New Low-Density Lipoprotein Receptor Upregulators Acting *via* a Novel Mechanism

Michael J. Ashton, Thomas J. Brown, Garry Fenton, Frank Halley,* Mark F. Harper, Peter M. Lockey, Barry Porter, Alan G. Roach, Keith A. J. Stuttle, Nigel Vicker, and Roger J. A. Walsh

Rhône-Poulenc Rorer, Dagenham Research Centre, Rainham Road South, Dagenham, Essex RM10 7XS, U.K.

Received February 26, 1996[⊗]

The synthesis and biological activity of a new series of benzamides and related compounds that upregulate the expression of the low-density lipoprotein (LDL) receptor in human hepatocytes (HepG2 cells) by a novel mechanism are described. The lead compound, *N*-[5-[(3-cyclohexylpropionyl)amino]-2-methylphenyl]-4-hydroxybenzamide (**1**, RPR102359), increased the expression of the LDL receptors in HepG2 cells by 80% when tested at a concentration of 3 μM. Mevinolin (lovastatin) was found to increase the LDL receptor expression by 70% at the same concentration. In contrast to mevinolin, **1** was found to have no effect on cholesterol biosynthesis in liver homogenates or in HepG2 cells at doses where substantial upregulation of the LDL receptor was observed and thus stimulated LDL receptor expression by a novel mechanism.

Introduction

Elevated levels of plasma cholesterol are associated with increased risk of premature atherosclerosis, particularly when associated with certain lipoprotein fractions including low-density lipoprotein (LDL).[1] The liver is responsible for clearance of approximately 80% of LDL from the circulation *via* specific LDL receptors on the plasma membrane of hepatocytes.[2] On binding LDL, the receptor is internalized in endocytic vesicles, the LDL particle is degraded, and the receptor is recycled. The capacity of the liver to control plasma LDL levels is critically dependent on the number of LDL receptors expressed on the cell membrane.

Familial hypercholesterolemia (FH) is a condition resulting from mutant alleles of the LDL receptor gene. Patients show abnormally high levels of plasma LDL as a consequence of either severely reduced numbers or a complete absence of hepatic LDL receptors. In the homozygote, accelerated atherosclerosis can lead to coronary heart disease even in childhood. Transplantation of normal liver into an FH patient resulted in a normalization of plasma cholesterol levels.[3] Hence the liver is the major target organ for hypolipidemic drugs which act by upregulation of LDL receptor expression.

LDL receptor expression is controlled primarily by feedback repression of the LDL receptor gene by cholesterol or its metabolites.[4] Hepatic cholesterol comes from two main sources: LDL uptake *via* the LDL receptor and synthesis from acetate, the rate-limiting step of which is catalyzed by 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase. Cholesterol is secreted from the liver as a component of lipoproteins or in the bile as either neutral or acidic sterols. Excess cholesterol is esterified and stored in the cytoplasm as lipid droplets.

The transcription rate of the LDL receptor gene appears to be the main mechanism by which the level of receptor expression is controlled. Either cholesterol itself, possibly in a regulatory pool, or an oxysterol derivative regulates transcription of the LDL receptor, HMG CoA reductase, and synthase genes. Cholesterol

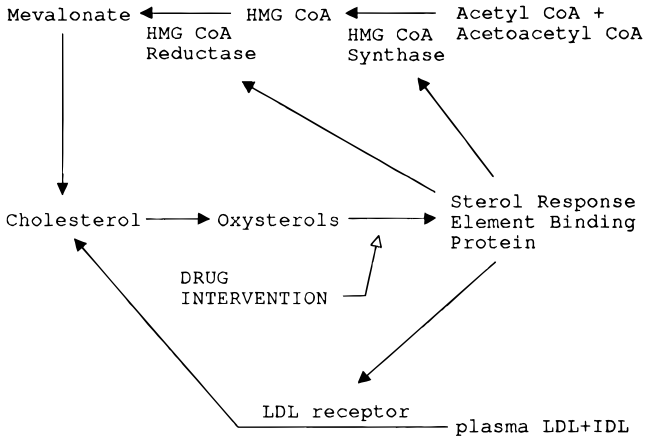


Figure 1. Hypothesis of transcriptional regulation and site of drug intervention.

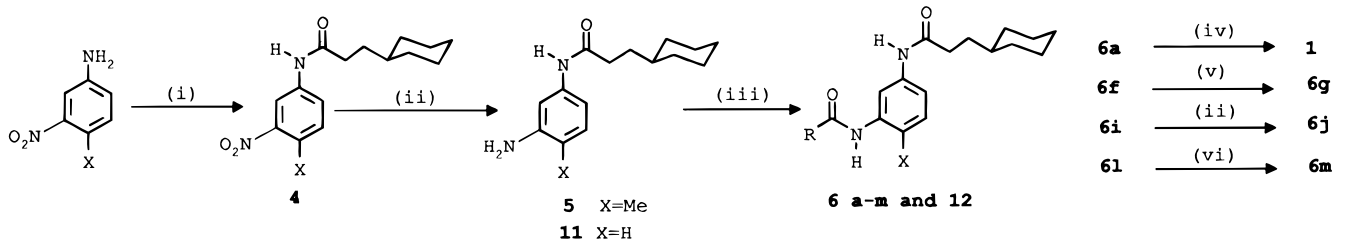
or an oxysterol regulates the function of a sterol response element-binding protein (SREBP) to downregulate expression of the LDL receptor and HMG CoA reductase genes. Consequently inhibition of cholesterol biosynthesis by HMG CoA reductase inhibitors including mevinolin, or inhibition of cholesterol oxidation to regulatory oxysterols by ketoconazole,[5] results in enhanced expression of LDL receptors. Additionally evidence now exists for regulation of LDL receptor expression independent of intracellular cholesterol-regulated pathways. Enhanced expression of LDL receptors in the presence of suppressive concentrations of 25-hydroxycholesterol has been observed with insulin,[6] growth factors,[7] and cyclic AMP.[8] Pharmacological regulation of hepatic LDL receptor expression by a sterol independent mechanism would represent a novel and attractive therapeutic target for the treatment of hypercholesterolemia avoiding potential toxic effects of inhibiting cholesterol synthesis.

The choice of where to target a new drug therapy was directed by an understanding of the regulatory process for controlling cellular cholesterol levels. Putative pathways, involving the SREBP, for the regulation of LDL receptors and cholesterol biosynthesis are shown in Figure 1. Several groups have shown interest in

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1996.

S0022-2623(96)00153-7 CCC: $12.00

Scheme 1[a]



6a X=Me R=4Acetoxyphenyl
6b X=Me R= Phenyl
6c X=Me R= Cyclohexyl
6d X=Me R= 3-Hydroxyphenyl
6e X=Me R= 2-Hydroxyphenyl
6f X=Me R= 4-Methoxycarbonylphenyl
6g X=Me R= 4-Hydroxymethylphenyl
6h X=Me R= 3,4-methylenedioxyphenyl
6i X=Me R= 4-Nitrophenyl
6j X=Me R= 4-Aminophenyl
6k X=Me R= 3-Pyridyl
6l X=Me R= 4-Pyridyl
6m X=Me R= 4-Pyridyl-N-oxide
12 X=H R=4Acetoxyphenyl

[a] Reagents: (i) cyclohexylpropionyl chloride, Et_3N, CH_2Cl_2; (ii) H_2−Pd/C, EtOH; (iii) RCOCl, Et_3N, CH_2Cl_2; (iv) NaOH (1 M), EtOH, room temperature; (v) $LiBH_4$, THF, room temperature; (vi) mCPBA, $CHCl_3$, room temperature.

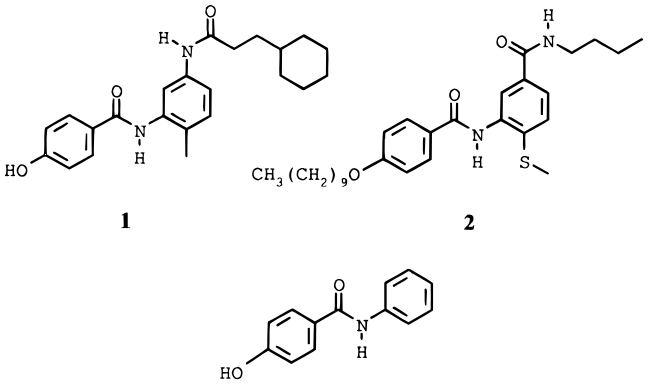
controlling HMG CoA reductase gene expression using oxysterols or oxysterol mimetics.[9] Indeed Larsen *et al.*[9j] have recently shown that a series of oxysterol mimetics may suppress HMG CoA reductase gene expression without concomitant suppression of the LDL receptor gene. Studies by Kandutsch[10] demonstrated a correlation between the binding affinity of oxysterols for an "oxysterol-binding protein" and repression of HMG CoA reductase activity. This suggested that compounds may be discovered which act as antagonists to selectively enhance LDL receptor gene expression by inhibition of oxysterol binding to a related SREBP. A recent publication showed indeed that some sterol derivatives are capable of upregulating the LDL receptors in CHO cells, in the presence of 25-hydroxycholesterol.[11]

Steroidal mimetics seemed more suitable for screening than oxysterols for the principal reason that they would have no steroid-related side effects. A series of benzamides (*e.g.*, RP 64477, **2**) were shown to be effective inhibitors of acyl coenzyme A:cholesterol acyltransferase (ACAT). It was proposed that these compounds mimic the structure of cholesteryl ester and thereby compete for the binding site of the natural enzyme substrate.[12]

Compounds with prototype structure **3** were therefore chosen from a 2D database search of registry compounds. It was assumed that the phenol group of **3** would substitute for the C-3 hydroxyl or ketone of a typical oxysterol, such as 25-hydroxycholesterol, and that the benzanilide would have some topographical identity with the steroid nucleus. Screening compounds in a HepG2 whole cell assay and measuring the number of LDL receptors expressed on the cell surface led to the discovery of compound **1** (RPR102359) which was found to increase the expression of the LDL receptors in HepG2 cells by 80% when tested at 3 μM (the standard, mevinolin, increased LDL receptor expression by 70% at 3 μM). The functional activity of the LDL receptors was confirmed by their ability to internalize human [^{125}I]LDL.[13]

Chemistry

The benzamides **1, 6a−m, 9a,g,l,** and **10b−f,i−k,m** were prepared in a regiospecific manner by acylation of the appropriate 3-nitroaniline followed by hydrogenation of the nitro group and acylation of the resulting



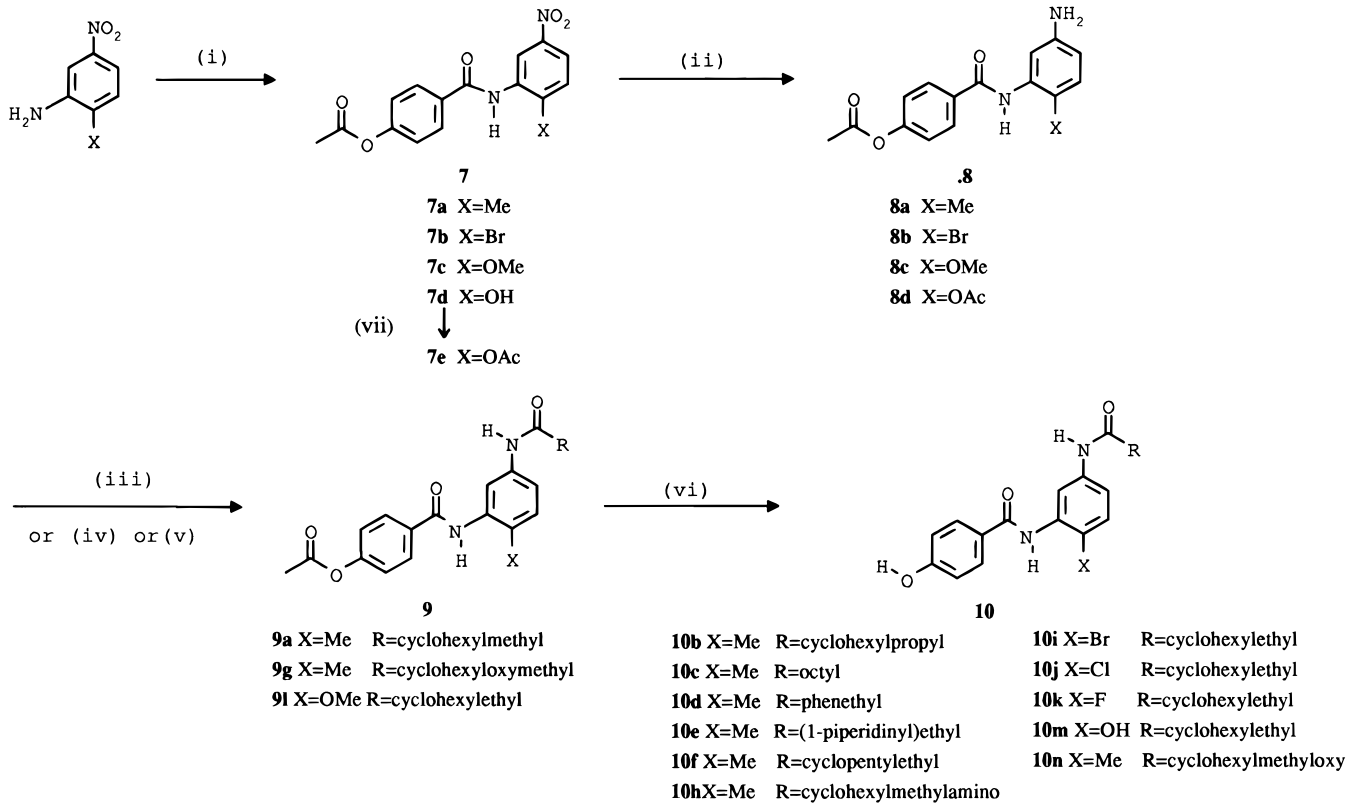
amine (Schemes 1 and 2). The carbamate **10n** and urea **10h** were prepared by treating *in situ* the isocyanate derived from the aniline **8a** with cyclohexylmethanol and cyclohexylmethylamine, respectively (Scheme 2). The benzamide **12** was prepared in two steps from 1,3-phenylenediamine, by successive acylation with 3-cyclohexylpropionyl chloride (to give **11**) and 4-acetoxybenzoyl chloride (Scheme 1).

The retroamide **14** was prepared by coupling 4-acetoxyaniline with 2-methyl-5-nitrobenzoyl chloride followed by hydrogenation and acylation of the nitro group and deprotection of the phenol (Scheme 3). The *N*-benzylaniline **15** was prepared by reductive alkylation of the aniline **5** with 4-acetoxybenzaldehyde using sodium borohydride (Scheme 4).

The 1,2-diphenylpropenonitriles **20-22** were prepared by Knoevenagel condensation of the appropriate arylacetonitrile with the benzaldehyde **19** (Scheme 5). The *Z* configuration assigned to the product is consistent with NMR spectroscopy. In the ^{1}H NMR, irradiation of the vinylic proton of compound **20** gave an NOE effect on the protons at positions 2 and 4 of the pyridine ring, indicating a *cis* relationship between the pyridine ring and the vinylic proton. In the coupled ^{13}C NMR spectrum, a coupling constant of 14.5 Hz between the nitrile carbon and the vinylic proton indicated a *trans* relationship between these two groups.

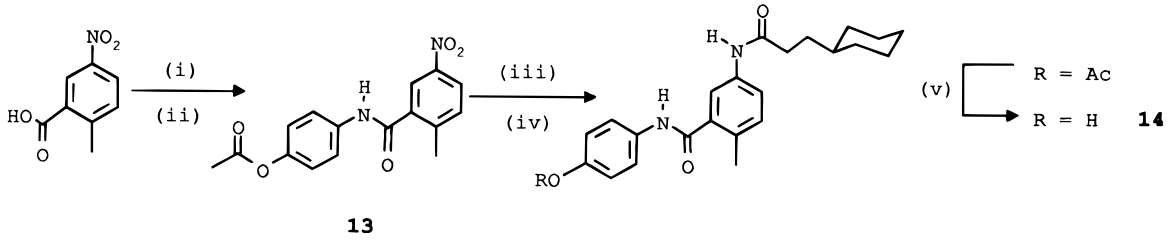
The 2-phenylbenzimidazoles **25−27** were prepared by treating the appropriate 1,2-benzenediamine with the benzoyl chloride derived from **24** in the presence of

Scheme 2[a]



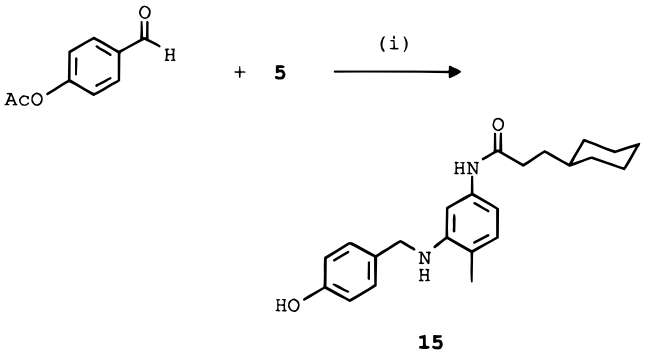
[a] Reagents: (i) 4-acetoxybenzoyl chloride, Et_3N, CH_2Cl_2; (ii) H_2, Pd/C, EtOH; (iii) RCOCl, Et_3N, CH_2Cl_2; (iv) triphosgene, THF, Et_3N, then cyclohexylmethylamine; (v) triphosgene, THF, Et_3N, then cyclohexylmethanol; (vi) aqueous NaOH, EtOH; (vii) acetic anhydride.

Scheme 3[a]



[a] Reagents: (i) $SOCl_2$, CH_2Cl_2; (ii) 4-acetoxyaniline, Et_3N, CH_2Cl_2; (iii) H_2, Pd/C, EtOH; (iv) 3-cyclohexylpropionyl chloride, Et_3N, CH_2Cl_2; (v) aqueous NaOH, EtOH.

Scheme 4[a]



[a] Reagents: (i) toluene, PTSA, reflux, then $NaBH_4$, EtOH.

triethylamine at −60 °C to give the *N*-(2-aminophenyl)-carboxamide (higher temperatures led to the formation of the bis-carboxamide). Cyclization to the benzimidazole was achieved by heating to 200−220 °C (Scheme 6).

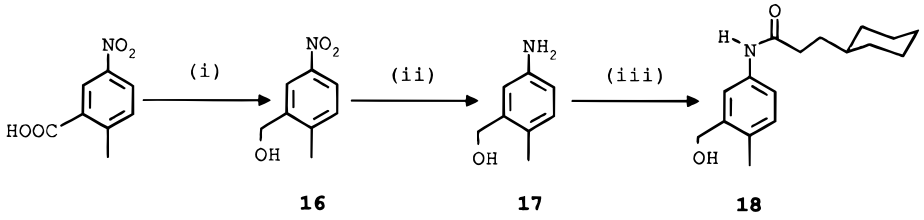
The formation of the retroamide **30** in the right-hand part of the molecule was achieved by standard methodology starting from 4-methyl-3-nitrobenzoyl chloride (Scheme 7). The ketones **34** and **35** were prepared in four steps from toluene *via* a Friedel−Crafts acylation followed by nitration, hydrogenation, and acylation (Scheme 8).

Results and Discussion

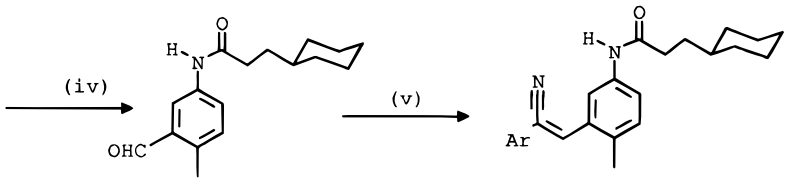
A chemistry program was initiated to increase the *in vitro* activity of the lead compound **1**. Chemical modifications to **1** have been examined in five main areas of the molecule as indicated in Figure 2. Each part of the molecule was systematically modified and the activity compared to that of **1** as shown in Tables 1−5. Mevinolin was used in the first assays as a standard for the upregulation of LDL receptors (see Table 1) and was later replaced by compound **20**.

Changes to the 4-hydroxyphenyl group (region 1) included replacement by aromatic and aliphatic groups, selections of which are listed in Table 1. The first two entries (compounds **1** and **6a**) show similar activities, more likely due to the fact that the acetoxy group is hydrolyzed in the biological test, presumably by me-

Scheme 5[a]



16 **17** **18**

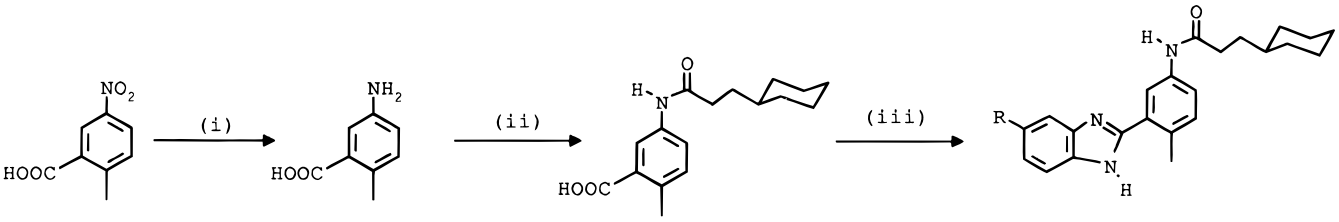


19

20 Ar = 3-pyridyl
21 Ar = 4-hydroxyphenyl
22 Ar = 3,4-methylenedioxyphenyl

[a] Reagents: (i) B_2H_6, THF; (ii) H_2, Pd/C, EtOAc; (iii) 3-cyclohexylpropionyl chloride, Et_3N, CH_2Cl_2; (iv) MnO_2, THF, reflux; (v) $ArCH_2CN$, MeOH, K_2CO_3, reflux.

Scheme 6[a]

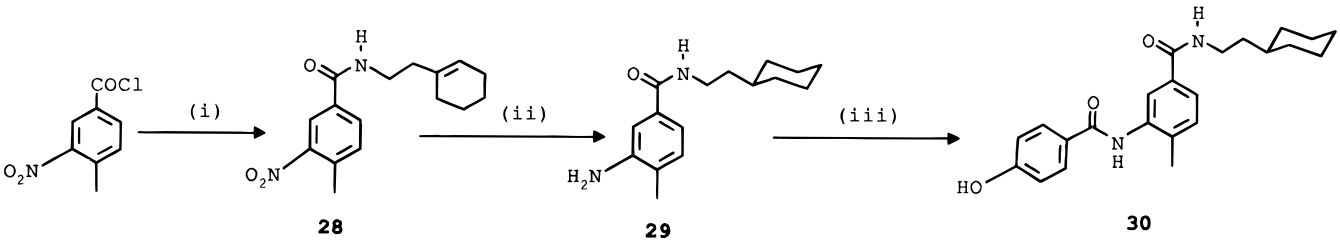


23 **24**

25 R = H
26 R = 5-Me
27 R = 5-OH

[a] Reagents: (i) H_2, Pd/C, EtOH; (ii) 3-cyclohexylpropionyl chloride, Et_3N, CH_2Cl_2; (iii) $SOCl_2$, toluene, reflux, then 1,2-NH_2-Ar, Et_3N, CH_2Cl_2, −60 °C, then 200−220 °C, neat, 0.5−2 h.

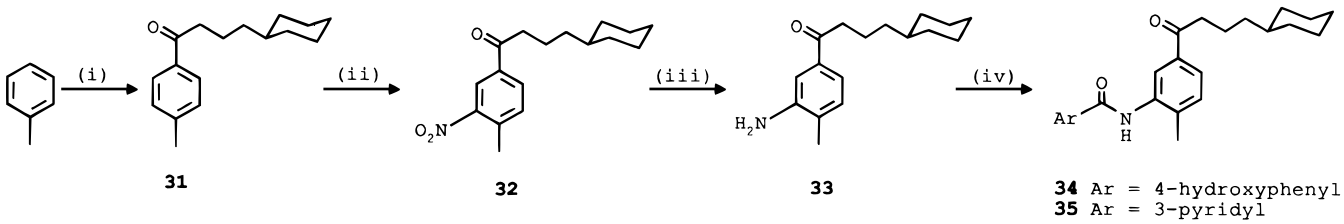
Scheme 7[a]



28 **29** **30**

[a] Reagents: (i) 2-(1-cyclohexenyl)ethylamine, Et_3N, CH_2Cl_2; (ii) H_2, Pd/C, EtOAc; (iii) 4-acetoxybenzoyl chloride, Et_3N, CH_2Cl_2, then aqueous NaOH, EtOH.

Scheme 8[a]

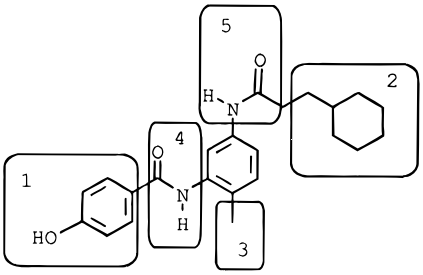


31 **32** **33**

34 Ar = 4-hydroxyphenyl
35 Ar = 3-pyridyl

[a] Reagents: (i) 4-cyclohexylbutyryl chloride, $AlCl_3$, reflux; (ii) H_2SO_4, HNO_3, −7 °C; (iii) H_2, Pd/C, EtOH; (iv) ArCOCl, CH_2Cl_2, Et_3N.

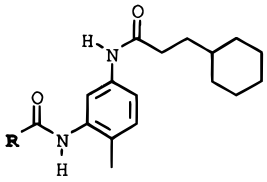
tabolism occurring in the whole cell assay during the 24 h incubation time. (This is also applicable to all acetoxyphenyl compounds in subsequent tables.) Replacement by aliphatic moieties resulted in loss of activity as indicated for the cyclohexyl derivative **6c**. The phenyl compound **6b** was equiactive with **1**, and aromatic groups substituted *meta* and *para* to the amide bond are tolerated with limited functionality (entries **6a,d,g,h,j**). In general when the *meta* and *para* positions have electron-donating groups, activity is retained;



1

Figure 2. Five areas for chemical modifications of compound **1**.

Table 1. Effect of Modification of R (Region 1) in Compound **1** *in Vitro* in HepG2 Cells[a]



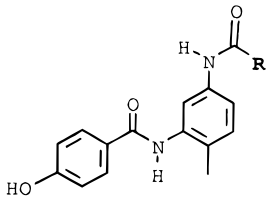
compd[c]	R	upregulation of the LDL receptors (%) (at 3 μM)	EC_{50}[b] (μM)
1	4-hydroxyphenyl	80	1.7
6a	4-acetoxyphenyl	82	2.5
6b	phenyl	50	2
6c	cyclohexyl	0	
6d	3-hydroxyphenyl	59	2
6e	2-hydroxyphenyl	0	
6f	4-(methoxycarbonyl)phenyl	3	
6g	4-(hydroxymethyl)phenyl	44	7.6
6h	3,4-(methylenedioxy)phenyl	111	0.6
6i	4-nitrophenyl	11	
6j	4-aminophenyl	58	3.8
6k	3-pyridyl	83	1.2
6l	4-pyridyl	−5	
6m	4-pyridyl *N*-oxide	7	

[a] Each assay was performed in five replicates, and the results correspond to a mean value (see the Experimental Section for details on the assay). [b] The EC_{50}, here, is the concentration at which one-half the maximum upregulation is observed and is measured for compounds increasing the number of LDL receptors by more than 40% at 3 μM. It was observed in repeat assays that the EC_{50} did not vary despite differences between assays in the degree of maximum upregulation of receptors achieved. [c] In the same assay mevinolin gave 70% upregulation at 3 μM with an EC_{50} of 0.2 μM.

when the positions are substituted with electron-withdrawing groups, the activity is abolished, as seen for compounds **6f,i**. Substitution at the *ortho* position is disfavored (compound **6e**) probably due to this position having the greatest conformational influence with respect to the orientation of the aromatic ring relative to the amide bond. The 3-pyridyl compound **6k** was surprisingly active, while compounds **6l,m** were devoid of activity. The 3,4-(methylenedioxy)phenyl derivative **6h** was the most potent compound in this series, being approximately 3-fold more potent than the lead compound **1**.

Modifications to the ethylcyclohexyl group in region 2 are listed in Table 2. Minor changes in this region have dramatic effects on activity. Altering the alkyl chain length by one carbon unit severely reduced the activity as indicated for the cyclohexylmethyl and cyclohexylpropyl derivatives **9a** and **10b**. A similar detrimental effect was observed when changing the ring

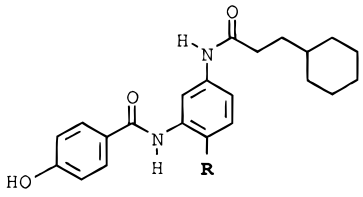
Table 2. Effect of Modifications to R (Region 2) in Compound **1** *in Vitro* in HepG2 Cells[a]



compd	R	upregulation of the LDL receptors (%) (at 3 μM)	EC_{50} (μM)
1	cyclohexylethyl	80	1.7
9a	cyclohexylmethyl[b]	3	
10b	cyclohexylpropyl	32	4
10c	octyl	−10	
10d	phenethyl	−20	
10e	(1-piperidinyl)ethyl	−2	
10f	cyclopentylethyl	25	
9g	(cyclohexyloxy)methyl[b]	17	

[a] See footnote a of Table 1. [b] Prepared as the acetate of the phenol residue.

Table 3. Effect of Modification of R (Region 3) in Compound **1** *in Vitro* in HepG2 Cells[a]



compd	R	upregulation of the LDL receptors (%) (at 3 μM)	EC_{50} (μM)
1	Me	80	1.7
12	H[b]	6	
10i	Br	6	
10j	Cl	8	
10k	F	12	
9l	OMe[b]	−13	
10m	OH	−3	

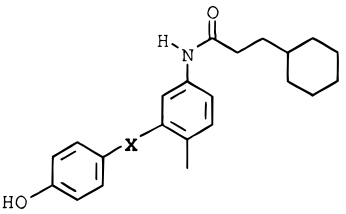
[a] See footnote a of Table 1. [b] Prepared as the acetate of the phenol residue.

size, the cyclopentylethyl derivative **10f** only being weakly active. Replacement of the cyclohexyl group by a straight alkyl chain (**10c**) and phenyl (**10d**) abolished activity. Introduction of heteroatoms, like in the (1-piperidinyl)ethyl **10e** and the (cyclohexyloxy)methyl **9g**, led to a loss of activity, indicating a hydrophobic interaction with the receptor. In this region the cyclohexylethyl moiety appears optimal for activity. This group has the requisite size and is able to attain a suitable conformation for hydrophobic interactions.

Substitutions for the methyl group in the central phenyl ring in region 3 were examined, and selected examples are collected in Table 3. Removal of the methyl group gave the unsubstituted analogue **12**, which was inactive. Replacement of the methyl group by bromine, chlorine, and fluorine abolished activity (entries **10i**−**k**). Substitution of the methyl group by methoxy and hydroxy also resulted in loss of activity as shown for compounds **9l** and **10m**. These results indicate that the methyl group not only is important for conformational reasons but also has a hydrophobic interaction. The syntheses of different substituents at

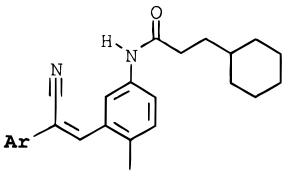
Table 4

1. Effect of Modification of the Central Amide (Region 4) in Compound **1** *in Vitro* in HepG2 Cells[a]



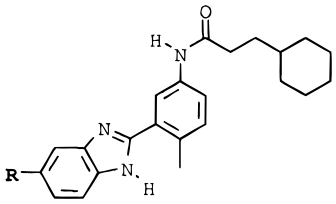
compd	X	upregulation of the LDL receptors (%) (at 3 μM)	EC_{50} (μM)
1	−CONH−	80	1.7
14	−NHCO−	60	7
15	$-CH_2NH-$	−11	

2. Effect of Modification of Ar in α,β-Unsaturated Nitrile Compounds Related to **1** *in Vitro* in HepG2 Cells[a]



compd	Ar	upregulation of the LDL receptors (%) (at 3 μM)	EC_{50} (μM)
20	3-pyridyl	126	1
21	4-hydroxyphenyl	21	
22	3,4-(methylenedioxy)phenyl	108	0.7

3. Effect of Modification of R in Benzimidazole Compounds Related to **1** *in Vitro* in HepG2 Cells[a]



compd	R	upregulation of the LDL receptors (%) (at 3 μM)	EC_{50} (μM)
25	H	45	1.3
26	Me	91	1.3
27	OH	134	0.7

[a] See footnote a of Table 1.

that position proved to be lengthy and difficult, and the priority was given to the investigation of the other parts of the molecule.

Modifications to the amide bond in region 4 are shown in Table 4-1. The reverse amide **14** had slightly reduced activity compared to **1**. Reduction of the amide carbonyl gave the benzylamine **15** which was devoid of activity. The amide bonds in both **1** and **14** have the transoid geometry, which is a conformation unlikely to be favored by the nonrigid benzylamine **15**. The position of the carbonyl function in the bond linking the two aromatic rings will also exert a profound electronic effect in this region, and the directional influence of this electronic effect is likely to play a role in the activity of a compound. Other replacements for the amide bond are depicted in Tables 4-2 and 4-3. The α,β-unsaturated nitriles **20**−**22** and the benzimidazoles **25**−**27** are rigid families of compounds that both fit well when superimposed with the preferred low-energy conformation of **1** (Figure 3). Both the α,β-unsaturated nitriles and the benzimidazoles would exert a directional electronic effect similar to that of a carbonyl of an amide moiety, and activities similar to that of the parent compound **1** are observed. Analogues from these different chemical series show comparable activities to the benzamide series, with compounds **22** and **27** being as potent as **6h**.

Changes to the amide bond in region 5 are listed in Table 5. Reversal of the amide bond gave compound **30** which was equipotent with **1**. Replacement of the amide bond by urea (**10h**) or carbamate (**10n**) moieties abolished activity. The ketomethylene group was a poor substitute for the amide bond in **1** as indicated for compound **34**. Replacement of the 4-hydroxyphenyl moiety of **34** with 3-pyridyl gave **35** with improved efficacy. The same effect was already observed in the α,β-unsaturated nitriles series (Table 4-2).

Conclusion

A new series of compounds possessing potent *in vitro* activity for upregulating LDL receptors of HepG2 cells has been discovered, and three new series related to compound **1** with good activities (exemplified by compounds **20, 27,** and **35**) have been identified. Further testing confirmed that compound **1** does not inhibit cholesterol biosynthesis: neither by direct enzyme inhibition of cholesterol biosynthesis nor by attenuating HMG CoA reductase gene transcription.[14] Figure 4

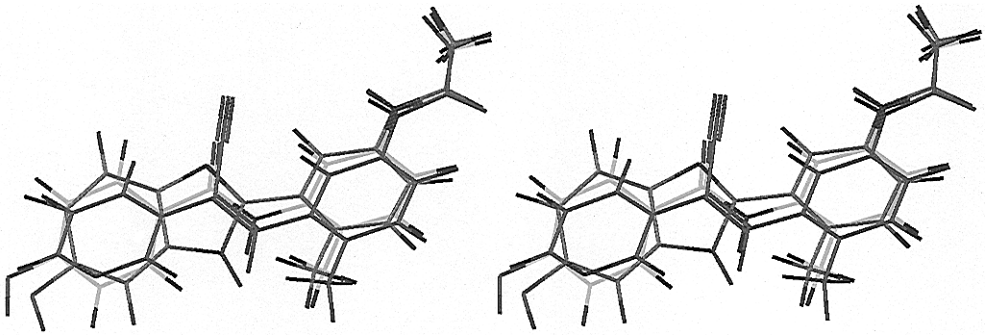
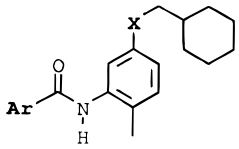


Figure 3. Stereoplot of an overlay of compounds **1** (yellow), **20** (red), and **27** (blue), showing the good superposition of the amide linker with the α,β-unsaturated nitriles and the imidazole moieties. The cyclohexylmethyl group is omitted for clarity.

Table 5. Effect of Modification of the Top Amide (Region 5) in Compound **1** *in Vitro* in HepG2 Cells[a]



compd	Ar	X	upregulation of the LDL receptors (%) (at 3 μM)	EC_{50} (μM)
1	4-hydroxyphenyl	$-NHCOCH_2-$	80	1.7
10h	4-hydroxyphenyl	$-NHCONH-$	10 (@ 1 μM)	
10n	4-hydroxyphenyl	$-NHCO_2-$	16 (@ 1 μM)	
30	4-hydroxyphenyl	$-CONHCH_2-$	75	2
34	4-hydroxyphenyl	$-COCH_2CH_2-$	10	
35	3-pyridyl	$-COCH_2CH_2-$	111	2

[a] See footnote a of Table 1.

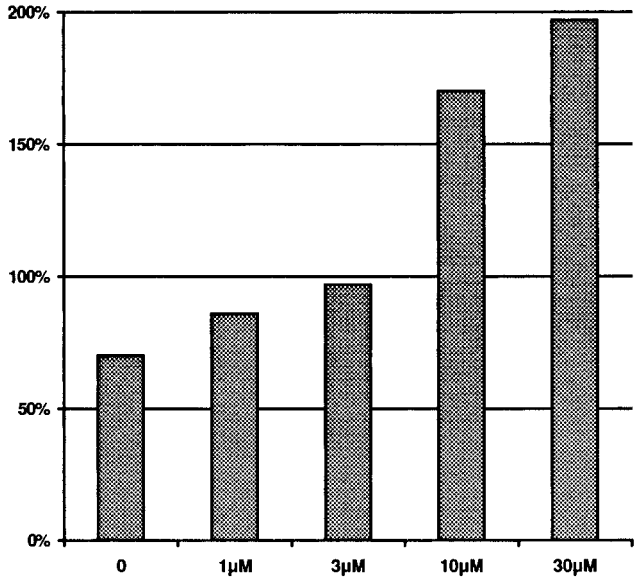


Figure 4. Effect of mevinolin (1 μM) on LDL receptor expression in HepG2 cells and in the presence of compound **1** at different concentrations.

shows that compound **1** is able to produce an additional degree of upregulation of receptors, in the presence of a maximally upregulating concentration of mevinolin, again suggesting that its mechanism of action is not through inhibition of sterol formation. Compound **1** was also shown not to stimulate or inhibit ACAT activity in HepG2 cells. The observation that the increase in LDL receptor expression still occurs in the presence of an inhibitory concentration of 25-hydroxycholesterol (Figure 5) supports the hypothesis that these compounds may be antagonists of a SREBP. According to our knowledge, this is the first example of nonsteroidal compounds with these properties.

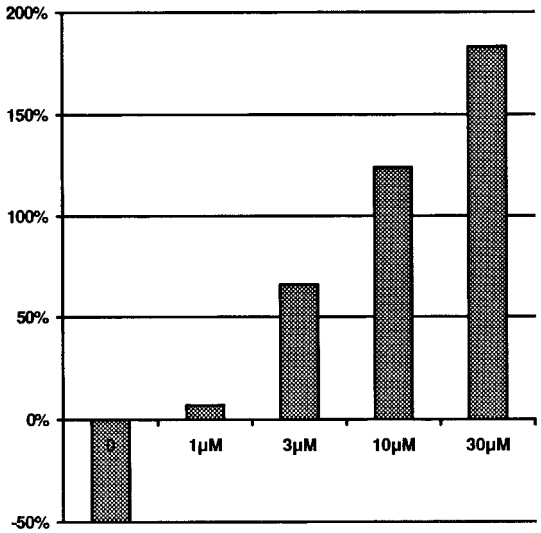


Figure 5. Effect of 25-hydroxycholesterol (2.5 μM) on LDL receptor expression in HepG2 cells and in the presence of compound **1** at different concentrations.

Experimental Section

Chemical Methods. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded in potassium bromide on a Nicolet 205XB FI spectrometer. Proton NMR spectra were recorded using a Varian VXR 400 (or a Varian XL 200 when specified) spectrometer; peak positions are reported in parts per million relative to internal tetramethylsilane on the δ scale. Mass spectra were recorded on a VG 7070E/250 spectrometer. Microanalyses were performed on a Carlo-Erba 1106 microanalyzer. All the reactions were performed at room temperature unless otherwise stated. All organic solutions were dried with magnesium sulfate. Yields were not optimized. The acyl chlorides used in the following syntheses were either purchased or prepared by treating the appropriate acid with thionyl chloride (1.2 equiv).

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-4-hydroxybenzamide, 1.** To a solution of **6a** (21 g, 0.05 mol) in ethanol (210 mL) was added dropwise sodium hydroxide solution (2 M, 50 mL). The mixture was stirred at room temperature for 30 min and then poured into water (1 L) containing 12 mL of concentrated HCl. The resultant white precipitate was collected by filtration, washed with water, and dried to give **1** (13.5 g, 71%) as a white solid: mp 171−173 °C (ethanol); ^1H NMR ($CDCl_3$) 0.85−0.96 (2H, m, C_6H_{11}), 1.18−1.31 (4H, m, C_6H_{11}), 1.53−1.76 (7H, m, $CH_2C_6H_{11}$), 2.27 (3H, s, Ar′H), 2.32 (2H, t, J = 8 Hz, $COCH_2$), 6.92 (2H, d, J_o = 8 Hz, ArH), 7.13 (1H, d, J_o = 8 Hz, Ar′H), 7.55 (1H, dd, J_o = 8

Hz, J_m = 2 Hz, Ar′H), 7.79 (2H, d, J_o = 8 Hz, ArH), 7.84 (1H, d, J_m = 2 Hz, Ar′H), 8.18 (1H, s, ArCONHAr′), 8.65 (1H, s, Ar′NHCOR). Anal. ($C_{23}H_{28}N_2O_3$) C,H,N.

3-Cyclohexyl-*N*-(4-methyl-3-nitrophenyl)propionamide, 4. To a solution of 4-methyl-3-nitroaniline (18.8 g, 0.124 mol) in dichloromethane (250 mL) was added dropwise 3-cyclohexylpropionyl chloride (24 g, 0.124 mol) followed by triethylamine (19 mL, 0.136 mol). After stirring for 1 h at room temperature, the solution was concentrated *in vacuo*. The residue was suspended in 5% sodium bicarbonate solution and then collected by filtration. The solid was dissolved in dichloromethane and then purified by filtration through silica gel. Concentration of the filtrate *in vacuo* gave a solid which was recrystallized from *tert*-butyl methyl ether to give **4** (23 g, 64%) as an off-white solid: mp 133−135 °C; ^{1}H NMR ($CDCl_3$) 0.85−0.97 (2H, m, C_6H_{11}), 1.17−1.32 (4H, m, C_6H_{11}), 1.57−1.75 (7H, m, $CH_2C_6H_{11}$), 2.31−2.43 (2H, t, J = 8 Hz, -$COCH_2$-), 2.54 (3H, s, CH_3Ar), 7.25 (1H, d, J_o = 12 Hz, ArH), 7.76 (1H, dd, J_o = 12 Hz, J_m = 3 Hz, ArH), 7.86 (1H, s, ArNHCO), 8.13 (1H, d, J_m = 3 Hz, ArH). Anal. ($C_{16}H_{22}N_2O_3$) C,H,N.

3-Cyclohexyl-*N*-(4-methyl-3-aminophenyl)propionamide, 5. A solution of **4** (100 g, 0.35 mol) in ethyl acetate (1100 mL) was hydrogenated under atmospheric pressure with 10% Pd/C (5 g) for 16 h. The suspension was filtered through Celite, and the filter was washed with hot ethyl acetate (1000 mL). The combined solution was concentrated *in vacuo*, and the residue was triturated with diethyl ether. The resultant white solid was collected by filtration and then dried *in vacuo* to give **5** (82 g, 91%) as a white solid: mp 134−136 °C; ^{1}H NMR ($CDCl_3$) 0.85−0.98 (2H, m, C_6H_{11}), 1.18−1.33 (4H, m, C_6H_{11}), 1.50−1.71 (7H, m, $CH_2C_6H_{11}$), 2.11 (3H, s, CH_3Ar), 2.32 (2H, t, J = 8 Hz, $COCH_2$), 3.30 (2H, s, NH_2Ar), 6.62 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 6.94 (1H, d, J_o = 8 Hz, ArH), 7.13 (1H, s, ArNHCO), 7.24 (1H, d, J_m = 2 Hz, ArH). Anal. ($C_{16}H_{24}N_2O$) C,H,N.

General Procedure for the Preparation of Compounds 6a−f,h,i,k,l. To a solution of **5** in dichloromethane was added the appropriate acyl chloride (1 equiv) followed by triethylamine (1.2 equiv). The solution was stirred at room temperature and the reaction monitored by TLC. Upon evaporation of the solvent, the residue was washed with water, filtered, dried, and recrystallized when needed.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-4-acetoxybenzamide, 6a.** Compound **6a** was obtained in 67% yield: mp 188−191 °C (2-propanol); ^{1}H NMR (200 MHz, $CDCl_3$) 0.82−1.02 (2H, m, C_6H_{11}), 1.08−1.36 (4H, m, C_6H_{11}), 1.54−1.82 (7H, m, $CH_2C_6H_{11}$), 2.24 (3H, s, CH_3Ar′), 2.30 (2H, t, J = 8 Hz, $COCH_2$), 2.36 (3H, s, CH_3CO_2Ar), 7.12 (1H, d, J_o = 8 Hz, Ar′H), 7.18 (2H, d, J_o = 8 Hz, ArH), 7.50 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.72 (1H, d, J_m = 2 Hz, Ar′H), 7.79 (2H, d, J_o = 8 Hz, ArH), 9.04 (1H, s, Ar′NHCO), 9.12 (1H, s, ArNHCOAr′). Anal. ($C_{25}H_{30}N_2O_4$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-benzamide, 6b.** Compound **6b** was obtained in 72% yield: mp 189−191 °C (ethanol); ^{1}H NMR ($CDCl_3$) 0.85−0.92 (2H, m, C_6H_{11}), 1.08−1.32 (4H, m, C_6H_{11}), 1.54−1.77 (7H, m, $CH_2C_6H_{11}$), 2.27 (3H, s, CH_3Ar′), 2.33 (2H, t, J = 8 Hz, $COCH_2$), 7.18 (1H, d, J_o = 8 Hz, Ar′H), 7.45−7.58 (4H, m, Ar′H, ArH), 7.83 (1H, d, J_m = 2 Hz, ArH), 7.95 (2H, m, Ar′H), 8.70 (1H, s, Ar′NHCOR), 8.97 (1H, s, ArNHCOAr′). Anal. ($C_{23}H_{28}N_2O_2$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-cyclohexanamide, 6c.** Compound **6c** was obtained in 71% yield: mp 207−208 °C; ^{1}H NMR (DMSO-d_6) 0.82−1.84 (23H, m, $CH_2C_6H_{11}$, C_6H_{10}), 1.93 (3H, s, CH_3Ar), 2.27 (2H, t, J = 8 Hz, $COCH_2$), 2.38 (1H, tt, J_a = 12 Hz, J_e = 4 Hz, CHCO), 7.07 (1H, d, J_o = 8 Hz, ArH), 7.35 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 7.58 (1H, d, J_m = 2 Hz, ArH), 9.11 (1H, s, ArNHCOR), 9.77 (1H, s, CyCONHAr). Anal. ($C_{23}H_{34}N_2O_3$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-3-hydroxybenzamide, 6d.** Compound **6d** was obtained in 76% yield as the acetate and then hydrolyzed following the method described for **1** to give a white solid: mp 213−215 °C; ^{1}H NMR ($CDCl_3$) 0.85−0.98 (2H, m, C_6H_{11}), 1.08−1.34 (4H, m, C_6H_{11}), 1.56−1.74 (7H, m, $CH_2C_6H_{11}$), 2.27 (3H, s, CH_3Ar), 2.34 (2H, t, J = 8 Hz, $COCH_2$), 7.01−7.06 (2H, m, ArH, ArOH), 7.15 (1H, d, J_o = 8 Hz, Ar′H), 7.27−7.46 (3H, m, ArH), 7.66 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.92 (1H, d, J_m = 2 Hz, Ar′H), 8.03 (1H, s, Ar′NHCOR), 8.29 (1H, s, ArCONHAr′). Anal. ($C_{23}H_{28}N_2O_3$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-2-hydroxybenzamide, 6e.** Compound **6e** was obtained in 99% yield as the acetate and then hydrolyzed following the method described for **1** to give a white solid: mp 185−186 °C; ^{1}H NMR ($CDCl_3$) 0.85−0.97 (2H, m, C_6H_{11}), 1.18−1.34 (4H, m, C_6H_{11}), 1.56−1.78 (7H, m, $CH_2C_6H_{11}$), 2.28 (3H, s, CH_3Ar′), 2.35 (2H, t, J = 8 Hz, $COCH_2$), 6.94 (1H, td, J_o = 8 Hz, J_m = 1 Hz, ArH), 6.99 (1H, dd, J_o = 8 Hz, J_m = 1 Hz, ArH), 7.16 (1H, d, J_o = 8 Hz, Ar′H), 7.40 (1H, td, J_o = 8 Hz, J_m = 1 Hz, ArH), 7.57 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.90 (1H, d, J_m = 2 Hz, Ar′H), 7.96 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 8.71 (1H, s, Ar′NHCOR), 9.56 (1H, s, ArCONHAr′). Anal. ($C_{23}H_{28}N_2O_3$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-4-(methoxycarbonyl)benzamide, 6f.** Compound **6f** was obtained in 77% yield: mp 220−222 °C (ethoxyethanol); ^{1}H NMR (DMSO-d_6) 0.82−0.94 (2H, m, C_6H_{11}), 1.08−1.27 (4H, m, C_6H_{11}), 1.48 (2H, q, J = 8 Hz, CH_2-cyclohexyl), 1.56−1.74 (5H, m, C_6H_{11}), 2.17 (3H, s, CH_3Ar′), 2.30 (2H, t, J = 8 Hz, $COCH_2$), 3.90 (3H, s, CH_3CO_2Ar), 7.17 (1H, d, J_o = 8 Hz, Ar′H), 7.39 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.66 (1H, d, J_m = 2 Hz, Ar′H), 8.09 (4H, s, ArH), 9.84 (1H, s, Ar′CONHR), 10.82 (1H, s, ArCONHAr′). Anal. ($C_{25}H_{30}N_2O_4$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-4-(hydroxymethyl)benzamide, 6g.** To a suspension of **6f** (0.25 g, 0.59 mmol) in THF (5 mL) was added a solution of $LiBH_4$ (2 M in THF, 1 mL, 2 mmol) under argon. The mixture was stirred for 7 h and allowed to stand for 16 h. The reaction was then quenched with a saturated solution of ammonium chloride (5 mL) at 0 °C. The aqueous solution was extracted with diethyl ether (20 mL). The organic layer was washed with water, dried, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluant CH_2Cl_2:MeOH, 19:1) to give **6g** (0.15 g, 63%) as a white solid: mp 165 °C; ^{1}H NMR (DMSO-d_6) 0.82−0.94 (2H, m, C_6H_{11}), 1.06−1.28 (4H, m, C_6H_{11}), 1.48 (2H, q, J = 8 Hz, C$H_2C_6H_{11}$), 1.56−1.74 (5H, m, C_6H_{11}), 2.16 (3H, s, CH_3Ar′), 2.29 (2H, t, J = 8 Hz, $COCH_2$), 4.58 (2H, d, J = 6 Hz, HOCH_2Ar), 5.35 (1H, t, J = 6 Hz, HOCH_2Ar), 7.05 (1H, d, J_o = 8 Hz, Ar′H), 7.38 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.45 (2H, d, J_o = 8 Hz, ArH), 7.55 (1H, d, J_m = 2 Hz, Ar′H), 7.94 (2H, d, J_o = 8 Hz, ArH), 9.82 (1H, s, Ar′NHCOR), 9.85 (1H, s, ArCONHAr′). Anal. ($C_{24}H_{30}N_2O_3$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-3,4-(methylenedioxy)benzamide, 6h.** Compound **6h** was obtained in 86% yield: mp 202−203 °C; ^{1}H NMR (DMSO-d_6) 0.82−0.94 (2H, m, C_6H_{11}), 1.06−1.27 (4H, m, C_6H_{11}), 1.46 (2H, q, J = 8 Hz, C$H_2C_6H_{11}$), 1.56−1.74 (5H, m, C_6H_{11}), 2.15 (3H, s, CH_3Ar′), 2.29 (2H, t, J = 8 Hz, $COCH_2$), 6.13 (2H, s, OCH_2O), 7.04 (1H, d, J_o = 8 Hz, ArH), 7.14 (1H, d, J_o = 8 Hz, Ar′H), 7.37 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.50 (1H, d, J_m = 2 Hz, Ar′H), 7.58 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 7.62 (1H, d, J_o = 8 Hz, ArH), 9.70 (1H, s, ArCONHAr′), 9.83 (1H, s, Ar′NHCOR). Anal. ($C_{24}H_{28}N_2O_4$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-4-nitrobenzamide, 6i.** Compound **6i** was obtained in 65% yield as a white solid: mp 198−200 °C; ^{1}H NMR (DMSO-d_6) 0.82−0.94 (2H, m, C_6H_{11}), 1.06−1.28 (4H, m, C_6H_{11}), 1.49 (2H, q, J = 8 Hz, C$H_2C_6H_{11}$), 1.58−1.76 (5H, m, C_6H_{11}), 2.18 (3H, s, CH_3Ar′), 2.30 (2H, t, J = 8 Hz, $COCH_2$), 7.18 (1H, d, J_o = 8 Hz, Ar′H), 7.49 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.69 (1H, d, J_m = 2 Hz, Ar′H), 8.20 (2H, d, J_o = 8 Hz, ArH), 8.38 (2H, d, J_o = 8 Hz, ArH), 9.82 (1H, s, Ar′NHCOR), 10.22 (1H, s, ArCONHAr′). Anal. ($C_{23}H_{27}N_3O_4$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-4-aminobenzamide, 6j.** Compound **6i** (2 g, 4.9 mmol) was hydrogenated at atmospheric pressure in ethanol (250 mL) with 5% Pd/C (0.1 g) until uptake of hydrogen was complete. The mixture was filtered through Celite and then concentrated *in vacuo*. The residue was recrystallized from ethyl acetate to give **6j** (2 g, 63%) as a white solid: mp 195−197 °C; ^{1}H NMR (DMSO-d_6) 0.82−0.94 (2H, m, C_6H_{11}), 1.06−1.27 (4H, m,

C_6H_{11}), 1.49 (2H, q, J = 8 Hz, $CH_2C_6H_{11}$), 1.56−1.74 (5H, m, C_6H_{11}), 2.14 (3H, s, CH_3Ar'), 2.29 (2H, t, J = 8 Hz, $COCH_2$), 5.71 (2H, s, NH_2Ar), 6.59 (2H, d, J_o = 8 Hz, ArH), 7.11 (1H, d, J_o = 8 Hz, Ar′H), 7.36 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.68 (1H, d, J_o = 2 Hz, Ar′H), 7.71 (2H, d, J_o = 8 Hz, ArH), 9.44 (1H, s, ArCONHAr′), 9.80 (1H, s, Ar′NHCOR). Anal. ($C_{23}H_{29}N_3O_2$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-nicotinamide, 6k.** Compound **6k** was obtained as a white solid in 74% yield: mp 179−180 °C (toluene); ^{1}H NMR (DMSO-d_6) 0.82−0.94 (2H, m, C_6H_{11}), 1.15−1.28 (4H, m, C_6H_{11}), 1.49 (2H, q, J = 8 Hz, $CH_2C_6H_{11}$), 1.56−1.74 (5H, m, C_6H_{11}), 2.18 (3H, s, CH_3Ar'), 2.30 (2H, t, J = 8 Hz, $COCH_2$), 7.17 (1H, d, J_o = 8 Hz, Ar′H), 7.39 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.57 (1H, m, PyH), 7.69 (1H, d, J_m = 2 Hz, Ar′H), 8.31 (1H, m, PyH), 8.76 (1H, m, PyH), 9.13 (1H, d, PyH), 9.87 (1H, s, Ar′NHCOR), 10.08 (1H, s, PyCONHAr′). Anal. ($C_{22}H_{23}N_3O_2$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-isonicotinamide, 6l.** Compound **6l** was obtained in 79% yield as a white solid: mp 158−160 °C (toluene); ^{1}H NMR (DMSO-d_6) 0.82−0.94 (2H, m, C_6H_{11}), 1.16−1.38 (4H, m, C_6H_{11}), 1.49 (2H, q, J = 8 Hz, $CH_2C_6H_{11}$), 1.57−1.74 (5H, m, C_6H_{11}), 2.18 (3H, s, CH_3Ar'), 2.30 (2H, t, J = 8 Hz, $COCH_2$), 7.18 (1H, d, J_o = 8 Hz, Ar′H), 7.40 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.68 (1H, d, J_m = 2 Hz, ArH), 7.87 (2H, m, PyH), 8.79 (2H, m, PyH), 9.88 (1H, s, Ar′NHCOR), 10.17 (1H, s, PyCONHAr′). Anal. ($C_{22}H_{27}N_3O_2$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methylphenyl]-isonicotinamide *N*-Oxide, 6m.** Compound **6l** (0.39 g, 1.07 mmol) was stirred with *m*-chloroperoxybenzoic acid (0.54 g, 1.6 mmol) in chloroform (40 mL) for 6 h. The organic solution was washed with sodium hydroxide solution (1 M, 25 mL) and water and then dried, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluant CH_2Cl_2:MeOH, 9:1) to give **6m** (0.2 g, 53%) as a white solid: mp 216−218 °C; ^{1}H NMR (DMSO-d_6) 0.82−0.94 (2H, m, C_6H_{11}), 1.05−1.28 (4H, m, C_6H_{11}), 1.48 (2H, q, J = 8 Hz, -CH_2-cyclohexyl), 1.51−1.74 (5H, m, C_6H_{11}), 2.15 (3H, s, CH_3Ar'), 2.30 (2H, t, J = 8 Hz, $COCH_2$), 7.18 (1H, d, J_o = 8 Hz, Ar′H), 7.48 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.67 (1H, d, J_m = 2 Hz, Ar′H), 7.95 (2H, m, PyH), 8.37 (2H, m, PyH), 9.88 (1H, s, Ar′NHCOR), 10.11 (1H, s, PyCONHAr′). Anal. ($C_{22}H_{27}N_3O_3$) C,H,N.

***N*-(2-Methyl-5-nitrophenyl)-4-acetoxybenzamide, 7a.** To a solution of 2-methyl-5-nitroaniline (37.5 g, 0.246 mol) in dichloromethane (800 mL) was added 4-acetoxybenzoyl chloride (50 g, 0.29 mol) in dichloromethane (300 mL) followed by triethylamine (103 mL, 0.73 mol). The mixture was stirred for 4 h and left to stand for 16 h. The solution was concentrated *in vacuo* and the residue washed with sodium bicarbonate solution. The solid was collected by filtration, washed with water, and dried to give **7a** (24 g, 33%) as a white solid: mp 196−200 °C (ethyl acetate); ^{1}H NMR (DMSO-d_6) 2.32 (3H, s, CH_3Ar'), 2.41 (3H, s, CH_3CO_2Ar), 7.33 (2H, d, J_o = 8 Hz, ArH), 7.58 (1H, d, J_o = 8 Hz, ArH), 8.1−8.7 (3H, m, ArH, Ar′H), 8.38 (1H, d, J_m = 2 Hz, Ar′H), 10.16 (1H, s, ArCONHAr′).

***N*-(2-Bromo-5-nitrophenyl)-4-acetoxybenzamide, 7b.** To a solution of 2-bromo-5-nitro aniline (10 g, 46 mmol) in dichloromethane (250 mL) were added 4-acetoxybenzoyl chloride (10.1 g, 50 mmol) and triethylamine (7 mL, 50 mmol). The solution was stirred for 2 h, left to stand for 72 h, and then washed with saturated sodium bicarbonate solution (100 mL), hydrochloric acid (1 M, 100 mL), and water (100 mL). The organic solution was dried, filtered, and concentrated *in vacuo* to give a solid. This was recrystallized from ethyl acetate to give **7b** (8.3 g, 48%) as a yellow solid: ^{1}H NMR (DMSO-d_6) 2.32 (3H, s, CH_3CO_2Ar), 7.34 (2H, d, J_o = 8 Hz, ArH), 8.03−8.1 (4H, m, ArH, Ar′H), 8.49 (1H, m, Ar′H), 10.36 (1H, s, ArCONHAr′).

***N*-(2-Methoxy-5-nitrophenyl)-4-acetoxybenzamide, 7c.** To a solution of 2-methoxy-5-nitroaniline (3 g, 18 mmol) in dichloromethane (80 mL) were added 4-acetoxybenzoyl chloride (3.9 g, 19.6 mmol) and triethylamine (2.7 mL, 19.6 mmol). The mixture was stirred for 4 h and left to stand for 16 h. The reaction mixture was washed with 1 M hydrochloric acid and water and then dried and concentrated *in vacuo* to give **7c** (4.8 g, 82%): ^{1}H NMR ($CDCl_3$) 2.36 (3H, s, CH_3CO_2Ar), 4.06 (3H, s, CH_3OAr'), 6.99 (1H, d, J_o = 8 Hz, Ar′H), 7.26 (2H, d, J_o = 8 Hz, ArH), 7.93 (2H, d, J_o = 8 Hz, ArH), 8.05 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 8.49 (1H, s, ArCONHAr′), 9.45 (1H, d, J_m = 2 Hz, Ar′H_6).

***N*-(2-Hydroxy-5-nitrophenyl)-4-acetoxybenzamide, 7d.** To a solution of 2-amino-4-nitrophenol (5 g, 32.5 mmol) in dichloromethane (150 mL) were added 4-acetoxybenzoyl chloride (13.5 g, 68 mmol) and triethylamine (13 mL, 97 mmol). The mixture was stirred for 2 h and left to stand for 16 h. The resultant precipitate was collected by filtration, washed with water, and dried to give **7d** (7.9 g, 77%) as a yellow solid: ^{1}H NMR (DMSO-d_6) 2.31 (3H, s, CH_3CO_2Ar), 7.09 (1H, d, J_o = 8 Hz, Ar′H), 7.31 (2H, d, J_o = 8 Hz, ArH), 8.01 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 8.04 (2H, d, J_o = 8 Hz, ArH), 8.75 (1H, d, J_m = 2 Hz, Ar′H), 9.69 (1H, s, ArCONHAr′).

***N*-(2-Acetyl-5-nitrophenyl)-4-acetoxybenzamide, 7e.** A suspension of **7d** (5 g, 15.8 mmol) in acetic anhydride (250 mL) was stirred for 6 h and then warmed gently until dissolution of the remaining solid. The solution was then poured onto ice/water (2 L) and stirred for 2 h. The resultant precipitate was collected by filtration, washed with water, and dried to give **7e** (5.4 g, 96%) as a white solid: ^{1}H NMR (DMSO-d_6) 2.10 (3H, s, CH_3CO_2Ar'), 2.34 (3H, s, CH_3CO_2Ar), 7.41 (2H, d, J_o = 8 Hz, ArH), 6.52 (1H, d, J_o = 8 Hz, Ar′H), 8.05 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 8.23 (2H, d, J_o = 8 Hz, ArH), 8.96 (1H, d, J_m = 2 Hz, Ar′H), 9.98 (1H, s, ArCONHAr′).

***N*-(5-Amino-2-methylphenyl)-4-acetoxybenzamide, 8a.** Compound **7a** (51 g, 0.162 mol) was hydrogenated at atmospheric pressure in ethyl acetate (1 L) with 5% Pd/C (5 g). The mixture was shaken for 24 h and then filtered through Celite and concentrated *in vacuo*. The residue was triturated with petroleum ether (500 mL, bp 40−60 °C), collected by filtration, and dried to give **8a** (44 g, 95%) as a white solid: mp 124−126 °C; ^{1}H NMR ($CDCl_3$) 2.20 (3H, s, CH_3Ar'), 2.33 (3H, s, CH_3CO_2Ar), 3.37 (2H, s, NH_2Ar'), 6.46 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 6.98 (1H, d, J_o = 8 Hz, Ar′H), 7.20 (2H, d, J_o = 8 Hz, ArH), 7.46 (1H, d, J_m = 2 Hz, Ar′H), 7.67 (ArCONHAr′), 7.88 (2H, d, J_o = 8 Hz, ArH). Anal. ($C_{16}H_{16}N_2O_3$) C,H,N.

***N*-(5-Amino-2-bromophenyl)-4-acetoxybenzamide, 8b.** A solution of **7b** (8.3 g, 22 mmol) in toluene (100 mL) was hydrogenated at atmospheric pressure with 5% Pd/C (0.6 g) for 16 h. The reaction mixture was heated to 100 °C to dissolve the solid precipitate and then filtered through Celite while hot. The solvent was concentrated *in vacuo* and the residue recrystallized from ethyl acetate to give **8b** (3 g, 41%) as a white solid: ^{1}H NMR ($CDCl_3$) 2.34 (3H, s, CH_3CO_2Ar), 3.80 (2H, br s, NH_2Ar'), 6.36 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.25 (2 H, d, J_o = 8 Hz, ArH), 7.29 (1H, d, J_o = 8 Hz, Ar′H), 7.95 (2H, d, J_o = 8 Hz, ArH), 8.00 (1H, d, J_m = 2 Hz, Ar′H), 8.36 (1H, s, ArCONHAr′).

***N*-(5-Amino-2-methoxyphenyl)-4-acetoxybenzamide, 8c.** Compound **7c** (4.5 g, 13.6 mmol) was hydrogenated at atmospheric pressure in ethyl acetate (200 mL) with 5% Pd/C (0.34 g) for 16 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **8c** (3.9 g, 95%) as a brown solid: ^{1}H NMR ($CDCl_3$) 2.34 (3H, s, CH_3CO_2Ar), 3.85 (3H, s, CH_3OAr'), 6.45 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 6.75 (1H, d, J_o = 8 Hz, Ar′H), 7.23 (2H, d, J_o = 8 Hz, ArH), 7.91 (2H, d, J_o = 8 Hz, ArH), 8.01 (1H, d, J_m = 2 Hz, Ar′H), 8.52 (1H, s, ArCONHAr′).

***N*-(2-Acetoxy-5-aminophenyl)-4-acetoxybenzamide, 8d.** A suspension of **7e** (5.4 g, 14.2 mmol) in ethanol (1 L) was hydrogenated at atmospheric pressure with 5% Pd/C (1.75 g) for 16 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **8d** (4.9 g, 100%) as a foamy solid: ^{1}H NMR (DMSO-d_6) 1.94 (3H, s, CH_3CO_2Ar'), 2.32 (3H, s, CH_3CO_2Ar), 5.12 (2H, br s, NH_2Ar'), 6.35 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 6.85 (1H, d, J_o = 8 Hz, Ar′H), 7.07 (1H, d, J_m = 2 Hz, Ar′H), 7.36 (2H, d, J_o = 8 Hz, ArH), 8.15 (2H, d, J_o = 8 Hz, ArH), 9.25 (1H, s, ArCONHAr′).

General Procedure for the Preparation of Compounds 9a,g,l. To a solution of **8a** or **8c** in dichloromethane was added the appropriate acyl chloride (1 equiv) followed by triethylamine (1.2 equiv). The solution was stirred at room temperature for 3 h and left to stand for 16 h. The solution was

concentrated *in vacuo*; then the residue was washed with water, filtered, and dried.

***N*-[5-[(2-Cyclohexylacetyl)amino]-2-methylphenyl]-4-acetoxybenzamide, 9a.** Compound **9a** was obtained in 78% yield as a white solid: mp 179−180 °C; ^{1}H NMR (DMSO-d_6) 0.90−1.03 (2H, m, C_6H_{11}), 1.06−1.29 (4H, m, C_6H_{11}), 1.57−1.74 (5H, m, C_6H_{11}), 2.17 (5H, m, $COCH_2$, CH_3Ar'), 2.31 (3H, s, CH_3CO_2Ar), 7.16 (1H, d, J_o = 8 Hz, Ar′H), 7.29 (2H, d, J_o = 8 Hz, ArH), 7.39 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.65 (1H, d, J_m = 2 Hz, Ar′H), 8.02 (2H, d, J_o = 8 Hz, ArH), 9.83 (Ar′NHCOR), 9.90 (1H, s, ArCONHAr′). Anal. ($C_{24}H_{28}N_2O_4$) C,H,N.

***N*-[5-[[2-(Cyclohexyloxy)acetyl]amino]-2-methylphenyl]-4-acetoxybenzamide, 9g.** Compound **9g** was obtained in 94% yield as a white solid: mp 159−161 °C; ^{1}H NMR ($CDCl_3$) 1.22−1.46 (5H, m, C_6H_{10}), 1.53−1.60 (1H, m, C_6H_{10}), 1.74−1.84 (2H, m, C_6H_{10}), 1.91−2.00 (2H, m, C_6H_{10}), 2.30 (3H, s, CH_3−Ar′), 2.35 (3H, s, CH_3CO_2Ar), 3.40 (1H, m, OCH), 4.06 (2H, s, $COCH_2O$), 7.29 (1H, d, J_o = 8 Hz, Ar′H), 7.39 (2H, d, J_o = 8 Hz, ArH), 7.63 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.70 (Ar′NHCOR), 7.71 (2H, d, J_o = 8 Hz, ArH), 7.79 (1H, d, J_m = 2 Hz, Ar′H), 8.40 (1H, s, ArCONHAr′). Anal. ($C_{24}H_{28}N_2O_5$) C,H,N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-methoxyphenyl]-4-acetoxybenzamide, 9l.** To a solution of **8c** (3.7 g, 12.3 mmol) in dichloromethane (90 mL) were added 3-cyclohexylpropionyl chloride (2.37 g, 13.5 mmol) and triethylamine (1.88 mL, 13.5 mmol). The mixture was stirred for 4 h and then washed with 1 M hydrochloric acid and water. The organic solution was dried, filtered, and concentrated *in vacuo* to give **9l** (3.4 g, 63%) as a white solid mp 195−196 °C (ethanol); ^{1}H NMR (DMSO-d_6) 0.82−0.95 (2H, m, C_6H_{11}), 1.09−1.26 (4H, m, C_6H_{11}), 1.49 (2H, q, J = 8 Hz, C$H_2C_6H_{11}$), 1.57−1.75 (5H, m, C_6H_{11}), 2.29 (2H, t, J = 8 Hz, $COCH_2$), 2.32 (3H, s, CH_3CO_2Ar), 3.80 (3H, s, CH_3OAr'), 7.00 (1H, d, J_o = 8 Hz, Ar′H), 7.29 (2H, d, J_o = 8 Hz, ArH), 7.50 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.97−8.03 (3H, m, ArH, Ar′H), 9.45 (1H, s, Ar′NHCOR), 9.79 (1H, s, ArCONHAr′). Anal. ($C_{25}H_{30}N_2O_5$) C,H,N.

General Procedure for the Preparation of Compounds 10b−f. To a solution of **9** (acetoxy derivative) in ethanol was added 2 equiv of sodium hydroxide (1 M). The mixture was stirred at room temperature for 2 h and then concentrated *in vacuo*. The residue was diluted with water and acidified to pH 1 with concentrated HCl. The precipitate was collected by filtration, washed with water, and dried.

***N*-[5-[(4-Cyclohexylbutyryl)amino]-2-methylphenyl]-4-hydroxybenzamide, 10b.** Compound **10b** was obtained as a white solid: mp 146−147 °C; ^{1}H NMR (DMSO-d_6) 0.80−0.91 (2H, m, C_6H_{11}), 1.04−1.27 (6H, m, $CH_2C_6H_{11}$), 1.53−1.72 (7H, m, $CH_2CH_2C_6H_{11}$), 2.15 (3H, s, CH_3Ar'), 2.25 (2H, t, J = 8 Hz, $COCH_2$), 6.85 (2H, d, J_o = 8 Hz, ArH), 7.13 (1H, d, J_o = 8 Hz, Ar′H), 7.37 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.62 (1H, d, J_m = 2 Hz, Ar′H), 7.85 (2H, d, J_o = 8 Hz, ArH), 9.58 (1H, s, Ar′NHCOR), 9.80 (1H, s, ArCONHAr′), 10.04 (1H, s, HOAr); MS *m*/*z* 395 (MH^+), 274 ($MH^+ - CH_2CH_2CH_2C_6H_{11}$), 242 ($MH^+ - HOC_6H_4CO$). Anal. ($C_{24}H_{30}N_2O_3 \cdot {}^3/_2H_2O$) C,H,N.

***N*-[5-(Nonanoylamino)-2-methylphenyl]-4-hydroxybenzamide, 10c.** Compound **10c** was obtained in 80% yield as a white solid: mp 160−161 °C; ^{1}H NMR (DMSO-d_6) 0.85 (3H, t, J = 6 Hz, RCH_3) 1.20−1.34 (10H, m, $C_5H_{10}CH_3$), 1.53−1.62 (2H, m, $COCH_2CH_2$), 2.15 (3H, s, CH_3Ar'), 2.28 (2H, t, J = 8 Hz, $COCH_2$), 6.85 (2H, d, J_o = 8 Hz, ArH), 7.14 (1H, d, J_o = 8 Hz, Ar′H), 7.37 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.62 (1H, d, J_m = 2 Hz, Ar′H), 7.75 (2H, d, J_o = 8 Hz, ArH), 9.60 (1H, s, Ar′NHCOR), 9.83 (1H, s, ArCONHAr′). Anal. ($C_{23}H_{30}N_2O_3$) C,H,N.

***N*-[5-[(3-Phenylpropionyl)amino]-2-methylphenyl]-4-hydroxybenzamide, 10d.** Compound **10d** was obtained in 55% yield as a white solid: mp 215−217 °C; ^{1}H NMR (DMSO-d_6) 2.15 (3H, s, CH_3Ar'), 2.61 (2H, t, J = 8 Hz, CH_2Ph), 2.90 (2H, t, J = 8 Hz, $COCH_2$), 6.85 (2H, d, J_o = 8 Hz, ArH), 7.15 (1H, d, J_o = 8 Hz, Ar′H), 7.17−7.31 (5H, m, Ph), 7.37 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.61 (1H, d, J_m = 2 Hz, Ar′H), 7.85 (2H, d, J_o = 8 Hz, ArH), 9.60 (1H, s, Ar′NHCOR), 9.88 (1H, s, ArCONHAr′). Anal. ($C_{23}H_{22}N_2O_3$) C,H,N.

***N*-[2-Methyl-5-[(3-piperidin-1-ylpropionyl)amino]-phenyl]-4-hydroxybenzamide, 10e.** Compound **8a** was treated with 3-bromopropionyl chloride as described in the general procedure, using 2.2 equiv of triethylamine. The resultant amide was dissolved in neat piperidine at room temperature and then stirred for 2 h. The reaction mixture was concentrated *in vacuo*, washed with water, filtered, and dried to give **10e** (15%) as a white solid: mp 206−208 °C; ^{1}H NMR (DMSO-d_6) 1.33−1.42 (2H, m, $C_5H_{10}N$), 1.46−1.60 (4H, m, $C_5H_{10}N$), 2.14 (3H, s, CH_3Ar'), 2.30−2.40 (4H, m, $C_5H_{10}N$), 2.43 (2H, t, J = 8 Hz, C$H_2C_5H_{10}$), 2.58 (2H, t, $COCH_2$), 6.86 (2H, d, J_o = 8 Hz, ArH), 7.15 (1H, d, J_o = 8 Hz, Ar′H), 7.35 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.61 (1H, d, J_m = 2 Hz, Ar′H), 7.85 (2H, d, J_o = 8 Hz, ArH), 9.60 (1H, s, Ar′NHCOR), 10.13 (1H, s, ArCONHAr′). Anal. ($C_{22}H_{27}N_3O_3 \cdot {}^1/_4H_2O$) C,H,N.

***N*-[5-[(3-Cyclopentylpropionyl)amino]-2-methylphenyl]-4-hydroxybenzamide, 10f.** Compound **8a** was acylated with cyclopentylpropionyl chloride and the intermediate acetoxy hydrolyzed to give **10f** (22%) as a white solid: mp 185−188 °C; ^{1}H NMR (DMSO-d_6) 1.04−1.16 (2H, m, C_5H_9), 1.42−1.64 (6H, m, $CH_2C_5H_9$), 1.69−1.81 (3H, m, C_5H_9), 2.15 (3H, s, CH_3-Ar′), 2.30 (2H, t, J = 8 Hz, $COCH_2$), 6.86 (2H, d, J_o = 8 Hz, ArH), 7.13 (1H, d, J_o = 8 Hz, Ar′H), 7.38 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.62 (1H, d, J_m = 2 Hz, Ar′H), 7.85 (2H, d, J_o = 8 Hz, ArH), 9.59 (1H, s, Ar′NHCOR), 9.83 (1H, s, ArCONHAr′), 10.06 (1H, s, HOAr). Anal. ($C_{22}H_{26}N_2O_3$) C,H,N.

1-(Cyclohexylmethyl)-3-[3-(4-hydroxybenzamido)-4-methylphenyl]urea, 10h. To a solution of triphosgene (0.99 g, 3.33 mmol) in dichloromethane (150 mL) were added compound **8a** (2.84 g, 10 mmol) and triethylamine (2.8 mL, 20 mmol). The mixture was heated under reflux for 7 h before addition of cyclohexylmethylamine (2.26 g, 20 mmol). The reaction mixture was left to stand at room temperature for 16 h and then concentrated *in vacuo*. The solid residue was washed with water and hydrolyzed (following the procedure described for compound **1**) to give **10h** (3 g, 70%) as a white solid: mp 210−212 °C; ^{1}H NMR (DMSO-d_6) 0.83−0.95 (2H, m, C_6H_{11}), 1.06−1.26 (3H, m, C_6H_{11}), 1.32−1.44 (1H, m, C_6H_{11}), 1.58−1.72 (5H, m, C_6H_{11}), 2.22 (3H, s, CH_3Ar), 2.92 (2H, t, J = 6 Hz, CONHC$H_2C_6H_{11}$), 6.08 (1H, t, J = 6 Hz, ArNH-CON*H*R), 6.85 (2H, d, J_o = 8 Hz, Ar′H), 7.06 (1H, d, J_o = 8 Hz, ArH), 7.14 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 7.43 (1H, d, J_m = 2 Hz, ArH), 7.85 (2H, d, J_o = 8 Hz, Ar′H), 8.31 (1H, s, HOAr′), 9.52 (1H, s, ArN*H*CONHR), 10.03 (1H, s, Ar′CONHAr). Anal. ($C_{22}H_{27}N_3O_3 \cdot {}^1/_3H_2O$) C,H,N.

***N*-[2-Bromo-5-[(3-cyclohexylpropionyl)amino]phenyl]-4-hydroxybenzamide, 10i.** To a solution of **8b** (1.4 g, 4 mmol) in dichloromethane (125 mL) were added 3-cyclohexylpropionyl chloride (0.77 g, 4.4 mmol) and triethylamine (0.62 mL, 0.44 mmol). The reaction mixture was stirred for 3 h and then washed with saturated sodium bicarbonate solution (50 mL), hydrochloric acid (1 M, 50 mL), and water (50 mL). The organic solution was dried, filtered, and concentrated *in vacuo* to give a gum. This was dissolved in ethanol (10 mL) and hydrolyzed (following the method described for the preparation of compound **1**) to give **10i** (0.4 g, 22% overall yield) as a white solid: mp 140−143 °C; ^{1}H NMR ($CDCl_3$) 0.84−0.97 (2H, m, C_6H_{11}), 1.08−1.32 (4H, m, C_6H_{11}), 1.54−1.77 (7H, m, $CH_2C_6H_{11}$), 2.33 (2H, t, J = 8 Hz, $COCH_2$), 6.96 (2H, d, J_o = 8 Hz, ArH), 7.47 (1H, d, J_o = 8 Hz, Ar′H), 7.76−7.84 (3H, m, ArH, Ar′H), 8.38 (1H, s, Ar′NHCOR), 8.41 (1H, d, J_m = 2 Hz, Ar′H_6), 8.77 (1H, s, ArCONHAr′). Anal. ($C_{22}H_{25}BrN_2O_3$) C,H,N.

***N*-[2-Chloro-5-[(3-cyclohexylpropionyl)amino]phenyl]-4-hydroxybenzamide, 10j.** To a solution of 4-chloro-3-nitroaniline (2.07 g, 12 mmol) in toluene (30 mL) were added 3-cyclohexylpropionyl chloride (2.3 g, 13 mmol) and triethylamine (2.5 mL, 18 mmol). The mixture was stirred for 2 h and heated to 100 °C for a further 2 h. The solvent was concentrated *in vacuo* and the residue partitioned between diethyl ether (100 mL) and hydrochloric acid (1 M, 50 mL). The organic solution was washed with water, dried, filtered, and concentrated *in vacuo*. The solid residue was recrystallized from *tert*-butyl methyl ether to give beige needles (1.72 g, 46%). This compound (1.6 g, 5.2 mmol) was hydrogenated in toluene (50 mL) at atmospheric pressure with 5% Pd/C (0.25 g) for 3 h. Ethanol (50 mL) was then added to dissolve the

solid precipitate, and the mixture was filtered through Celite. The filtrate was concentrated *in vacuo* to give a light brown solid (1.4 g, 97%). To a solution of this solid (1.3 g, 4.6 mmol) in dichloromethane (30 mL) were added 4-acetoxybenzoyl chloride (1 g, 5.1 mmol) and triethylamine (0.8 mL, 5.8 mmol). The solution was stirred for 2 h, left to stand for 24 h, and then washed with hydrochloric acid (1 M, 100 mL) and water (100 mL), dried, and filtered. Concentration *in vacuo* gave a brown viscous oil which was dissolved in ethanol (10 mL) and hydrolyzed (following the method described for the preparation of compound **1**) to give **10j** (0.6 g, 36%) as a white solid: mp 147−149 °C; ^{1}H NMR (DMSO-d_6) 0.82−0.94 (2H, m, C_6H_{11}), 1.16−1.29 (4H, m, C_6H_{11}), 1.50 (2H, q, J = 8 Hz, C$H_2C_6H_{11}$), 1.57−1.75 (5H, m, C_6H_{11}), 2.32 (2H, t, J = 8 Hz, $COCH_2$), 6.87 (2H, d, J_o = 8 Hz, ArH), 7.42 (1H, d, J_o = 8 Hz, Ar′H), 7.52 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.86 (2H, d, J_o = 8 Hz, ArH), 7.91 (1H, d, J_m = 2 Hz, Ar′H), 9.70 (1H, s, Ar′NHCOR), 10.06 (1H, s, ArCONHAr′). Anal. ($C_{22}H_{25}ClN_2O_3$) C,H.N.

***N*-[5-[(3-Cyclohexylpropionyl)amino]-2-fluorophenyl]-4-hydroxybenzamide, 10k.** Compound **10k** was prepared using a similar route to compound **10j** and obtained as a white solid in 51% overall yield: mp 103−105 °C; ^{1}H NMR (DMSO-d_6) 0.82−0.94 (2H, m, C_6H_{11}), 1.08−1.29 (4H, m, C_6H_{11}), 1.49 (2H, q, J = 8 Hz, C$H_2C_6H_{11}$), 1.56−1.75 (5H, m, C_6H_{11}), 2.30 (2H, t, J = 8 Hz, $COCH_2$), 6.86 (2H, d, J_o = 8 Hz, ArH), 7.19 (1H, t, J = 8Hz, Ar′H), 7.40−7.48 (1H, m, Ar′H), 7.82−7.90 (3H, m, ArH, Ar′H), 9.80 (1H, s, Ar′NHCOR), 9.95 (1H, s, ArCONHAr′). Anal. ($C_{22}H_{25}FN_2O_3$) C,H,N.

***N*-[2-Hydroxy-5-[(3-cyclohexylpropionyl)amino]phenyl]-4-hydroxybenzamide, 10m.** To a solution of **8d** (2.4 g, 7.3 mmol) in dichloromethane (75 mL) were added 3-cyclohexylpropionyl chloride (1.5 g, 8.7 mmol) and triethylamine (1.5 mL, 11 mmol). The mixture was stirred for 6 h and left to stand for 16 h. The reaction mixture was washed with hydrochloric acid (1 M, 50 mL) and water (50 mL) and then dried, filtered, and concentrated *in vacuo* to give an off-white solid. This was dissolved in ethanol (85 mL) and hydrolyzed (following the method described for the preparation of compound **1**) to give **10m** (0.7 g, 30% overall yield) as a white solid: mp 209−216 °C; ^{1}H NMR (DMSO-d_6) 0.82−0.94 (2H, m, C_6H_{11}), 1.09−1.28 (4H, m, C_6H_{11}), 1.48 (2H, q, J = 8 Hz, C$H_2C_6H_{11}$), 1.57−1.75 (5H, m, C_6H_{11}), 2.27 (2H, t, J = 8 Hz, $COCH_2$), 6.81 (1H, d, J_o = 8 Hz, Ar′H$_3$), 6.88 (2H, d, J_o = 8 Hz, ArH), 7.28 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.84 (2H, d, J_o = 8 Hz, ArH), 7.95 (1H, d, J_m = 2 Hz, Ar′H), 9.35 (1H, s, Ar′NHCOR), 9.70 (1H, s, ArCONHAr′). Anal. ($C_{22}H_{26}N_2O_4$) C,H,N.

Cyclohexylmethyl *N*-[3-(4-Hydroxybenzamido)-4-methylphenyl]carbamate, 10n. To a solution of triphosgene (0.99 g, 3.33 mmol) in THF (150 mL) were added compound **8a** (2.84 g, 10 mmol) and triethylamine (2.8 mL, 20 mmol). The reaction mixture was heated under reflux for 5 h and then cooled to room temperature. Upon addition of cyclohexylmethanol (2.3 g, 20 mmol), the mixture was heated under reflux for 2 h and then left to stand at room temperature for 16 h. The solution was concentrated *in vacuo*, and the residue was triturated with diethyl ether to give a solid. This was hydrolyzed (following the procedure described for compound **1**) to give **10n** (1.2 g, 30%) as a white solid: mp 112−115 °C; ^{1}H NMR ($CDCl_3$) 0.91−1.03 (2H, m, C_6H_{11}), 1.10−1.31 (4H, m, C_6H_{11}), 1.59−1.80 (5H, m, C_6H_{11}), 2.24 (3H, s, CH_3Ar), 3.95 (2H, d, J = 6 Hz, OC$H_2C_6H_{11}$), 6.08 (1H, t, J = 6 Hz, OCH$_2$C*H*), 6.79 (1H, s, HOAr′), 6.86 (2H, d, J_o = 8 Hz, Ar′H), 7.12 (1H, d, J_o = 8 Hz, ArH), 7.20 (1H, br s, ArNHCO_2R), 7.33 (1H, s, Ar′CONHAr), 7.64−7.73 (3H, m, ArH, Ar′H), 7.36 (1H, d, J_m = 2 Hz, ArH). Anal. ($C_{22}H_{26}N_2O_4 \cdot {}^1/_5H_2O$) C,H,N.

3-(3-Cyclohexylpropionamido)aniline, 11. To a stirred solution of 1,3-phenylenediamine (3.25 g, 30 mmol) in dichloromethane (100 mL) was added 3-cyclohexylpropionyl chloride (1.75 g, 10 mmol). The mixture was stirred for 5 h and left to stand for 16 h. A solution of saturated sodium bicarbonate (150 mL) was added to the mixture, and the phases were separated. The organic phase was washed with water, dried, and concentrated *in vacuo* to give **11** (2.1 g, 85%) as an off-white solid: ^{1}H NMR ($CDCl_3$) 0.82−0.98 (2H, m, C_6H_{11}), 1.06−1.34 (4H, m, C_6H_{11}), 1.49−1.78 (7H, m, $CH_2C_6H_{11}$), 2.33 (2H, t, J = 8 Hz, $COCH_2$), 3.72 (2H, br s, $ArNH_2$), 6.42 (1H, d, J_o = 8 Hz, ArH), 6.67 (1H, d, J_o = 8 Hz, ArH), 7.06 (1H, t, J_o = 8 Hz, ArH), 7.15−7.27 (2H, m, ArH, ArNHCOR).

***N*-[3-[(3-Cyclohexylpropionyl)amino]phenyl]-4-acetoxybenzamide, 12.** To a solution of **11** (2 g, 8.1 mmol) in dichloromethane (100 mL) and triethylamine (1.16 mL, 11 mmol) was added 4-acetoxybenzoyl chloride (1.8 g, 9 mmol). The mixture was stirred for 5 h and then treated with saturated sodium bicarbonate solution (75 mL). The phases were separated, and the organic layer was washed with water and dried. Concentration of the organic solution left a gum, which, after trituration with cyclohexane, gave **12** (2.7 g, 82%) as a white solid: mp 149−150 °C; ^{1}H NMR ($CDCl_3$) 0.84−0.96 (2H, m, C_6H_{11}), 1.07−1.33 (4H, m, C_6H_{11}), 1.54−1.76 (7H, m, $CH_2C_6H_{11}$), 2.30 (2H, t, J = 8 Hz, $COCH_2$), 2.35 (3H, s, CH_3-CO_2Ar), 7.15 (2H, d, J_o = 8 Hz, ArH), 7.23−7.30 (1H, m, Ar′H), 7.38−7.44 (2H, m, Ar′H), 7.52 (1H, s, Ar′H), 7.82 (2H, d, J_o = 8 Hz, ArH), 7.94 (1H, s, Ar′NHCOR), 8.13 (1H, s, ArCONHAr′). Anal. ($C_{24}H_{28}N_2O_4$) C,H,N.

2-Methyl-5-nitro-*N*-(4-acetoxyphenyl)benzamide, 13. To a solution of 4-acetoxyaniline (4.14 g, 27.4 mmol), in dichloromethane (200 mL), were added 2-methyl-5-nitrobenzoyl chloride (6.6 g, 33 mmol) and triethylamine (3 mL, 41 mmol). The reaction mixture was stirred for 5 h. The resultant solid was filtered and dried to give **13** (6 g, 71%) as a white solid: ^{1}H NMR ($CDCl_3$) 2.30 (3H, s, CH_3CO_2Ar), 2.60 (3H, s, CH_3Ar), 7.07 (2H, d, J_o = 8 Hz, Ar′H), 7.45 (1H, d, J_o = 8 Hz, ArH), 7.80 (2H, d, J = 8 Hz, Ar′H), 8.19 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 8.38 (1H, d, J_m = 2 Hz, ArH), 9.98 (1H, s, Ar′NHCOAr).

2-Methyl-5-[(3-cyclohexylpropionyl)amino]-*N*-(4-hydroxyphenyl)benzamide, 14. A solution of **13** (5.5 g, 17.5 mmol) was hydrogenated at atmospheric pressure in ethyl acetate (200 mL) with 5% Pd/C (0.5 g) for 24 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give a solid which was dissolved in dichloromethane (80 mL). To this solution were added triethylamine (2.5 mL, 18 mmol) and 3-cyclohexylpropionyl chloride (3 g, 17.5 mmol). The mixture was stirred for 3 h, washed with 1 M hydrochloric acid, sodium bicarbonate solution, and water, and then dried and concentrated *in vacuo* to give a brown gum. This was hydrolyzed (following the method described for the preparation of compound **1**) to give **14** (1.65 g, 25% overall yield) as a white solid: mp 215 °C; ^{1}H NMR (DMSO-d_6) 0.83−0.92 (2H, m, C_6H_{11}), 1.06−1.28 (4H, m, C_6H_{11}), 1.49 (2H, q, J = 8 Hz, C$H_2C_6H_{11}$), 1.56−1.74 (5H, m, C_6H_{11}), 2.26−2.35 (5H, m, CH_3-Ar, $COCH_2$), 6.72 (2H, d, J_o = 8 Hz, Ar′H), 7.18 (1H, d, J_o = 8 Hz, ArH), 7.50 (2H, d, J_o = 8 Hz, Ar′H), 7.58 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 7.64 (1H, d, J_m = 2 Hz, ArH), 9.22 (1H, s, Ar′OH), 9.92 (1H, s, Ar′CONHAr), 10.03 (1H, s, ArNHCOR). Anal. ($C_{23}H_{28}N_2O_3 \cdot {}^1/_3H_2O$) C,H,N.

3-Cyclohexyl-*N*-[3-[(4-hydroxybenzyl)amino]-4-methylphenyl]propionamide, 15. To compound **5** (4.5 g, 17.3 mmol) in toluene (210 mL) were added 4-acetoxybenzaldehyde (5.67 g, 34.5 mmol) and *p*-toluenesulfonic acid (50 mg). The mixture was heated under reflux with a Dean−Stark apparatus for 3 h and then concentrated *in vacuo*. The oily, yellow residue was dissolved in ethanol (400 mL); then sodium borohydride (1.5 g, 39 mmol) was added portionwise. The reaction mixture was stirred for 2 h, left to stand for 16 h, and then concentrated *in vacuo* to give a solid. This was triturated with ethyl acetate, collected by filtration, and dried to give **15** (3.5 g, 50%) as a white solid: mp 171−172 °C; ^{1}H NMR (DMSO-d_6) 0.80−0.92 (2H, m, C_6H_{11}), 1.08−1.25 (4H, m, C_6H_{11}), 1.43 (2H, q, J = 8 Hz, C$H_2C_6H_{11}$), 1.56−1.72 (5H, m, C_6H_{11}), 2.05 (3H, s, CH_3Ar), 2.21 (2H, t, J = 8 Hz, $COCH_2$), 4.16 (2H, br d, Ar′CH_2NHAr), 5.31 (1H, br t, Ar′CH_2N*H*Ar) 6.55−6.84 (5H, m, ArH), 7.15 (2H, d, J_o = 8 Hz, Ar′H), 9.20 (1H, s, Ar′OH), 9.44 (1H, s, ArNHCOR). Anal. ($C_{23}H_{30}N_2O_2 \cdot {}^1/_2H_2O$) C,H,N.

2-(Hydroxymethyl)-4-nitrotoluene, 16. A solution of diborane in THF (800 mL, 1 M diborane in THF, 0.8 mol) was added over 1 h to a solution of 2-methyl-5-nitrobenzoic acid (100 g, 0.55 mol) in THF (400 mL), cooled to 0 °C under nitrogen. The stirred reaction mixture was allowed to reach room temperature overnight. The mixture was then cooled to 0 °C again, and water (500 mL) was added over 30 min,

followed by sodium hydroxide solution (400 mL, 1 M). The resultant solid was collected by filtration, washed with water, and dried to give **16** (86 g, 92%); ^{1}H NMR ($CDCl_3$) 2.00 (1H, t, J = 6 Hz, CH_2OH), 2.24 (3H, s, CH_3Ar), 4.78 (2H, d, CH_2OH), 7.21 (1H, d, J_o = 8 Hz, ArH), 8.15 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 8.30 (1H, d, J_m = 2 Hz, ArH).

3-(Hydroxymethyl)-4-methylaniline, 17. Compound **16** (76 g, 0.45 mol) was hydrogenated at atmospheric pressure in ethyl acetate (750 mL) with 5% Pd/C (9.5 g) for 24 h. The resulting mixture was boiled and then filtered through Celite while hot. The filtrate was concentrated *in vacuo* and the residue triturated with diethyl ether to give a solid. This was collected by filtration and dried to give **17** (62 g, 87%) as a white solid: mp 106−111 °C; ^{1}H NMR ($CDCl_3$) 2.22 (3H, s, CH_3Ar), 3.58 (2H, br s, $ArNH_2$), 4.61 (2H, s, $ArCH_2OH$), 6.56 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 6.74 (1H, d, J_m = 2 Hz, ArH), 6.86 (1H, d, J_o = 8 Hz, ArH).

***N*-[3-(Hydroxymethyl)-4-methylphenyl]-3-cyclohexylpropionamide, 18.** To a solution of **17** (49 g, 0.36 mol) in dichloromethane (1 L) was added 3-cyclohexylpropionyl chloride (62.6 g, 0.36 mol) and triethylamine (51 mL, 0.36 mol). The reaction mixture was stirred for 1 h and then washed with water (940 mL). The organic layer was separated, dried, filtered, and concentrated *in vacuo* to give **18** (86 g, 87%) as a white solid: mp 121−125 °C; ^{1}H NMR ($CDCl_3$) 0.85−0.98 (2H, m, C_6H_{11}), 1.08−1.34 (4H, m, C_6H_{11}), 1.55−1.81 (8H, m, $CH_2C_6H_{11}$, $ArCH_2OH$), 2.28 (3H, s, CH_3Ar), 2.33 (2H, t, J = 8 Hz, $COCH_2$), 4.63 (2H, s, $ArCH_2OH$), 7.10 (1H, d, J_o = 8 Hz, ArH), 7.32 (1H, s, ArNHCOR), 7.37 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 7.46 (1H, d, J_m = 2 Hz, ArH).

3-Cyclohexyl-*N*-(3-formyl-4-methylphenyl)propionamide, 19. To a solution of **18** (83.7 g, 0.3 mol) in THF (1 L) was added activated manganese dioxide (85 g, 0.97 mol) portionwise. The reaction mixture was stirred for 4 h at room temperature and then heated to 60 °C for 2 h, left to stand at room temperature for 16 h, and filtered through Celite. The solvent was concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant CH_2Cl_2:MeOH, 98:2). Concentration of the solvent *in vacuo* yielded a residue which was triturated with diethyl ether to give **19** (59 g, 71%) as a white solid: mp 134−137 °C; ^{1}H NMR ($CDCl_3$) 0.86−0.99 (2H, m, C_6H_{11}), 1.08−1.35 (4H, m, C_6H_{11}), 1.59−1.78 (7H, m, $CH_2C_6H_{11}$), 2.40 (2H, t, J = 8 Hz, $COCH_2$), 2.62 (3H, s, CH_3Ar), 7.21 (1H, d, J_o = 8 Hz, ArH), 7.51 (1H, s, ArNHCOR), 7.78 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 7.87 (1H, d, J_m = 2 Hz, ArH_2), 10.22 (1H, s, ArCHO).

General Procedure for the Preparation of Compounds 20−22. To a solution of **19** in methanol (10 mL) were added the appropriate arylacetonitrile (1 equiv) and potassium carbonate (2 equiv). The mixture was heated under reflux for 2 h and then cooled to room temperature and diluted with ethyl acetate. The mixture was washed with water, dried, filtered, and concentrated *in vacuo* to give a yellow solid which was triturated with diethyl ether.

***N*-[3-[2-Cyano-2-(3-pyridyl)vinyl]-4-methylphenyl]-3-cyclohexylpropionamide, 20.** Compound **20** was obtained in 51% yield as a white solid: mp 140−141 °C; ^{1}H NMR ($CDCl_3$) 0.86−0.99 (2H, m, C_6H_{11}), 1.08−1.35 (4H, m, C_6H_{11}), 1.59−1.78 (7H, m, $CH_2C_6H_{11}$), 2.30 (3H, s, CH_3Ar), 2.42 (2H, t, J = 8 Hz, $COCH_2$), 7.22 (1H, d, J_o = 8 Hz, ArH), 7.43 (1H, m, PyH), 7.55 (1H, br s, PyH), 7.75−7.88 (2H, s, olefinic-H, ArH), 7.91 (1H, d, J_m = 2 Hz, ArH), 7.98 (1H, m, PyH), 8.66 (1H, m, PyH), 8.93 (1H, s, ArNHCOR). Anal. ($C_{24}H_{27}N_3O$) C,H,N.

***N*-[3-[2-Cyano-2-(4-hydroxyphenyl)vinyl]-4-methylphenyl]-3-cyclohexylpropionamide, 21.** Compound **21** was obtained in 37% yield as a cream solid: mp 186−187 °C; ^{1}H NMR (DMSO-d_6) 0.82−0.95 (2H, m, C_6H_{11}), 1.06−1.29 (4H, m, C_6H_{11}), 1.49 (2H, q, J = 8 Hz, $CH_2C_6H_{11}$), 1.56−1.75 (5H, m, C_6H_{11}), 2.29 (3H, s, CH_3-Ar), 2.32 (2H, t, J = 8 Hz, $COCH_2$), 6.89 (2H, d, J_o = 8 Hz, Ar′H), 7.21 (1H, d, J_o = 8 Hz, ArH), 7.57−7.65 (3H, m, ArH, Ar′H), 7.89 (1H, s, olefinic-H), 7.93 (1H, d, J_m = 2 Hz, ArH), 9.95 (1H, s, Ar′OH), 9.96 (1H, s, ArNHCOR). Anal. ($C_{25}H_{28}N_2O_2 \cdot {}^1/_5H_2O$) C,H,N.

***N*-[3-[2-Cyano-2-[3,4-(methylenedioxy)phenyl]vinyl]-4-methylphenyl]-3-cyclohexylpropionamide, 22.** Compound **22** was obtained in 76% yield as an off-white solid: mp 179−181 °C; ^{1}H NMR (DMSO-d_6) 0.82−0.95 (2H, m, C_6H_{11}), 1.06−1.29 (4H, m, C_6H_{11}), 1.50 (2H, q, J = 8 Hz, $CH_2C_6H_{11}$), 1.56−1.75 (5H, m, C_6H_{11}), 2.26−2.36 (5H, m, CH_3Ar, $COCH_2$), 6.12 (2H, s, OCH_2O), 7.06 (1H, d, J_o = 8 Hz, ArH), 7.20−7.27 (2H, m, ArH, Ar′H), 7.46 (1H, d, J_m = 2 Hz, Ar′H), 7.62 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.96 (1H, d, J_m = 2 Hz, ArH), 8.01 (1H, s, olefinic-H), 9.96 (1H, s, ArNHCOR). Anal. ($C_{26}H_{28}N_2O_4$) C,H,N.

5-Amino-2-methylbenzoic Acid, 23. 2-Methyl-5-nitrobenzoic acid (1.8 g, 10 mmol) in ethanol (30 mL) was hydrogenated at atmospheric pressure with 5% Pd/C (0.2 g). The mixture was stirred for 1 h and then filtered through Celite. Concentration of the filtrate *in vacuo* gave **23**[15] (1.5 g, 100%) as a white solid: mp 193−197 °C.

5-[(3-Cyclohexylpropionyl)amino]-2-methylbenzoic Acid, 24. To a solution of **23** (1.5 g, 10 mmol) in dichloromethane (35 mL) were added 3-cyclohexylpropionyl chloride (1.75 g, 10 mmol) and triethylamine (3 mL, 22 mmol). The reaction mixture was stirred for 1 h and left to stand for 16 h. The mixture was washed with water, dried, and concentrated *in vacuo* to give a solid. This was recrystallized from aqueous ethanol to give **24** (2.65 g, 91%) as a white solid: mp 221−223 °C; ^{1}H NMR (DMSO-d_6) 0.71−0.95 (2H, m, C_6H_{11}), 1.06−1.29 (4H, m, C_6H_{11}), 1.49 (2H, q, J = 8 Hz, $CH_2C_6H_{11}$), 1.56−1.74 (5H, m, C_6H_{11}), 2.30 (2H, t, J = 8 Hz, $COCH_2$), 2.45 (3H, s, CH_3-Ar), 7.20 (1H, d, J_o = 8 Hz, ArH), 7.68 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 8.08 (1H, d, J_m = 2 Hz, ArH), 9.94 (1H, s, ArNHCOR). Anal. ($C_{17}H_{23}NO_3 \cdot {}^1/_5H_2O$) C,H,N.

General Procedure for the Preparation of Compounds 25−27. To a solution of the appropriate 1,2-arylenediamine in dichloromethane, at −60 °C, were added 5-(3-cyclohexylpropionamido)-2-methylbenzoylchloride (0.5 equiv, prepared by reacting **24** with 1 equiv of thionyl chloride in toluene under reflux for 8 h) and triethylamine (2 equiv). The mixture was stirred for 15 min and allowed to reach room temperature. The solution was then washed with water, dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* and the residue triturated with ethyl acetate to give an off-white solid. This was heated to 200 °C neat for 30 min. The residue was boiled in acetonitrile and then treated with charcoal and filtered through Celite while hot. The filtrate was concentrated *in vacuo* to give a solid which was collected by filtration and dried.

***N*-[3-(1*H*-Benzimidazol-2-yl)-4-methylphenyl]-3-cyclohexylpropionamide, 25.** Compound **25** was obtained in 20% yield as a light brown solid: mp 197−200 °C; ^{1}H NMR ($CDCl_3$) 0.83−0.96 (2H, m, C_6H_{11}), 1.07−1.32 (4H, m, C_6H_{11}), 1.52−1.76 (7H, m, $CH_2C_6H_{11}$), 2.30−2.41 (5H, m, $COCH_2$, CH_3Ar), 6.98 (1H, d, J_o = 8 Hz, ArH), 7.29−7.37 (3H, m, ArH), 7.63 (1H, d, ArH), 7.61−7.70 (2H, m, ArH), 8.55 (1H, s, ArNHCOR). Anal. ($C_{23}H_{27}N_3O$) C,H,N.

***N*-[3-(5-Methyl-1*H*-benzimidazol-2-yl)-4-methylphenyl]-3-cyclohexylpropionamide, 26.** Compound **26** was obtained in 22% overall yield as an off-white solid: mp 157−159 °C; ^{1}H NMR ($CDCl_3$) 0.80−0.93 (2H, m, C_6H_{11}), 1.05−1.28 (4H, m, C_6H_{11}), 1.54 (2H, q, J = 8 Hz, $-CH_2C_6H_{11}$), 1.59−1.73 (5H, m, C_6H_{11}), 2.25 (3H, s, CH_3Ar), 2.31 (2H, t, J = 8 Hz, $COCH_2$), 2.47 (3H, s, CH_3-benzimidazole), 6.90 (1H, d, J_o = 8 Hz, ArH), 7.09 (1H, d, J = 8 Hz, ArH), 7.29−7.38 (3H, m, ArH), 7.49 (1H, d, J = 8 Hz, ArH), 8.56 (1H, s, ArNHCOR). Anal. ($C_{24}H_{29}N_3O$) C,H,N.

***N*-[3-(5-Hydroxy-1*H*-benzimidazol-2-yl)-4-methylphenyl]-3-cyclohexylpropionamide, 27.** Starting from 4-hydroxy-1,2-phenylenediamine (freshly prepared by hydrogenation of 3-nitro-4-aminophenol at atmospheric pressure, in ethanol with 5% Pd/C), compound **27** was obtained in 12% overall yield as an off-white solid: mp 167−175 °C; ^{1}H NMR (DMSO-d_6) 0.83−0.96 (2H, m, C_6H_{11}), 1.06−1.30 (4H, m, C_6H_{11}), 1.50 (2H, q, J = 8 Hz, $-CH_2$-cyclohexyl), 1.57−1.76 (5H, m, C_6H_{11}), 2.33 (2H, t, J = 8 Hz, $COCH_2$), 2.47 (3H, s, CH_3Ar), 6.78 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, benzimidazole-H), 7.30 (1H, d, J_o = 8 Hz, ArH), 7.46 (1H, d, J_o = 8 Hz, benzimidazole-H), 7.56 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 8.02 (1H, d, J_m = 2 Hz, ArH), 9.36 (1H, s, benzimidazole-H), 10.02 (1H, s, ArNHCOR). Anal. ($C_{23}H_{27}N_3O_2 \cdot H_2O$) C,H,N.

4-Methyl-3-nitro-3-[(cyclohexen-1-ylethyl)amino]-benzamide, 28. To a solution of 4-methyl-3-nitrobenzoyl chloride (6 g, 30 mmol; prepared from 4-methyl-3-nitrobenzoic acid and 3 equiv of thionyl chloride in toluene under reflux for 2 h) were added 2-(cyclohexen-1-yl)ethylamine (3.75 g, 30 mmol) and triethylamine (6 g, 60 mmol). The mixture was stirred for 1 h and then left to stand for 16 h. The reaction mixture was washed with hydrochloric acid (1 M, 100 mL), saturated sodium bicarbonate (200 mL), and water and then dried, filtered, and concentrated *in vacuo*. The residue was triturated with diethyl ether and collected by filtration to give **28** (6.8 g, 79%) as a white solid: ^{1}H NMR ($CDCl_3$) 1.53−1.69 (4H, m, C_6H_9), 1.94−2.08 (4H, m, C_6H_9), 2.27 (2H, t, J = 8 Hz, $CH_2C_6H_9$), 2.96 (3H, s, CH_3Ar), 3.54 (2H, m, CONHCH_2R), 5.55 (1H, m, olefinic-H), 6.21 (1H, br s, ArCONHR), 7.43 (1H, d, J_o = 8 Hz, ArH), 7.91 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 8.30 (1H, d, J_m = 2 Hz, ArH).

3-Amino-4-methyl-*N*-[(cyclohexylethyl)amino]benzamide, 29. Compound **28** (6.8 g, 23.6 mmol) was hydrogenated at atmospheric pressure in ethyl acetate (175 mL) with 5% Pd/C (0.7 g) for 16 h. The reaction mixture was then warmed and filtered through Celite while hot. The filtrate was concentrated *in vacuo*, and the residue was triturated with diethyl ether to give **29** (5.1 g, 83%) as a yellow solid: ^{1}H NMR ($CDCl_3$) 0.86−1.01 (2H, m, C_6H_{11}), 1.09−1.27 (4H, m, C_6H_{11}), 1.45−1.78 (7H, m, $CH_2C_6H_{11}$), 2.19 (3H, s, CH_3-Ar), 3.45 (2H, m, CONHCH_2R), 6.05 (1H, br, s, ArCONHR), 6.94 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 7.08 (1H, d, J_o = 8 Hz, ArH), 7.14 (1H, d, J_m = 2 Hz, ArH).

3-(4-Hydroxybenzamido)-4-methyl-*N*-[(2-cyclohexylethyl)amino]benzamide, 30. To a solution of 4-acetoxybenzoyl chloride (0.76 g, 3.87 mmol) in dichloromethane (100 mL) were added compound **29** (1 g, 3.87 mmol) and triethylamine (0.86 g, 8.5 mmol). The mixture was stirred for 3 h, left to stand for 16 h, and then washed with hydrochloric acid (1 M, 75 mL), saturated sodium bicarbonate (75 mL), and water (75 mL). The organic solution was filtered and then concentrated *in vacuo* to give a solid. This was hydrolyzed (following the method described for compound **1**) to give **30** (0.3 g, 20% overall) as a white solid: mp 211−212 °C; ^{1}H NMR (DMSO-d_6) 0.83−0.96 (2H, m, C_6H_{11}), 1.09−1.27 (4H, m, C_6H_{11}), 1.42 (2H, q, J = 8 Hz, $CH_2C_6H_{11}$), 1.57−1.77 (5H, m, C_6H_{11}), 2.25 (3H, s, CH_3-Ar), 3.28 (2H, m, CONHCH_2R), 6.87 (2H, d, J_o = 8 Hz, Ar′H), 7.33 (1H, d, J_o = 8 Hz, ArH), 7.64 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 7.70 (1H, d, J_m = 2 Hz, ArH), 7.78 (2H, d, J_o = 8 Hz, Ar′H), 8.38 (1H, br t, ArCONHR), 9.75 (1H, s, Ar′CONHAr). Anal. ($C_{23}H_{28}N_2O_3 \cdot {}^2/_3H_2O$), C,H,N.

4-Cyclohexyl-1-(4-methylphenyl)butan-1-one, 31. To a suspension of aluminum chloride (27.87 g, 0.2 mol) in dry toluene (425 mL) was added 4-cyclohexylbutyryl chloride (38.6 g, 0.2 mol; prepared from 4-cyclohexylbutyric acid and 1.5 equiv of thionyl chloride at room temperature for 56 h) in dry toluene (270 mL). The mixture was heated under reflux for 1.5 h, cooled to room temperature, and then washed with water (5 × 250 mL), dried, filtered, and concentrated *in vacuo* to give a yellow oil. This was purified by distillation under reduced pressure (bp 142−146 °C, 0.2 mbar) to give **31** (42.5 g, 85%) as a colorless oil which solidified on standing: ^{1}H NMR ($CDCl_3$) 0.82−0.96 (2H, m, C_6H_{11}), 1.07−1.31 (6H, m, $COCH_2CH_2$-$CH_2C_6H_{11}$), 1.49−1.79 (7H, m, $CH_2C_6H_{11}$), 2.40 (3H, s, CH_3-Ar), 2.91 (2H, t, J = 8 Hz, $COCH_2$), 7.25 (2H, d, J_o = 8 Hz, ArH), 7.85 (2H, d, J_o = 8 Hz, ArH).

4-Cyclohexyl-1-(4-methyl-3-nitrophenyl)butan-1-one, 32. Compound **31** (38 g, 0.16 mol) was added portionwise to a stirred solution of concentrated sulfuric acid (86 mL) and concentrated nitric acid (70 mL), maintained at −7 °C. After addition, the mixture was stirred for 20 min at −7 °C and then poured onto ice. The resultant yellow oil was extracted with diethyl ether (3 × 200 mL). The combined ether extracts were washed with water, dried, filtered, and concentrated *in vacuo* to give an oil. This was purified by filtration through silica gel (eluant cyclohexane:ethylacetate, 3:1) to give **32** (42.3 g, 93%) as a yellow oil: ^{1}H NMR ($CDCl_3$) 0.82−0.97 (2H, m, C_6H_{11}), 1.08−1.31 (6H, m, $COCH_2CH_2CH_2C_6H_{11}$), 1.60−1.81 (7H, m, $CH_2C_6H_{11}$), 2.68 (3H, s, CH_3Ar), 2.96 (2H, t, J = 8 Hz, $COCH_2$), 7.46 (1H, d, J_o = 8 Hz, ArH), 8.09 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, ArH), 8.52 (1H, d, J_m = 2 Hz, ArH); MS *m*/*z* 190 (MH^+).

4-Cyclohexyl-1-(3-amino-4-methylphenyl)butan-1-one, 33. Compound **32** was hydrogenated at atmospheric pressure in ethanol (75 mL) with 5% Pd/C (0.43 g) for 16 h. The mixture was then filtered through Celite and concentrated *in vacuo* to give a brown solid. This was purified by flash column chromatography on silica gel (eluant dichloromethane) to give **33** (1.86 g, 48%) as a yellow solid: ^{1}H NMR ($CDCl_3$) 0.80−0.95 (2H, m, C_6H_{11}), 1.07−1.32 (6H, m, $COCH_2CH_2$-$CH_2C_6H_{11}$), 1.58−1.78 (7H, m, $CH_2C_6H_{11}$), 2.21 (3H, s, CH_3-Ar), 2.87 (2H, t, J = 8 Hz, $COCH_2$), 3.75 (2H, br s, $ArNH_2$), 7.11 (1H, d, J_o = 8 Hz, ArH), 7.5−7.31 (2H, m, ArH).

***N*-[5-(4-Cyclohexylbutyryl)-2-methylphenyl]-4-hydroxybenzamide, 34.** To a solution of compound **33** (4 g, 15 mmol) in dichloromethane (400 mL) were added 4-acetoxybenzoyl chloride (3.37 g, 17 mmol) and triethylamine (5.6 mL, 40 mmol). The solution was left to stand for 24 h and then washed with water, dried, filtered, and concentrated *in vacuo* to give a yellow solid. This was triturated with diethyl ether to give a white solid which was collected by filtration and hydrolyzed (following the procedure described for compound **1**) to give **34** (1.6 g, 30% overall yield) as a white solid: mp 177 °C; ^{1}H NMR (DMSO-d_6) 0.72−0.99 (2H, m, C_6H_{11}), 1.08−1.29 (6H, m, $COCH_2CH_2CH_2C_6H_{11}$), 1.56−1.72 (7H, m, CH_2-C_6H_{11}), 2.29 (3H, s, CH_3Ar), 2.95 (2H, t, J = 8 Hz, $COCH_2$), 6.86 (2H, d, J_o = 8 Hz, ArH), 7.40 (1H, d, J_o = 8 Hz, Ar′H), 7.74 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 7.88 (2H, d, J_o = 8 Hz, ArH), 7.91 (1H, d, J_m = 2 Hz, Ar′H), 9.71 (1H, s, ArCONHAr′). Anal. ($C_{24}H_{29}NO_3$) C,H,N.

***N*-[5-(4-Cyclohexylbutyryl)-2-methylphenyl]pyridine-3-carboxamide, 35.** To a solution of compound **33** (1.86 g, 7.2 mmol) in dichloromethane (300 mL) were added nicotinoyl chloride hydrochloride (1.28 g, 7.9 mmol) and triethylamine (2.6 mL, 19 mmol). The solution was stirred for 5 h and then washed with water, dried, filtered, and concentrated *in vacuo*. The residue was triturated with pentane to give a white solid which was recrystallized (toluene:cyclohexane, 3:1) to give **35** (0.95 g, 36%) as a white solid: mp 93−94 °C; ^{1}H NMR ($CDCl_3$) 0.82−0.94 (2H, m, C_6H_{11}), 1.11−1.31 (6H, m, $COCH_2CH_2$-$CH_2C_6H_{11}$), 1.60−1.81 (7H, m, $CH_2C_6H_{11}$), 2.41 (3H, s, CH_3-Ar), 2.95 (2H, t, J = 8 Hz, $COCH_2$), 7.35 (1H, d, J_o = 8 Hz, Ar′H), 7.50 (1H, m, PyH), 7.35 (1H, s, PyCONHAr′), 7.78 (1H, dd, J_o = 8 Hz, J_m = 2 Hz, Ar′H), 8.26 (1H, m, PyH), 8.47 (1H, br s, Ar′H), 8.83 (1H, m, PyH), 9.14 (1H, br s, PyH). Anal. ($C_{23}H_{28}N_2O_2$) C,H,N.

Biological Methods. Materials. HepG2 cells were obtained from ECCAC at Porton Down. All cell culture reagents were obtained from Gibco BRL. MAC-C7, a mouse anti-human LDL receptor monoclonal, was produced by biofermentation of the C7 cell clone. All other antibodies were obtained from Boehringer Mannheim. 25-Hydroxycholesterol was obtained from Sigma Ltd. ATTAPHOS was obtained from Millipore.

Cell Culture. Cells were maintained in Dulbecco's modified Eagle's medium supplemented with fetal calf serum in 75 cm^2 culture flasks in a humidified 5% CO_2 atmosphere at 37 °C and subcultured every 3−4 days. Cells beyond passage 10 were not used in assays.

LDL Receptor Assay. LDL receptors were quantitated by a fluorescence method using the monoclonal antibody MAC-C7. HepG2 cells were plated in 96-well culture plates at 10 000 cells/well and grown for 3 days to 80% confluence; compounds were added in DMEM containing 1% bovine serum albumin (BSA) and incubated for 24 h. The culture medium was aspirated, and the cell monolayers were washed with phosphate-buffered saline (PBS) and fixed with 3% formaldehyde at 4 °C. The formaldehyde solution was removed, and the cells were washed with ammonium sulfate solution followed by PBS. MAC-C7 solution, 0.5 μg/mL in PBS containing 10% FCS, was added and incubated for 60 min at 4 °C. Following removal of the MAC-C7 solution and washing with PBS, the monolayers were incubated with an anti-mouse IgG monoclonal antibody conjugated to alkaline phosphatase and incubated for 60 min at 4 °C. The second antibody solution was removed, and the alkaline phosphatase substrate AT-

TOPHOS, 0.6 mg/mL, in diethanolamine buffer (pH 10) was added with propidium iodide at 20 μg/mL. The culture plates were incubated at 4 °C for 1 h and the reaction terminated by addition of 6 M NaOH. Fluorescence readings at 436 and 590 nm were taken in a Cytofluor 2400 fluorescence plate reader; an increase in fluorescence reading denoted an increase in MAC-C7 binding and hence LDL receptor numbers. Cell numbers per well were determined by propidium iodide fluorescence at 530 and 640 nm.

Acknowledgment. We are grateful to Barry Wyman, Imtiaz Ahmed, and Clare Howells for technical assistance, Iain McLay for modeling studies, Michael Podmore, Mark Vine, and Don Daley for spectroscopy, and Anne Stevens for microanalysis. We are also grateful to Anne White, Julia Lloyd, and Melanie Wong for the *in vitro* assays on HepG2 cells.

References

(1) Goldstein, J. L.; Brown, M. S. The low-density lipoprotein pathway and its relation to atherosclerosis. In *Annual Review in Biochemistry*; Snell, E. E., Boyer, P. D., Meister, A., Richardson, C. C., Eds.; Annual Reviews Inc.: CA, **1977**; Vol. 46, pp 897−903.

(2) Goldstein, J. L.; Brown, M. S. A receptor-mediated pathway for cholesterol homeostasis. *Science* **1986**, *232*, 34−47.

(3) Bilheimer, D. W.; Goldstein, J. L.; Grundy, T. E.; Startz, T. E.; Brown, M. S. Liver transplantation to provide Low-Density-Lipoprotein receptors and lower plasma cholesterol in a child with homozygous familial hypercholesterolemia. *N. Engl. J. Med.* **1984**, *311*, 1658−1664.

(4) Goldstein, J. L.; Brown, M. S. Regulation of the mevalonate pathway. *Nature* **1990**, *343*, 425−430.

(5) (a) Ellsworth, J. L.; Carlstrom, A. J.; Deikman, J. Ketoconazole and 25-hydroxycholesterol produce reciprocal changes in the rate of transcription of the human LDL receptor gene. *Biochem. Biophys. Acta* **1994**, *1210*, 321−328. (b) Miettinen, T. A. Cholesterol metabolism during ketoconazole treatment in man. *J. Lipid Res.* **1988**, *29*, 43−51.

(6) Wade, D. P.; Knight, B. L.; Soutar, A. K. Hormonal regulation of low-density lipoprotein (LDL) activity in human Hep G2 cells. Insulin increases LDL receptors activity and diminishes its suppression by exogenous LDL. *Eur. J. Biochem.* **1988**, *174* (1), 213−218.

(7) Marcus, A. J.; Hajjar, D. P. Vascular transcellular signaling. *J. Lipid Res.* **1993**, *34*, 2017−2032.

(8) Middleton, B. Lysosome Inhibitors Enhance The Ability of Cyclic AMP-Elevating Agents to Induce the LDL Receptor in Human Vascular Smooth Muscle Cells. *Biochem. Biophys. Res. Commun.* **1992**, *182*, 830−835.

(9) (a) Schroepfer, J. G.; Walker, V.; Parish, E. J.; Kisic, A. Inhibitors of sterol synthesis. Hypercholesterolemic action of dietary 9α-fluoro-5α-cholest-8(14)-en-3β-ol-15-one. *Biochem. Biophys. Res. Commun.* **1980**, *93*, 813. (b) Chorvat, R. J. 25-Alkyl- or -halo-5α-cholestane-3,22(S)-diol(s) and ester(s) − useful as HMG CoA reductase inhibitors which inhibit formation of serum cholesterol. U.S. Pat. 4348328, 1982. (c) Sonoda, Y.; Sato, Y. Hypolidemic effects of dietary 7-oxo-24,25-dihydrolanosterol. *J. Pharmacobio-Dyn.* **1985**, *8*, 518−524. (d) Panini, S. R.; Sexton, R. C.; Gupta, A. K.; Parish, E. J.; Chitrakorn, S.; Rudney, H. Regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity and cholesterol biosynthesis by oxylanosterols. *J. Lipid Res.* **1986**, *27*, 1190−1204. (e) Needleman, D. H.; Strong, K.; Stemke, K. A.; Brabson, J. S.; Kisic, A.; Schroepfer, G. J. Inhibitors of sterol synthesis. Effect of dietary 5α-cholest-8(14)-en-3β-ol-15-one on ACAT activity of jejunal microsomes of the rat. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 920−925 and references cited therein. (f) Gaylor, J. L.; Johnson, R. P.; Ko, S. S.; Magolda, R. L.; Stam, S. H.; Trzaskos, J. M. 14,15-Substituted lanosterols and their use as hypocholesterolemic agents. E.P. Pat. 276,823, 1988. (g) Kreiser, W. H.; Scharein, P.; Granzer, E. New 3β-hydroxy-26,27-bis-nor-cholesta-5,23-dien-25-ol derivatives with HMG CoA reductase inhibiting activity. E.P. Pat. 346759, 1989. (h) Ko, S. S.; Trzaskos, J. M. Heterocyclic steroid compounds. WO 91/13909, 1991. (i) Adams, J. L.; Gallagher, T. F.; Mayer, R. J.; Metcalf, B. W. 14α-Carboxyalkyl steroid(s) for lowering serum cholesterol act by regulation of HMG CoA reductase and lanosterol de-methylase, are also antifungal. U.S. Pat. 5023250, 1991. (j) Larsen, S. D.; Spilman, C. H.; Yagi, Y.; Dinh, D. M.; Hart, K. L.; Hess, G. F. Design and synthesis of *seco*-oxysterol analogs as potential inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase gene transcription. *J. Med. Chem.* **1994**, *37*, 2343−2351.

(10) Taylor, F. R.; Saucier, S. E.; Shown, E. P.; Parish, E. J.; Kandutsch, A. A. Correlation between oxysterol binding to a cytosolic binding protein and potency in the repression of hyroxymethylglutaryl coenzyme A reductase. *J. Biol. Chem.* **1984**, *259*, 12382−12387.

(11) Lin, H. S.; Rampersaud, A. A.; Archer, R. A.; Pawlak, J. M.; Beavers, L. S.; Schmidt, R. J.; Kauffman, R. F.; Bensch, W. R.; Bumol, T. F.; Apelgren, L. D.; Eacho, P. I.; Perry, D. N.; McClure, D. B.; Gadski, R. A. Synthesis and Biological Evaluation of a series of Sterols as Potential Hypocholesterolemic Agents. *J. Med. Chem.* **1995**, *38*, 277−288.

(12) Ashton, M. J.; Bridge, A. W.; Bush, R. C.; Dron, D. I.; Joannou, P.; Riddell, D.; Roberts, S.; Stevenson, G. V. W.; Warne, P. J. RP64477: a potent inhibitor of ACAT. 9th International Symposium on Atherosclerosis, Chicago, IL, 1991.

(13) Bowyer, D. E. Unpublished results.

(14) Brown, T. J.; White, A.; Lloyd, J.; Vicker, N.; Lockey, P. RPR102359 upregulates LDL receptors in a cultured human hepatocyte cell line by a sterol-independent mechanism. *Atherosclerosis* **1994**, *109*, 113−114.

(15) Sucholeiki, I.; Lynch, V.; Phan, L.; Wilcox, C. S. Molecular Armatures. Synthesis and Structure of Troger's Base Analogues Derived from 4-,2,4-,3,4 and 2,4,5-Substituted Aniline Derivatives. *J. Org. Chem.* **1988**, *53*, 98−104.

JM960153Q