-SE spectrometer. TLC was performed 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 the compositions stated

in the text]. Compounds were purified by flash column chromatography[18] 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.[19] Test compounds were homogenous by TLC or HPLC unless otherwise stated. Chemical yields were not optimized.

4-Acetoxy-3-methoxyaniline Hydrochloride (1b). 2-Methoxy-4-nitrophenol was acetylated by treatment with acetic anhydride following the method of Fisher and Hibbert[5] to give 4-acetoxy-3-methoxynitrobenzene (82% yield). This compound (8 g, 38 mmol) was hydrogenated in 200 mL of EtOAc containing 200 mg of 10% Pd/C for 4 h. The catalyst was removed by filtration through Celite and washed with 100 mL of EtOAc. A stream of HCl gas was passed through the solution, causing colorless crystals to precipitate. The crystals were collected by filtration and dried *in vacuo* and used without further purification, yield 7.1 g (86%).

***N*-(4-Acetoxy-3-methoxyphenyl)nonanamide (2b).** Compound **1b** (2 g, 9.2 mmol), was suspended in 50 mL of EtOAc, and triethylamine (1.9 g, 18.8 mmol) was added. The mixture was stirred on ice during the dropwise addition of nonanoyl chloride (1.63 g, 9.2 mmol). The reaction mixture was stirred for 12 h before the addition of H_2O (50 mL) and the separation of the phases. The organic layer was washed with 2 N HCl, water, and then saturated NaCl solution and then dried over Na_2SO_4. Solvent was removed *in vacuo* leaving a colorless oil which crystallized on cooling, yield 2.6 g (89%).

***N*-(4-Hydroxy-3-methoxyphenyl)nonanamide (3b).** Compound **2b** was deprotected in a similar fashion to that described for **8a** from **7a**[6] (see supplementary material) and was recrystallized from petroleum ether (bp 100–120 °C)/ether to give colorless crystals: yield 26%; mp 90–94 °C; TLC (silica; CH_2Cl_2/MeOH 25:1) R_f 0.35; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.3 (12H, env, alkyl CH_2), 2.35 (2H, t, $COCH_2CH_2$), 3.9 (3H, s, $ArOCH_3$), 5.6 (1H, br s, ArOH), 6.7 (1H, d of d, J = 2 Hz, J' = 8.5 Hz, ArH_6), 6.9 (1H, d, J' = 8.5 Hz, ArH_5), 7.3 (1H, br s, amide NH), 7.55 (1H, d, J = 2 Hz, ArH_2); MS m/e 279 (M^+). Anal. ($C_{18}H_{25}NO_3 \cdot 0.1H_2O$) C, H, N.

***N*-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]nonanamide (3c).** *N*-(Nonanoyloxy)succinimide[20] (1.2 g, 4.7 mmol) was dissolved in dry EtOAc (10) mL and added, dropwise, to a solution of 3-*O*-methyldopamine hydrochloride (0.96 g, 4.7 mmol) and triethylamine (0.52 g, 5 mmol) in EtOAc (15 mL). The mixture was stirred for 12 h before washing the solution with 2 N HCl (50 mL), H_2O, and saturated NaCl and finally drying over Na_2SO_4. The solvent was removed *in vacuo* to leave a colorless solid, which was recrystallized from petroleum ether (bp 100–120 °C) to give colorless crystals: 0.67 g (46% yield); mp 83–88 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.4; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.3 (12H, env, alkyl CH_2), 2.15 (2H, t, $COCH_2CH_2$), 2.75 (2H, m, CH_2NH), 3.85 (3H, s, $ArOCH_3$), 5.75 (2H, br s, amide NH and ArOH), 6.75 (3H, m, ArH); MS m/e 307 (M^+). Anal. ($C_{18}H_{29}NO_3$) C, H, N.

***N*-(3-Methoxy-4-hydroxybenzyl)-*N*-methylnonanamide (3d).** *N*-Methylvanillylamine hydrochloride[21] (0.4 g, 2 mmol), together with triethylamine (0.22 g, 2.2 mmol), was stirred under N_2 in DMF (2 mL). *N*-(Nonanoyloxy)succinimide (0.5 g, 1.9 mmol), in DMF (1 mL), was slowly added and the resulting mixture stirred overnight. The solvent was evaporated *in vacuo* and the residue dissolved in CH_2Cl_2. The solution was washed with water, 1 N HCl, and, finally, saturated NaCl before drying over Na_2SO_4. The residue, on removal of the solvent *in vacuo*, was recrystallized from petroleum ether (bp 100–120 °C)/EtOAc at −20 °C to give a white crystalline solid: yield 0.38 g (62%); mp 57–58 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.39; ^{1}H NMR [400 MHz, d_6-DMSO, 150 °C (rotamers, due to restricted rotation about the benzyl position, were observed at lower temperatures)] δ 0.9 (3H, t, alkyl CH_3), 1.30 (10H, env, alkyl CH_2), 1.58 (2H, m, $COCH_2CH_2$), 2.34 (2H, t, $COCH_2CH_2$), 2.87 (3H, s, NCH_3), 3.76 (3H, s, $ArOCH_3$), 4.42 (2H, s, $ArCH_2CO$), 6.64 (1H, d of d, J = 2 Hz, J' = 8 Hz, ArH_6), 6.75 (1H, d, J = 2 Hz, ArH_2), 6.75 (1H, d, J' = 8 Hz, ArH_5), 8.0 (1H, s, ArOH); MS m/e 307 (M^+). Anal. ($C_{18}H_{29}NO_3$) C, H, N.

3-Methoxy-4-(nonanoyloxy)benzyl nonanoate (2f). 4-Hydroxy-3-methoxybenzyl alcohol (**1f**) (2 g, 14.5 mmol) was stirred, on ice, in EtOAc (10 mL) together with triethylamine (2.9 g, 29 mmol). A solution of nonanoyl chloride (5.1 g, 29 mmol) in EtOAc (20 mL) was slowly added and the mixture stirred for 12 h. TLC indicated incomplete conversion after this time, so the mixture was refluxed for 2 h during which time all the benzyl alcohol was consumed. The solution was washed with 2 N HCl (50 mL), water, and then saturated NaCl solution and finally dried over Na_2SO_4. The title compound was obtained as a yellow oil which was crystallized from petroleum ether (bp 100–120 °C) at −20 °C: yield 2.3 g (40.5%); TLC (silica, cyclohexane/EtOAc 1:1) R_f 0.63; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.3 (24H, env, alkyl CH_2), 2.3–2.6 (4H, m, $ArOCOCH_2CH_2$ and $OCOCH_2CH_2$), 3.85 (3H, s, $ArOCH_3$), 5.1 (2H, s, $ArCH_2O$), 7.0 (3H, m, ArH); IR ν 1765 (ArO*CO*), 1735 ($ArCH_2O$*CO*) cm^{-1}.

(4-Hydroxy-3-methoxy)benzyl nonanoate (3f). Compound **2f** was deprotected with pyrrolidine in CH_2CH_2 in an analogous fashion to that described for **8f** from **7f**[1] (see supplementary material). The crude product was purified by flash column chromatography (silica, cyclohexane/EtOAc 3:1) to give the title compound as a colorless oil: yield 49%; TLC (silica, cyclohexane/EtOAc 1:1) R_f 0.5; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.25 (12H, env, alkyl CH_2), 2.35 (2H, t, CH_2CO), 3.85 (3H, s, $ArOCH_3$), 5.02 (2H, s, $ArCH_2OCO$), 5.9 (1H, br s, ArOH), 6.85 (3H, m, ArH); MS m/e 294 (M^+); HRMS m/e calcd for $C_{17}H_{26}O_4$ 294.1831, found 294.1827; IR ν 3450 (ArOH), 1730 ($ArCH_2O$*CO*R) cm^{-1}; HPLC RP_{16} (gradient 10–70% CH_3CN in 0.1% aqueous TFA) >99% pure.

***N*-Octyl-4-hydroxy-3-methoxybenzamide (8b).** This compound was synthesized from vanillic acid in three steps as described for **8a**[6] (see supplementary material). Acetylvanillic acid (**6b**) (60% yield) and *N*-octyl-4-acetoxy-3-methoxybenzamide (**7b**) (47% yield) were intermediates. 69%; yield **8b**: mp 64–68 °C; TLC (silica, $CHCl_3$/MeOH 25:1) R_f 0.31; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.3 (12H, env, alkyl CH_2), 3.45 (2H, m, $NHCH_2CH_2$), 3.9 (3H, s, $ArOCH_3$), 5.8–6.4 (2H, br s, amide NH and ArOH), 6.8–7.5 (3H, m, ArH); MS m/e 279 (M^+). Anal. ($C_{18}H_{25}NO_3$) C, H, N.

3-(4-Acetoxy-3-methoxyphenyl)propionic Acid (6c). This compound was synthesized in a similar manner to acetylhomovanillic acid[5] in 36% yield.

***N*-Octyl-3-(4-acetoxy-3-methoxyphenyl)propionamide (7c).** Compound **6c** (2.03 g, 8.53 mmol) was dissolved in dry EtOAc (30 mL) containing *N*-methylmorpholine (0.86 g, 8.53 mmol) and cooled to −15 °C under N_2. Isobutyl chloroformate (1.27 g, 9.33 mmol) was added dropwise, the temperature being kept below −10 °C, and stirred for 8 min following complete addition. A solution of octylamine (1.1 g, 8.53 mmol) in dry EtOAc (2 mL) was slowly added, again the temperature being kept below −10 °C. The reaction was stirred for 12 h before the addition of water (10 mL) and the separation of the phases. The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to give a yellow oil which was used without further purification, yield 2.8 g (94%).

***N*-Octyl-3-(4-hydroxy-3-methoxyphenyl)propionamide (8c).** Compound **7c** was deacetylated in a manner similar to that of **8a** from **7a**[6] (see supplementary material): yield 51%; mp 90–91 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.35; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.0 (3H, t, alkyl CH_3), 1.25 (12H, env, alkyl CH_2), 2.4 (2H, t, CH_2CH_2CO), 3.0 (2H, t, $ArCH_2CH_2$), 3.2 (2H, m, $NHCH_2CH_2$), 3.85 (3H, s, $ArOCH_3$), 4.9 (1H, br s, amide NH), 5.6 (1H, br s, ArOH), 6.85–7.0 (3H, m, ArH); MS m/e 307 (M^+). Anal. ($C_{18}H_{29}NO_3$) C, H, N.

***N*-Octyl-*N*-methyl-4-hydroxy-3-methoxyphenylacetamide (8d).** This compound was synthesized from acetylhomovanillic acid[5] in two steps in a manner similar to that described for **8a**[6] (see supplementary material). *N*-Octyl-*N*-methyl-4-acetoxy-3-methoxyphenylacetamide (**7d**) (74% yield) was an intermediate. 76%; yield **8d**: mp 57–58 °C; TLC (silica, $CHCl_3$/MeOH 20:1) R_f 0.4; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.8 (3H, t, alkyl CH_3), 1.1 (12H, env, alkyl CH_2), 2.75 (3H, s, NCH_3), 3.1 (2H, t, $NCH_3CH_2CH_2$), 3.45 (2H, s, $ArCH_2CO$), 3.7 (3H, s, $ArOCH_3$), 5.7 (1H, br s, ArOH), 6.75–7.0 (3H, m, ArH); MS m/e 308 (M^+). Anal. ($C_{18}H_{29}NO_3$) C, H, N.

DL-*N*-(**Octylvanillyl**)**mandelamide (8e).** This compound was synthesized from DL-vanillylmandelic acid in three steps by analogy with **8a**.[6] Diacetylvanillylmandelic acid **6e** (55% yield) and *N*-octyl-4-acetoxy-3-methoxy-*O*-acetylmandelamide (**7e**), purified by flash column chromatography (alumina, CH_2Cl_2/MeOH 25:1, 31% yield), were intermediates. **8e** was purified by flash column chromatography (silica, CH_2Cl_2/MeOH 25:1): yield 37%; mp 76–82 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.24; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.85 (3H, t, alkyl CH_3), 1.25 (12H, env, alkyl CH_2), 3.2 (2H, m, $NHCH_2CH_2$), 3.82 (3H, s, $ArOCH_3$), 4.9 (1H, s, $ArCHOHCO$), 5.9 (1H, br s, ArOH), 6.2 (1H, br s, amide NH), 6.8–7.0 (3H, m, ArH); MS *m/e* 309 (M^+). Anal. ($C_{17}H_{27}NO_4$) C, H, N.

***S*-Octyl-4-hydroxy-3-methoxyphenylthioacetate (8g).** Condensation of acetylhomovanilloyl chloride with octanethiol in the presence of triethylamine, by analogy with the synthesis of **7a**[6] (see supplementary material), gave the intermediate *S*-octyl-4-acetoxy-3-methoxyphenylthioacetate (**7g**). This was purified by flash column chromatography; TLC (silica; cyclohexane/EtOAc 10:1) R_f 0.4, yield 35%. **7g** was deprotected by treatment with pyrrolidine in CH_2Cl_2 and was purified by flash column chromatography (silica, cyclohexane/EtOAc 10:1) R_f 0.15, yield 43%: mp 34–36 °C; TLC (silica, cyclohexane/EtOAc 10:1) R_f 0.09; ^{1}H NMR (60 MHz $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.26 (12H, env, alkyl CH_2), 2.85 (2H, t, SCH_2CH_2), 3.72 (2H, s, $ArCH_2CO$), 3.88 (3H, s, $ArOCH_3$), 5.61 (1H, s, ArOH), 6.8 (3H, m, ArH); MS *m/e* 310 (M^+). Anal. ($C_{17}H_{26}O_3S$) C, H.

(***E*)-*N*-Octyl-4-hydroxy-3-methoxycinnamamide (8h).** This compound was synthesized from (*E*)-4-hydroxy-3-methoxycinnamic acid (**6h**) in three steps as exemplified for **8a**[6] (see supplementary material). (*E*)-4-Acetoxy-3-methoxycinnamic acid (**6h**) (93% yield) and (*E*)-*N*-octyl-4-acetoxy-3-methoxycinnamamide (**7h**) (77% yield) were intermediates. **8h**: yield 59%; mp 92–94 °C; TLC (silica, cyclohexane/EtOAc 1:1) R_f 0.2; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.45 (12H, env, alkyl CH_2), 3.35 (2H, m, $NHCH_2CH_2$), 3.8 (3H, s, $ArOCH_3$), 6.35 (1H, br s, amide NH), 6.45 (1H, d, J = 15 Hz, *trans* alkene CHAr), 6.6 (1H, br s, ArOH), 6.8–7.0 (3H, m, ArH), 7.65 (1H, d, J = 15 Hz, *trans* alkene CHCO); MS *m/e* 305 (M^+). Anal. ($C_{18}H_{27}NO_3$) C, H, N.

(***Z*)-*N*-Octyl-4-hydroxy-3-methoxycinnamamide (8i).** A solution of **8h** (0.25 g, 0.8 mmol) in 250 mL of MeOH was irradiated under N_2 (λ = 254 nm) for 2 days, with stirring. The solvent was removed *in vacuo* and the resulting oil purified by flash column chromatography (silica, cyclohexane/EtOAc 1:1) to give the title compound as a colorless crystalline solid: 0.1 g (40% yield); mp 95–97.5 °C; TLC (silica, cyclohexane/EtOAc 1:1) R_f 0.25; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.8 (3H, t, alkyl CH_3), 1.2 (12H, env, alkyl CH_2), 3.2 (2H, m, $NHCH_2CH_2$), 3.85 (3H, s, $ArOCH_3$), 5.25 (1H, br s, amide NH), 5.8 (1H, d, J = 12.6 Hz *cis* alkene CH), 5.68 (1H, br s, ArOH), 6.6 (1H, d, J = 12.6 Hz *cis* alkene CH), 6.9 (3H, m, ArH); MS *m/e* 305 (M^+). Anal. ($C_{18}H_{27}NO_3$) C, H, N.

***N*-Octyl-*N'*-(4-acetoxy-3-methoxyphenyl)thiourea (13b).** Compound **1b** (2 g, 9.2 mmol) was dissolved in 100 mL of H_2O and 1 N Na_2CO_3 was added until the pH was 9. The aqueous solution was then extracted with CH_2Cl_2 (2 × 100 mL), and the phases were separated. The organic phase was washed with saturated NaCl and then dried over Na_2SO_4. The solvent was removed *in vacuo*, leaving the free base (1.66 g, 9.2 mmol) as a colorless oil. The amine was dissolved in EtOAc (50 mL) and a solution of octyl isothiocyanate (1.5 g, 10 mmol) in EtOAc (10 mL) was added, dropwise. The mixture was stirred for 12 h after which time the EtOAc solution was washed with 2N HCl, H_2O, and then saturated NaCl before drying over Na_2SO_4. The solvent was removed *in vacuo*, leaving the title compound as a colorless oil which crystallized on standing: yield 2.9 g (78%); TLC (silica, CH_2Cl_2/MeOH 25:1) R_f 0.55; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.88 (3H, t, alkyl CH_3), 1.28 (12H, env, alkyl CH_2), 2.3 (3H, 2, ArOAc), 3.65 (2H, m, $NHCH_2CH_2$), 3.81 (3H, s, $ArOCH_3$), 6.18 (1H, br s, thiourea NH), 6.7–7.2 (3H, m, ArH), 8.2 (1H, br s, ArNH thiourea).

***N*-Octyl-*N'*-(4-hydroxy-3-methoxyphenyl)thiourea (14b).** Compound **13b** was deprotected by treatment with sodium bicarbonate in a similar fashion to that of **7a**[6] (see supplementary material) and recrystallized from petroleum ether (bp 100–120 °C)/ether to give colorless crystals: yield 27%; mp 98–102 °C; TLC (silica, CH_2Cl_2/MeOH 25:1) R_f 0.4; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.25 (12H, env, alkyl CH_2), 3.6 (2H, m, $NHCH_2CH_2$), 3.9 (3H, s, $ArOCH_3$), 5.15 (1H, br s, ArOH), 5.95 (1H, br t, thiourea NH), 6.7–6.9 (3H, m, ArH), 8.0 (1H, br s, thiourea ArNH); MS *m/e* 310 (M^+). Anal. ($C_{16}H_{26}N_2O_2S$) C, H, N.

***N*-(3-Methoxy-4-hydroxybenzyl)-*N*-methyl-*N'*-octylthiourea (14c).** *N*-Methylvanillylamine hydrochloride[21] (0.69 g, 3.4 mmol) and triethylamine (0.38 g, 3.7 mmol) were stirred under N_2 in DMF (2 mL). Octyl isothiocyanate (0.62 g, 3.4 mmol), in DMF (1 mL), was slowly added and the mixture stirred overnight. The solvent was removed *in vacuo* and the residue taken up in CH_2Cl_2. The solution was washed with water, 1 N HCl, and, finally, saturated NaCl before drying over Na_2SO_4. The residue, on removal of the solvent *in vacuo*, was recrystallized from petroleum ether (bp 100–120 °C)/diethyl ether to give colorless crystals: yield 0.43 g (38%); mp 67–68 °C; TLC (silica, CH_2Cl_2/MeOH 20:1) R_f 0.6; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.3 (12H, env, alkyl CH_2), 3.15 (3H, s, NCH_3), 3.65 (2H, m, $NHCH_2CH_2$), 3.9 (3H, s, $ArOCH_3$), 5.0 (2H, s, $ArCH_2NCH_3$), 5.5 (1H, br s, ArOH), 5.7 (1H, br s, NH), 6.9 (3H, m, ArH), MS *m/e* 338 (M^+). Anal. ($C_{17}H_{28}N_2O_2S$) C, H, N.

4-(2-Ethoxyethoxy)-3-methoxybenzyl isothiocyanate. Compound **9**[4] (1 g, 4.4 mmol) was dissolved in CH_2Cl_2 containing triethylamine (0.99 g, 9.7 mmol) and the solution was stirred on ice, under N_2. A solution of thiophosgene (0.51 g, 4.4 mmol) in CH_2Cl_2 was added during 10 min and the reaction allowed to stir for a further 10 min. The reaction mixture was then washed twice with water and then saturated NaCl and finally dried over Na_2SO_4. The solvent was removed *in vacuo* to leave a brown oil which was purified by flash chromatography (silica, cyclohexane/EtOAc, 5:1) to give 0.3 g (25% yield) of the pure protected isothiocyanate as a pale yellow oil: TLC (silica, cyclohexane/EtOAc 5:1) R_f 0.3; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.20 (3H, t, ethyl CH_3), 1.45 (3H, d, acetal CH_3), 3.65 (2H, q, ethyl CH_2), 3.85 (3H, s, $ArOCH_3$), 4.60 (2H, s, $ArCH_2NCS$), 5.35 (1H, q, acetal CH), 6.90 (3H, m, ArH).

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-methyl-*N'*-octylthiourea (14d).** 4-(2-Ethoxyethoxy)-3-methoxybenzyl isothiocyanate (0.3 g, 1.1 mmol) was dissolved in EtOAc and stirred on ice, under N_2. *N*-Methyloctylamine (0.16 g, 1.1 mmol) in EtOAc was slowly added and the reaction then stirred overnight. The solvent was then removed *in vacuo* to give an off-white oil. The crude product, in THF (25 mL), was deprotected without further purification by the addition of 1 N HCl (5 mL). The reaction was complete by TLC after stirring, under N_2, for 10 min. The solvent was removed *in vacuo* to leave an off-white solid which was recrystallized from petroleum ether (bp 100–120 °C)/EtOAc to give white crystals: yield 0.2 g (54%): mp 84–85 °C; TLC (silica, CH_2Cl_2/MeOH 25:1) R_f 0.7; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.29 (12H, env, alkyl CH_2), 3.16 (3H, s, NCH_3), 3.75 (2H, t, $N(CH_3)CH_2CH_2$), 3.89 (3H, s, $ArOCH_3$), 4.78 (2H, d, $ArCH_2NH$), 5.54 (1H, br t, thiourea NH), 5.71 (1H, br s, ArOH), 6.85–6.97 (3H, m, ArH); MS *m/e* 338 (M^+). Anal. ($C_{18}H_{30}N_2O_2S \cdot 0.16H_2O$) C, H, N.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-nonanoylthiourea (15).** The compound was synthesized as described for **11**[7] (see supplementary material), from **9** and nonanoyl isothiocyanate.[6] **15** was purified by flash column chromatography (silica, cyclohexane/EtOAc 4:1) and recrystallized from cyclohexane to give colorless crystals: yield 18%; mp 72–75 °C; TLC (silica, cyclohexane/EtOAc 1:1) R_f 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, alkyl CH_3), 1.2–1.34 (10H, env, alkyl CH_2), 1.65 (2H, m, $COCH_2CH_2$), 2.31 (2H, t, $COCH_2CH_2$), 3.85 (3H, s, $ArOCH_3$), 4.75 (2H, d, $ArCH_2CO$), 5.66 (1H, s, ArOH), 6.82–6.90 (3H, m, ArH), 8.85 (1H, br s, thiourea NH), 10.75 (1H, br s, thiourea *NH*CO); MS *m/e* 352 (M^+). Anal. ($C_{18}H_{28}N_2O_3S$) C, H, N.

***N*-(3-Methoxy-4-hydroxybenzyl)-*N'*-octyl-*S*-methylthiouronium Iodide (16).** A solution of **14a** (0.5 g, 1.5 mmol) in dry acetone (20 mL) was stirred at room temperature while methyl iodide (1.2 mL, 19 mmol) was added. The mixture was stirred overnight before the removal of solvent and excess methyl iodide *in vacuo*. The colorless crystalline residue was recrystallized from diethyl ether/acetone to give colorless crystals: yield 0.31 g (43%); mp 88–92 °C; TLC (silica, CH_2Cl_2/MeOH 10:1) R_f 0.2; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.85 (3H, t, alkyl CH_3), 1.25 (12H, env, alkyl CH_2), 2.9 (3H, s, SCH_3), 3.7 (2H, m, $=N^+CH_2$), 3.85

(3H, s, $ArOCH_3$), 4.80 (2H, br s, $ArCH_2NH$), 6.7–7.4 (3H, m, ArH), 7.9–8.8 (2H, br s, ArOH and NH); MS *m/e* 339 (M^+). Anal. ($C_{18}H_{31}N_2O_2SI$) C, H, N.

***N*-Cyano-*N'*-octyl-*O*-phenylisourea.** To a suspension of diphenyl cyanocarbonimidate (3 g, 12.5 mmol) in iPrOH (20 mL) was added a solution of octylamine (1.6 g, 12.5 mmol) in iPrOH (10 mL). After 10 min of stirring the reaction mixture was completely solubilized. The solution was stirred overnight and then cooled on ice, precipitating colorless needles. The crystals were collected by filtration, washed with water, and dried *in vacuo*: yield 0.75 g (22%); TLC (silica, cyclohexane/EtOAc 1:1) R_f 0.6; ^1H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.25 (12H, env, alkyl CH_2), 3.40 (2H, m, $NHCH_2CH_2$), 7.0–7.5 (6H, m, ArH and NH, 5H on D_2O shake).

***N*-(4-Hydroxy-3-methoxybenzyl)-*N'*-octyl-*N''*-cyanoguanidine (17).** To a stirred suspension of *N*-cyano-*N'*-octyl-*O*-phenylisourea (0.75 g, 2.7 mmol) in iPrOH (10 mL), under N_2, was added triethylamine (0.37 g, 3.7 mmol) and **9** (0.62 g, 3.7 mmol). The mixture was refluxed for 2 h, after which time the solvent was removed *in vacuo* and the crude product was deprotected without further purification. The crude protected product was taken up in THF (15 mL) and stirred on ice, under N_2, during the addition of 1 N HCl (10 mL). The mixture was stirred for a further 1 h before the addition of water (100 mL) and extraction with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and the solvent removed *in vacuo* to give a colorless solid. The compound, which was purified by flash column chromatography (silica, cyclohexane/EtOAc 1:1), crystallized from the column solvent to give colorless crystals: yield 0.33 g (36%); mp 94–96 °C; TLC (silica, cyclohexane/EtOAc 1:1) R_f 0.14; ^1H NMR (60 MHz, $CDCl_3$) δ 0.86 (3H, t, alkyl CH_3), 1.30 (12H, env, alkyl CH_2), 3.10 (2H, m, $NHCH_2CH_2$), 3.90 (3H, s, $ArOCH_3$), 4.30 (2H, d, $ArCH_2NH$), 5.0 (1H, br s, $NCNNHCH_2$), 5.55 (1H, br s, $ArCH_2NH$), 5.75 (1H, s, ArOH), 6.90–6.95 (3H, m, ArH); MS *m/e* 332 (M^+). Anal. ($C_{18}H_{28}N_4O_4$) C, H, N.

1-Nitro-2-(methylthio)-2-[(3-methoxy-4-hydroxybenzyl)amino]ethene. To a solution of vanillylamine hydrochloride (7.58 g, 40 mmol) and triethylamine (4.04 g, 40 mmol) in EtOH (40 mL) was added 1,1-bis(methylthio)-2-nitroethene (6.12 g, 40 mmol) in EtOH (10 mL). The solution was refluxed, under N_2, for 60 min. After this time, the solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (3 × 100 mL) and water (100 mL). The combined organic extracts were washed with saturated NaCl and dried over $MgSO_4$. The solvent was removed *in vacuo* to leave a yellow oil which was purified by flash column chromatography (silica, $CHCl_3$) and recrystallized from diethyl ether/petroleum ether (bp 100–120 °C) to give a pale yellow crystalline solid: yield 6.7 g (62%); mp 138–141 °C; TLC (silica, CH_2Cl_2/MeOH 10:1) R_f 0.75; ^1H NMR (60 MHz, $CDCl_3$) δ 2.38 (3H, s, SCH_3), 3.82 (3H, s, $ArOCH_3$), 4.45 (2H, d, J = 6 Hz, $ArCH_2NH$), 5.64 (1H, s, ArOH), 6.55 (1H, s, $=CHNO_2$), 6.8 (3H, m, ArH), 10.65 (1H, br s, NH); MS *m/e* 270 (M^+). Anal. ($C_{11}H_{14}N_2O_4S$) C, H, N.

1-Nitro-2-(octylamino)-2-[(3-methoxy-4-hydroxybenzyl)amino]ethene (18). To a solution of 1-nitro-2-(methylthio)-2-[(3-methoxy-4-hydroxybenzyl)amino]ethene (1.0 g, 3.7 mmol) in tBuOH (25 mL) was added *n*-octylamine (0.5 g, 3.7 mmol) in acetonitrile (25 mL). The solution was refluxed, under N_2, for 5 h, after which time the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica, $CHCl_3$) and then recrystallized from EtOAc/petroleum ether (bp 100–120 °C) to give colorless crystals: yield 0.63 g (48.5%); mp 143–144 °C; TLC (silica, CH_2Cl_2/MeOH 25:1) R_f 0.6; ^1H NMR (60 MHz, $CDCl_3$) δ 0.95 (3H, t, alkyl-CH_3), 1.1–1.8 (12H, m, alkyl CH_2), 3.25 (2H, br s, $NHCH_2CH_2$), 3.84 (3H, s, $ArOCH_3$), 4.32 (2H, br s, $ArCH_2NH$), 4.9 (1H, br s, NH), 6.12 (1H, s, ArOH), 6.55 (1H, s, $=CHNO_2$), 6.79 (3H, m, ArH), 10.4 (1H, br s, NH); MS *m/e* 351 (M^+). Anal. ($C_{18}H_{29}N_3O_4$) C, H, N.

[4-(Benzyloxy)-3-methoxyphenyl]acetaldehyde. 1-[4-(Benzyloxy)-3-methoxyphenyl]ethan-2-ol[22] (7.6 g, 30 mmol) and pyridinium chlorochromate (18.9 g, 111 mmol) were stirred in dry CH_2Cl_2 (50 mL) for 45 min. The resulting brown solution was diluted with diethyl ether (150 mL) and passed through a short pad of silica to remove the chromium salts. The ether was removed *in vacuo* leaving a pale yellow oil which was purified by flash column chromatography (silica, cyclohexane/EtOAc 5:1) to give a pale yellow oil: yield 2.7 g (36%); TLC (silica, cyclohexane/EtOAc 4:1) R_f 0.25; ^1H NMR (60 MHz, $CDCl_3$) δ 3.6 (2H, d, $ArCH_2CHO$), 3.9 (3H, s, $ArOCH_3$), 5.2 (2H, s, OCH_2Ar), 6.8 (3H, m, vanillyl ArH), 7.4 (5H, m, benzyl ArH), 9.8 (1H, t, CH_2CHO); MS *m/e* 256 (M^+).

1-[4-(Benzyloxy)-3-methoxyphenyl]undecan-2-ol. Nonylmagnesium bromide was prepared *in situ* by warming (to 40 °C) magnesium (0.75 g, 31 mmol) and bromononane (3.3 g, 16 mmol) in dry diethyl ether together with a crystal of iodine, until all the metal had dissolved. The solution was cooled on ice and stirred under N_2 while [4-(benzyloxy)-3-methoxyphenyl]acetaldehyde (4 g, 16 mmol), in dry ether (100 mL), was added. The mixture was stirred at room temperature for 1 h before it was poured onto ice. The mixture was acidified with 15% H_2SO_4 and then extracted with ether. The organic extracts were washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed *in vacuo*, leaving a yellow oil which was purified by flash column chromatography to give a colorless solid: yield 2.4 g (40%); TLC (silica, cyclohexane/EtOAc 4:1) R_f 0.25; ^1H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.1–1.45 (16H, env, alkyl CH_2), 2.55–2.9 (2H, m, $ArCH_2CHOH$), 3.8 (1H, m, $CH_2CHOHCH_2$), 3.9 (3H, s, $ArOCH_3$), 5.1 (2H, s, $ArCH_2O$), 6.7–6.9 (3H, m, vanillyl ArH), 7.2–7.5 (benzyl rH); MS *m/e* 384 (M^+).

1-[4-(Benzyloxy)-3-methoxyphenyl]undecan-2-one. 1-[4-(Benzyloxy)-3-methoxyphenyl]undecan-2-ol (1.2 g, 3.1 mmol) and pyridinium chlorochromate (2 g, 9.3 mmol) were stirred in dry CH_2Cl_2 (90 mL) for 2 h. The brown solution was diluted with ether (100 mL) and passed through a short pad of silica. The solvent was removed *in vacuo* from the colorless solution, leaving an oil which was purified by flash column chromatography (silica, cyclohexane/EtOAc 4:1) to give a solid which was recrystallized from petroleum ether (bp 100–120 °C) to give colorless crystals: yield 0.7 g (59%); mp 46–47 °C; TLC (silica, cyclohexane/EtOAc 4:1) R_f 0.4; ^1H NMR (60 MHz, $CDCl_3$) δ 0.88 (3H, t, alkyl CH_3), 1.3 (14H, env, alkyl CH_2), 2.42 (2H, t, $COCH_2CH_2$), 3.58 (2H, s, $ArCH_2CO$), 3.86 (3H, s, $ArOCH_3$), 5.12 (2H, s, OCH_2Ar), 6.8 (3H, m, vanillyl ArH), 7.3–7.5 (5H, m, benzyl ArH); MS *m/e* 382 (M^+).

1-(4-Hydroxy-3-methoxyphenyl)undecan-2-one (21). 1-[4-(Benzyloxy)-3-methoxyphenyl]undecan-2-one (0.5 g, 1.3 mmol) was added to a suspension of 10% Pd/C (50 mg) in MeOH (30 mL) under an atmosphere of H_2. The mixture was stirred for 18 h before removal of the catalyst by filtration through Celite. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica, CH_2Cl_2) to give a colorless oil: yield 0.36 g (94%); TLC (silica, cyclohexane/EtOAc 4:1) R_f 0.2; ^1H NMR (60 MHz, $CDCl_3$ δ 0.89 (3H, t, alkyl CH_3), 1.25 (14H, env, alkyl CH_2), 2.45 (2H, t, $COCH_2CH_2$), 3.60 (2H, s, $ArCH_2CO$), 3.88 (3H, s, $ArOCH_3$), 5.58 (1H, s, ArOH), 6.8 (3H, m, ArH); MS *m/e* 292 (M^+); HRMS *m/e* calcd for $C_{18}H_{26}O_3$ 292.2038, found 292.2064; HPLC RP_{18} (gradient 10–70% CH_3CN/0.1% aqueous TFA) >99% pure.

1-(4-Hydroxy-3-methoxyphenyl)-1-hydroxyundecane. Vanillin (3.5 g, 23 mmol) was refluxed with hexamethyldisilazane (20 mL) for 3 h before removal of the silylating agent *in vacuo*. The TMS-protected vanillin was added, as a solution in dry diethyl ether (without further purification), to a solution of decylmagnesium bromide at 0 °C. The Grignard reagent was prepared *in situ* by warming (to 40 °C) magnesium (0.6 g, 25 mmol) and bromodecane (5.0 g, 22.6 mmol) in dry ether together with a crystal of iodine, until all the metal had dissolved. The mixture was allowed to warm to room temperature and was stirred for 1 h and then poured on ice, acidified with 15% H_2SO_4, and extracted with ether. The organic layer was dried with Na_2SO_4 and the crude product was purified by flash column chromatography (silica, cyclohexane/EtOAc 10:1) to give a white solid on evaporation: yield 2.0 g (30%); mp 82–84 °C; TLC (silica, cyclohexane/EtOAc 1:1) R_f 0.7; ^1H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.3 (18H, env, alkyl CH_2), 3.89 (3H, s, $ArOCH_3$), 4.6 (1H, t, $CHOH$), 5.7 (1H, br s, ArOH), 6.9 (3H, m, ArH).

1-(4-Hydroxy-3-methoxyphenyl)undec-1-ene. 1-(4-Hydroxy-3-methoxyphenyl)-1-hydroxyundecane (0.4 g, 1.4 mmol) and $NaHSO_4$ (0.1 g, 0.83 mmol) were refluxed in xylene (10 mL) in a Dean–Stark apparatus for 2 h. The $NaHSO_4$ was removed by filtration and the solvent removed *in vacuo* to leave a brown oil which was purified by flash column chromatography (silica, cyclohexane/EtOAc 10:1) to give a colorless oil: yield 0.28 g (75%);

^{1}H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.3 (14H, env, alkyl CH_2), 2.2 (2H, d of t, =CHCH_2), 3.9 (3H, s, $ArOCH_3$), 5.6 (1H, br s, ArOH), 6.2–6.5 (2H, m, CH=CH), 6.8 (3H, m, ArH).

1-(4-Hydroxy-3-methoxyphenyl)undecane (22). 1-(4-Hydroxy-3-methoxyphenyl)undec-1-ene (0.28 g, 1.0 mmol) was stirred with 10% Pd/C (10 mg) in MeOH (10 mL), under an atmosphere of H_2, for 2 h. The catalyst was removed by filtration through Celite and the crude product was purified by flash column chromatography (silica, cyclohexane/EtOAc 10:1) to leave a colorless solid which was recrystallized from methanol/water to give colorless crystals: yield 0.18 g (65%); mp 31–33 °C; TLC (silica, cyclohexane/EtOAc 1:1) R_f 0.65; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.9 (3H, t, alkyl CH_3), 1.3 (18H, env, alkyl CH_2), 2.55 (2H, t, $ArCH_2CH_2$), 3.9 (3H, s, $ArOCH_3$), 5.5 (1H, s, ArOH), 6.8 (3H, m, ArH); MS *m/e* 278 (M^+). Anal. ($C_{18}H_{30}O_2$) 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 (4 pages). Ordering information is given on any current masthead page.

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