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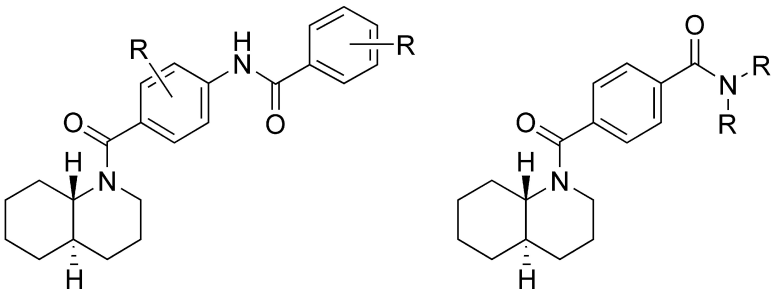

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Perhydroquinolylbenzamides as Novel Inhibitors of 11β-Hydroxysteroid Dehydrogenase Type 1

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High-throughput screening identified **5** as a weak inhibitor of 11β-HSD1. Optimization of the structure led to a series of perhydroquinolylbenzamides, some with low nanomolar inhibitory potency. A tertiary benzamide is required for biological activity and substitution of the terminal benzamide with either electron-donating or -withdrawing groups is tolerated. The majority of the compounds show selectivity of >20 to >700-fold over 11β-HSD2. Analogues which showed >50% inhibition of 11β-HSD1 at 1 μM in an cellular assay were screened in an ADX mouse model. A maximal response of >70% reduction of liver corticosterone levels was observed for three compounds; **9m**, **25** and **49**.

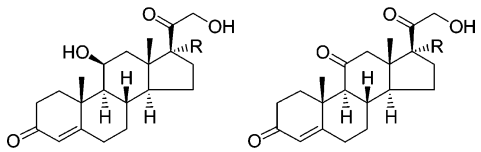
Introduction

Diabetes is a disease in which the body does not produce or properly use insulin, a hormone that is needed to convert glucose, starches and other food into energy needed for daily life. While the cause of diabetes is not clearly understood, both genetics and environmental factors such as obesity and lack of exercise appear to play roles. There are 18.2 million people or 6.3% of the population in the United States who have diabetes. While an estimated 13 million have been diagnosed, unfortunately, 5.2 million people are not aware that they have the disease primarily due to the lack of symptoms during the early stages of the disease. According to the American Diabetes Association, each day approximately 3600 people are diagnosed with diabetes. About 1.3 million people will be diagnosed this year.[1] The more prevalent form of diabetes (type 2) accounts for more than 90% of these cases. The pathogenesis of type 2 diabetes is characterized by high plasma glucose levels resulting from peripheral insulin resistance, insufficient insulin secretion from pancreatic β-cells and increased hepatic glucose production.[2−4]

Microvascular complications associated with diabetes are responsible for a substantial portion of related morbidity and mortality. Each year as many as 24 000 people lose their sight due to diabetic retinopathy.[1,5] Ten to 21% of all people with diabetes develop kidney disease due to nephropathy, and 56 200 people require foot or leg amputations each year as a result of diabetic neuropathy.[1,6,7] Dyslipidemia with its associated cardiovascular risk factors accounts for approximately 80% of all diabetic mortality.[8,9] Diabetes with its associated complications results in the death of at least 190 000 people yearly and is the seventh leading cause of death (sixth-leading cause of death by disease) in the United States.[1]

A variety of mechanistic approaches have been taken to normalize the levels of blood glucose in the diabetic state.[10,11] These include the sulfonylurea receptor/ATP−K^+ channel,[12,13] carnitine palmitoyltranferase (CPT),[14] glucokinase (GK),[15,16] peroxisome-proliferator activated receptor$_\gamma$ (PPAR$_\gamma$),[17−19] dipeptidylpeptidase 4 (DPP-4),[20,21] α-glucosidase,[22] and glycogen phosphorylase.[23]

A conceptually different approach is to target the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD).[24] This microsomal membrane-bound enzyme controls the interconversion of the receptor active hormone cortisol (**1a**) and its inactive keto-form cortisone (**2a**, in man) as well as corticosterone (**1b**) and dehydrocorticosterone (**2b**, in rodents).[25] The significance of the glucocorticoids in glucose homeostasis is exemplified in the clinical condition known as Cushing's syndrome where cortisol excess is characterized by impaired glucose tolerance, obesity and hypertension.[26,27] Cortisol from the liver together with plasma cortisol derived from the adrenal gland stimulates gluconeogenesis by enhancing the activity of enzymes such as PEPCK and glucose 6-phosphatase. It also promotes adipogenesis and induces lipolysis and the release of free fatty acids in the adipocytes.



Two isoforms of the enzyme have been identified. The type I isoform (11β-HSD1), located primarily in the liver and adipose tissue, is a low-affinity, NADPH-dependent bidirectional enzyme which acts predominantly as an

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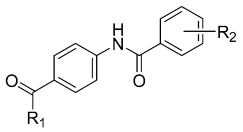
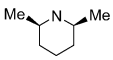
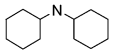
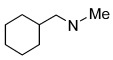
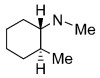
Table 1. Initial Modifications of **5.** In Vitro Data.

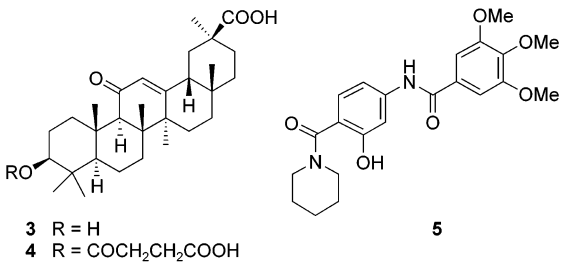


No.	R_1	R_2	11β-HSD1 IC_{50} (μM)	11β-HSD2 % Inh. at 10 μM
9a		3,4,5-$(OMe)_3$	71.54	
9b		4-F	99.37	
9c		2,4-$(Cl)_2$	19.67	
9d		2,4-$(Cl)_2$	7.89	61
9e		2,4-$(Cl)_2$	1.06	11
9f		2,4-$(Cl)_2$	1.83	38
9g		2,4-$(Cl)_2$	1.72	33
9h		2,4-$(Cl)_2$	48.08	
9i		2,4-$(Cl)_2$	NA	
9j		2,4-$(Cl)_2$	4.40	64
9k		2,4-$(Cl)_2$	0.37	73
9l		2,4-$(Cl)_2$	1.00	64
9m		2,4-$(Cl)_2$	0.22	42
9n		2,4-$(Cl)_2$	a	
9o		2,4-$(Cl)_2$	0.73	71

[a] 13% Inhibition at 1 μM. NA = not active.

oxidoreductase to form the active glucocorticoids, whereas the type II isoform (11β-HSD2), located primarily in the kidney, is a high-affinity, unidirectional enzyme functioning exclusively as a NAD-dependent dehydrogenase producing inactive 11-keto metabolites.[28−32] It has been demonstrated that the anti-ulcer drug carbenoxolone (**4**), a nonselective inhibitor of 11β-HSD1, increases hepatic insulin sensitivity in man.[33,34] Furthermore, 11β-HSD1 knockout mice are resistant to hyperglycemia provoked by a high-fat fed diet or stress and have reduced PEPCK activity.[35] 11β-HSD2 plays an important role in mineralocorticoid target tissues by allowing aldosterone access to the mineralocorticoid receptors (MR) which binds cortisol with equal affinity.[29] Overstimulation of the MR by cortisol leads to sodium retention, severe hypertension and hypokalemia.[29,36−40] Indeed, it has been shown that adult 11β-HSD2 knockout mice are markedly hypertensive.[28] Therefore, se-

lectively inhibiting 11β-HSD1 should reduce hepatic glucose production and decrease lipolysis in adipose tissue without the risk of adverse hypertension effects.



3 R = H
4 R = $COCH_2CH_2COOH$

5

Glycyrrhetinic acid (**3**), the active pharmacological component of licorice root (*Glycyrrhiza glabra*; *Glycyrrhiza uralensis* Fisch.)[41−44] and carbenoxolone[45,46] (**4**), the synthetic succinyl ester[47−49] of glycyrrhetinic acid, have been reported to be low nanomolar inhibitors of 11β-HSD[50,51] and were used as reference compounds in the present work. Both are nonselective inhibitors actually favoring 11β-HSD2 over 11β-HSD1[52] (see Table 2. Recently, arylsulfonamidothiazoles were reported to be selective inhibitors of 11β-HSD1.[53] High-capacity screening of 300 000 in-house compounds identified the nonsteroidal CGP013289 (**5**) as a hit (IC_{50} = 9.7 μM)[54] and provided a starting point for structural optimization.

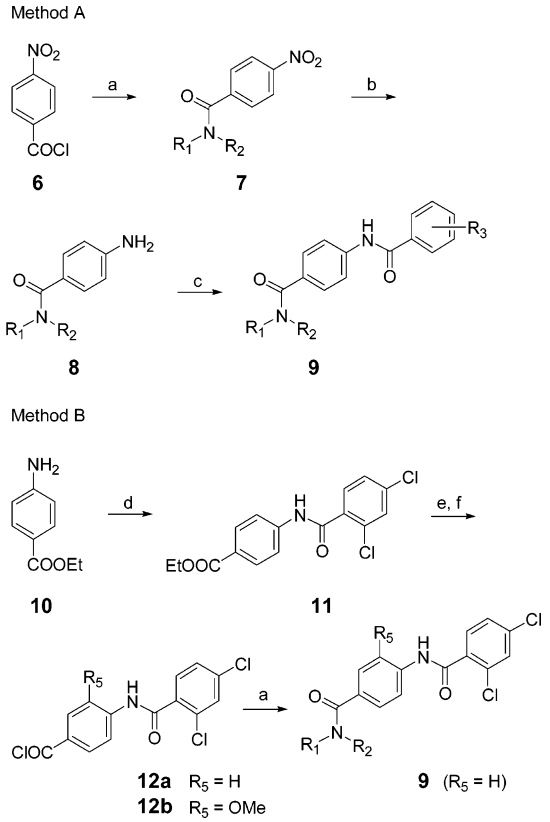
Chemistry

The initial compounds **9** listed in Table 1 were synthesized via key intermediates **8** and **12** as outlined in Scheme 1. Two approaches were employed. The first method constructs the product by initially forming the tertiary amide bond then the benzamide linkage. This is accomplished by acylation of an appropriate amine (e.g., piperidine) with 4-nitrobenzoyl chloride followed by catalytic reduction of the nitro group to the corresponding aniline **8**. Reaction with a benzoyl chloride furnishes the product. The second method reverses the bond-forming steps. Ethyl 4-aminobenzoate (**10**) was acylated with 2,4-dichlorobenzoyl chloride to provide amide **11**. Base hydrolysis of the ester followed by treatment with oxalyl chloride furnished the acid chloride **12** in high yield. Reaction of **12** with a variety of amines gave the desired product **9**. Both of these methods are amenable to multiparallel solution-phase synthesis using scavenger resins to sequester HCl and excess reagents or intermediates.

Derivatives of **9** based on noncommercially available secondary amines were prepared according to Scheme 2 but similar to Method A. Acylation of *exo*-2-aminonorbornane (**13**) with 4-nitrobenzoyl chloride gave the amide **14** in good yield. Methylation of the nitrogen with methyl iodide and sodium hydride yielded tertiary amide **15** in high yield. Catalytic reduction of the nitro group followed by acylation with 2,4-dichlorobenzoyl chloride proceeded smoothly to give analogue **9k**. Likewise, *trans*-2-methylcyclohexylamine was converted to **9l** using an analogous series of steps.

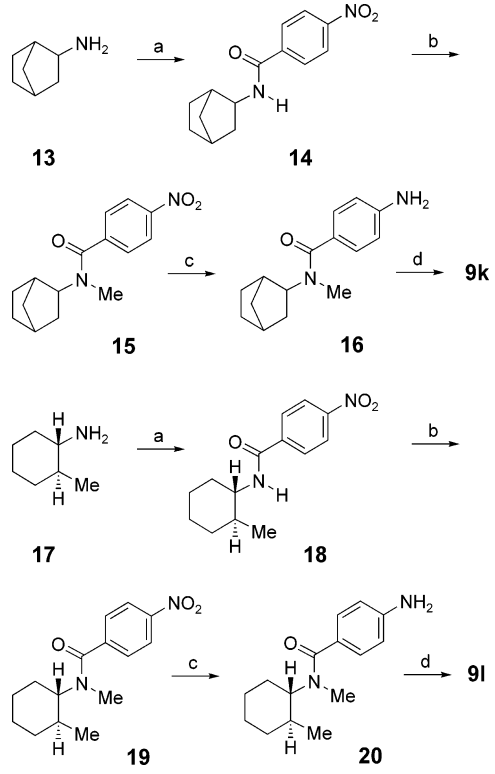
Compounds **24**−**55** listed in Table 2 are based on *trans*-decahydroquinoline and the synthesis of these derivatives is outlined in Scheme 3. Commercially

Scheme 1[a]



[a] Reagents: (a) R_1NHR_2, *i*-Pr_2NEt; (b) H_2, Pd/C; (c) $R_3PhCOCl$, base; (d) 2,4-dichlorobenzoyl chloride, *i*-Pr_2NEt; (e) NaOH; (f) $(COCl)_2$, DMF (cat.).

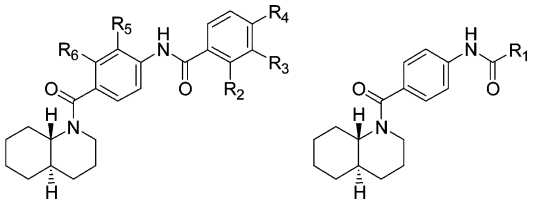
Scheme 2[a]



[a] Reagents: (a) 4-nitrobenzoyl chloride, Et_3N; (b) NaH, MeI; (c) H_2 (40 psi), 10% Pd/C; (d) 2,4-dichlorobenzoyl chloride, Et_3N.

available *trans*-decahydroquinoline (containing 5−15% cis isomer) was acylated with 4-nitrobenzoyl chloride

Table 2. Decahydroquinoline Analogues: Benzene Ring Modifications. In Vitro Data



no.	R_2	R_3	R_4	R_5	R_6	11β-HSD1 IC_{50} (μM)	11β-HSD2 % inhib at 10 μM
24	H	H	H	H	H	0.60	0
25	H	H	F	H	H	0.56	2
26	H	H	Cl	H	H	1.09	0
27	H	H	OMe	H	H	0.41	0
28	H	H	Me	H	H	0.49	23
29	H	H	CN	H	H	0.58	0
30	H	H	COOH	H	H	0.53	4
31	H	H	SO_2Me	H	H	0.50	9
32	H	H	SO_2NH_2	H	H	0.39	0
33	H	H	SO_2NPr_2	H	H	0.16	33
34	H	F	H	H	H	0.58	70
35	F	H	H	H	H	0.55	47
36	OMe	H	H	H	H	0.15	51
37	Cl	H	H	H	H	1.59	8
38	F	H	F	H	H	0.48	2
39	Me	H	Cl	H	H	0.52	13
40	OMe	H	Cl	H	H	0.36	71
41	Cl	H	Cl	Me	H	0.79	60
42	Cl	H	Cl	OMe	H	0.28	6
43	Cl	H	Cl	NH_2	H	0.59	62
44	Cl	H	Cl	NHAc	H	1.14	33
45	Cl	H	Cl	(N)[a]	H	0.32	12
46	Cl	H	Cl	H	Cl	0.10	37
47	Cl	H	Cl	H	OMe	0.12	81
48	Cl	H	Cl	H	OPr	0.12	17
49	Cl	H	Cl	CH=CH−CH=CH		0.10	22

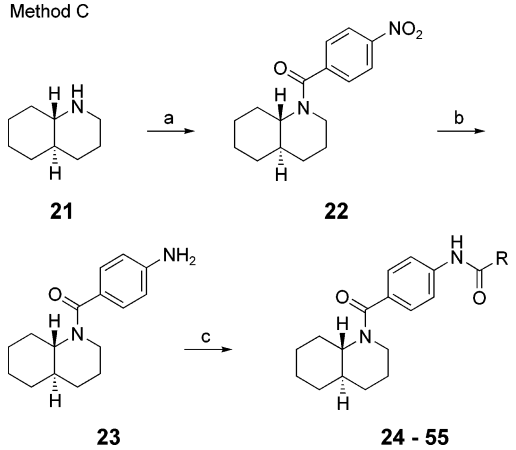
	R_1		
50	4-pyridyl	0.43	34
51	2-furyl	0.44	30
52	1- methyl-2-pyrrolyl	0.32	26
53	cyclohexyl	2.21	58
54	isopropyl	2.7	47
55	1-adamantyl	1.45	7
3		0.011	0.006[b]
4		0.110	0.010[b]

[a] Central ring is derived from 2-aminopyridine-5-carboxylic acid. [b] IC_{50} (μM) (in-house data).

to give **22**. Separation of the cis and trans isomers was possible at this stage either by multiple crystallizations from ether/hexane (51% yield of the trans isomer) or alternatively, by multiple flash chromatographies using 60:40 hexane/ethyl acetate (82% yield of the trans isomer). Reduction of the nitro group furnished **23**, then acylation with various acid chlorides or condensation with acids under peptide-coupling conditions provided the desired products. This method was also amenable to multiparallel solution-phase synthesis.

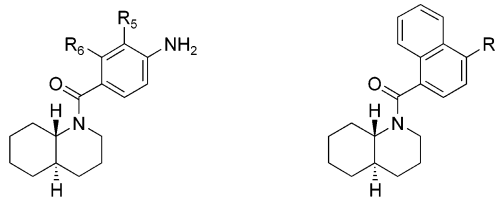
Substitution on the central aromatic ring required the preparation of intermediates **56**−**60** and **62**. Acylation of **21** with 3-methyl-4-nitrobenzoyl chloride furnished the corresponding nitrobenzamide in 48% yield. Reduction of the nitro group yielded the 4-aminobenzamide **56** in quantitative yield. Compound **57** was prepared in good yield by direct coupling of **21** with 4-amino-3-nitrobenzoic acid in the presence of HOBt/EDCI. Similarly, **58** was synthesized by the coupling of **21** with 2-chloro-4-nitrobenzoic acid followed by the reduction

Scheme 3[a]



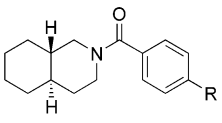
[a] Reagents: (a) 4-nitrobenzoyl chloride, *i*-Pr_2NEt; (b) H_2, Pd/C; (c) RCOCl, *i*-Pr_2NEt or RCOOH, EDCl, HOBt.

of the nitro group to the desired aniline. Conversion of commercially available 2-methoxy-4-nitrobenzoic acid to its corresponding acid chloride was accomplished with oxalyl chloride in the presence of a catalytic amount of DMF. Subsequent reaction with **21** gave the intermediate nitrobenzamide which was catalytically reduced to **59** in moderate yield. The 2-propoxy intermediate **60** was prepared in four steps from 2-hydroxy-4-nitrobenzoic acid. Treatment of the starting material with sodium hydride followed by allyl bromide produced the 2-allyloxy-4-nitrobenzoic acid allyl ester. Hydrolysis of the ester with sodium hydroxide and subsequent reaction with oxalyl chloride gave the acid chloride in good yield. Direct reaction with **21** furnished the 2-allyloxy-4-nitrobenzamide which was reduced under catalytic conditions to give the desired intermediate.

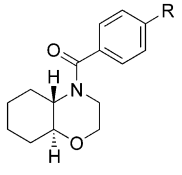


56 R_5 = Me R_6 = H
57 R_5 = NO_2 R_6 = H
58 R_5 = H R_6 = Cl
59 R_5 = H R_6 = OMe
60 R_5 = H R_6 = OPr

61 R = NO_2
62 R = NH_2



63 R = NO_2
64 R = NH_2

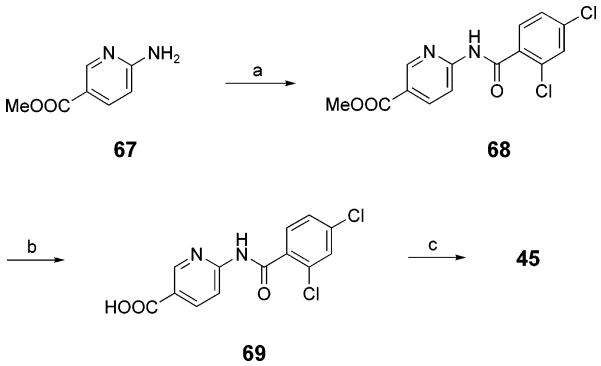


65 R = NO_2
66 R = NH_2

Synthesis of the pyridine analogue **45** is outlined in Scheme 4. Acylation of 6-aminonicotinic acid methyl ester (**67**) with 2,4-dichlorobenzoyl chloride gave amide **68**. Hydrolysis of the ester with 4 N sodium hydroxide gave the acid **69** which was directly coupled with **21** in the presence of EDCI/DMAP to give the desired product in low yield.

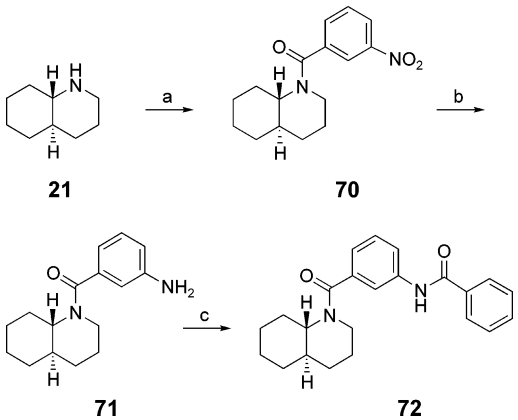
Replacement of the *trans*-decahydroquinoline heterocycle with the isomeric *trans*-decahydroisoquinoline was

Scheme 4[a]



[a] Reagents: (a) 2,4-dichlorobenzoyl chloride, Et_3N; (b) NaOH; (c) *trans*-decahydroquinoline, EDCl, DMAP.

Scheme 5[a]



[a] Reagents: (a) 3-nitrobenzoyl chloride, Et_3N; (b) H_2, Pd/C; benzoyl chloride, PS-DIEA resin.

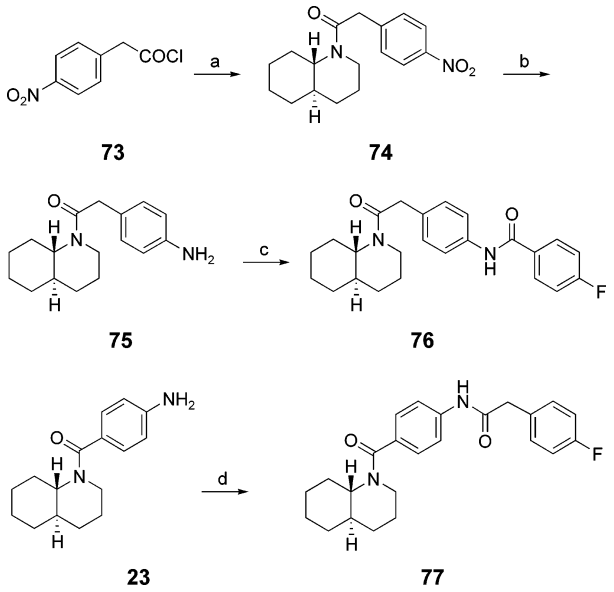
easily accomplished by acylation of the commercially available *trans*-decahydroisoquinoline with 4-nitrobenzoyl chloride to furnish **63** followed by reduction of the nitro group to the anilino intermediate **64**. Synthesis of the oxazino intermediate **66** required the preparation of the corresponding *trans*-decahydro-1,4-benzoxazine. This was readily accomplished by epoxide ring opening of cyclohexene oxide with ethanolamine followed by dehydrative cyclization with 70% sulfuric acid.[55] Analogous reaction with 4-nitrobenzoyl chloride followed by reduction of the nitro group furnished **66**.

The isomeric *meta* analogue of **24**, compound **72**, was prepared from **21** and 3-nitrobenzoyl chloride as shown in Scheme 5. The amide **71** was acylated with benzoyl chloride following Method C using PS-DIEA and PS-trisamine resins as capturing agents for excess reagents and byproducts.

Homologated analogues of **25**, compounds **76** and **77**, were synthesized as outlined in Scheme 6. Treatment of **21** with 4-nitrophenylacetyl chloride provided **74** in modest yield. Reduction of the nitro group followed by acylation of the anilino nitrogen with 4-fluorobenzoyl chloride afforded the phenylacetamide **76**. Condensation of **23** with 4-fluorophenylacetyl chloride directly furnished amide **77**.

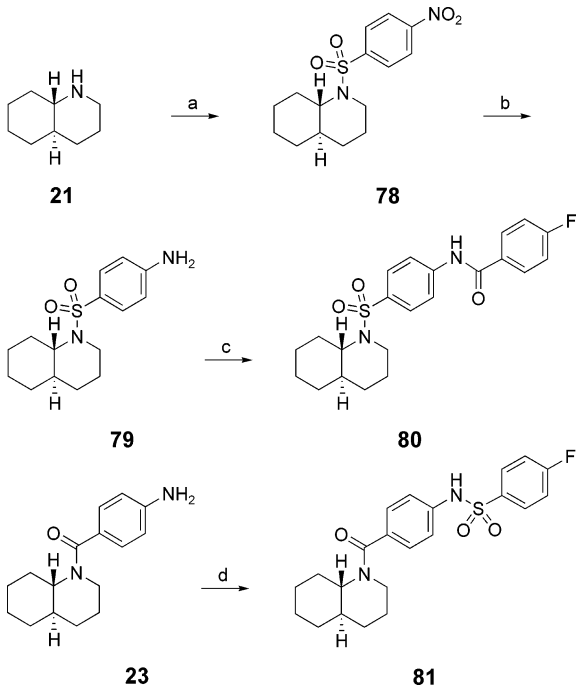
Replacement of each of the amide carbonyl groups with sulfonyl groups was accomplished according to the route shown in Scheme 7. Reaction of **21** with 4-nitrobenzenesulfonyl chloride furnished sulfonamide **78** in moderate yield. Reduction of the nitro group and acyl-

Scheme 6[a]



[a] Reagents: (a) *trans*-decahydroquinoline, Et_3N; (b) H_2, Pd/C; (c) 4-fluorobenzoyl chloride, *i*-Pr_2NEt; (d) 4-fluorophenylacetyl chloride, *i*-Pr_2NEt.

Scheme 7[a]

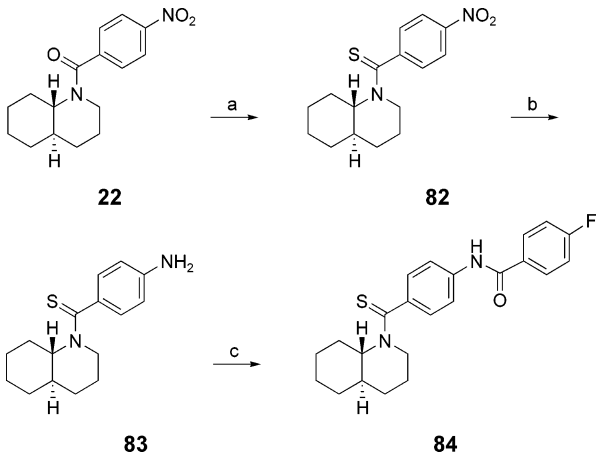


[a] Reagents: (a) 4-nitrobenzenesulfonyl chloride, Et_3N; (b) H_2, PtO_2; (c) 4-fluorobenzoyl chloride, PS-DIEA resin; (d) 4-fluorobenzenesulfonyl chloride, Et_3N.

ation of the amine with 4-fluorobenzoyl chloride gave the desired product **80**. Conversely, the secondary sulfonamide **81** was obtained from **23** by condensation with 4-fluorobenzenesulfonyl chloride in the presence of triethylamine. Replacement of the tertiary amide carbonyl group by a thiocarbonyl was accomplished by treating **22** with Lawesson's reagent in toluene (Scheme 8) to give thioamide **82**. Reduction of the nitro group followed by acylation of the amine with 4-fluorobenzoyl chloride gave the desired **84**.

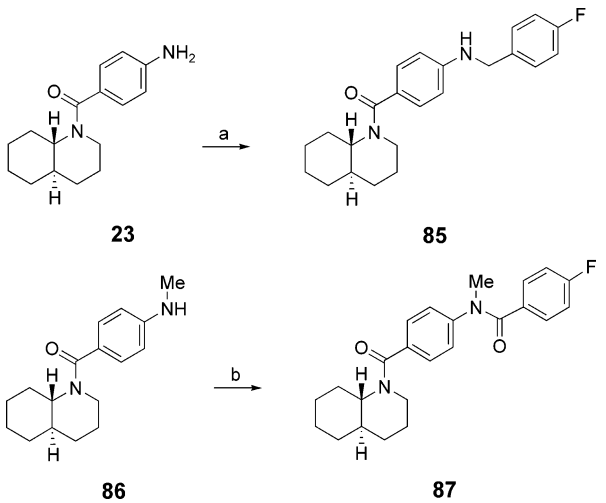
The reduced version of **25**, compound **85**, was easily prepared as shown in Scheme 9 by reductive amination

Scheme 8[a]



[a] Reagents: (a) Lawesson's Reagent; (b) H_2, Pd/C; (c) *i*-Pr2NEt, 4-fluorobenzoyl chloride.

Scheme 9[a]



[a] Reagents: (a) *i.* 4-fluorobenzaldehyde, *p*-TsOH, *ii.* $NaBH_4$; (b) 4-fluorobenzoyl chloride, *i*-Pr_2NEt.

of **23** with 4-fluorobenzaldehyde. The *N*-methyl analogue **87** was prepared by coupling 4-methylaminobenzoic acid with **21** in the presence of EDCI/HOBt to give **86** followed by reaction with 4-fluorobenzoyl chloride.

A series of compounds where the secondary amide carbonyl and nitrogen atom are reversed are shown in Table 4. These terephthalate derivatives **92**−**100** were synthesized according to the route outlined in Scheme 10. Acylation of **21** with 4-carbomethoxymethylbenzoyl chloride provided ester **89** in good yield. Hydrolysis of the ester function with 1 N NaOH afforded the corresponding benzoic acid **90**. This intermediate was either converted to acid chloride **91** with thionyl chloride and reacted with an appropriate amine to produce the amide or was coupled directly with an amine using EDCI/HOBt.

Results and Discussion

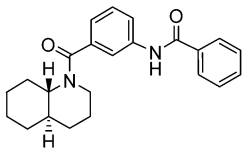
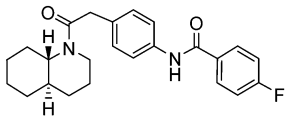
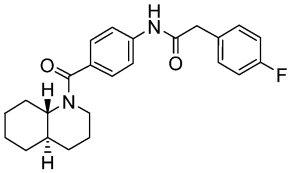
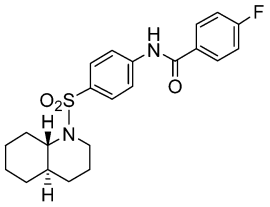
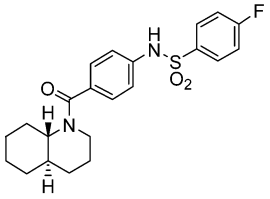
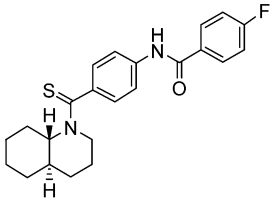
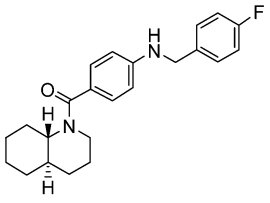
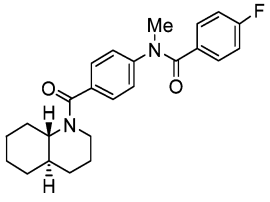
The 4-aminobenzamide derivative **5** was identified (IC_{50} = 9.7 μM, pig 11β-HSD1; 128 μM, human 11β-HSD1)[54] as a potentially interesting target during high-capacity screening of 300,000 in-house compounds. The results of initial modifications of this structure are shown in Table 1. Removal of the aromatic hydroxy group from compound **5** (**9a**) nearly doubled its biological activity. Simultaneous investigation of the benzamide substituents and tertiary amide further increased 11β-HSD1 inhibition to low micromolar values. A 2,4-dichlorobenzamide group in conjunction with a methyl group at the 2 position of the piperidine ring (i.e., **9d**) improved activity to less than 10 μM. Increasing the length of the alkyl group (i.e., ethyl, **9e**) further improved activity to 1 μM. *N*,*N*-Disubstituted amides are tolerated. For example, replacement of the piperidine ring with an N-cyclohexyl-*N*-methylamide (**9g**) retained activity. However, changing the cyclohexyl to aryl (**9h**) or changing methyl to a larger alkyl group (cyclohexyl, **9i**) resulted in considerable loss of activity. Addition of a methyl group to the cyclohexane ring of **9g** trans to the amide nitrogen (**9l**) nearly doubled the 11β-HSD1 activity. This observation, in conjunction with the fact that the 2-alkylpiperidine derivatives such as **9e** are favorable, suggested that combining the two rings in a trans fashion might further enhance activity. In fact, the *trans*-decahydroquinoline analogue **9m** gained a factor of 4−5 over either **9e** or **9l**. The corresponding decahydroisoquinoline analogue **9o** lost 3 to 4-fold activity relative to **9m** and was not as selective against 11β-HSD2. Incorporation of an oxygen into the hetero ring (i.e., **9n**) resulted in nearly complete loss of activity.

At this point it was decided that any further SAR would be performed on derivatives possessing the *trans*-decahydroquinoline heterocycle. Furthermore, we defined criteria for moving compounds along the developmental pathway. Those analogues with IC_{50} values less than 1 μM were screened for 11β-HSD2 inhibition.[56] Compounds which showed less than 50% inhibition at 10 μM were further screened in primary rat hepatocytes to ascertain relative cell permeability. Only those compounds which produced greater than 50% inhibition of cellular 11β-HSD1 at 1 μM were tested in vivo in the adrenalectomized (ADX) mouse to determine liver corticosterone concentrations relative to untreated controls.

Modifications were continued around the new core structure **24** and the results are listed in Tables 2 and 3. We initially investigated substituent effects on the secondary benzamide phenyl ring. Within a series of 4-substituted derivatives (**25**−**33**) it was found that nearly all inhibited 11β-HSD1 equally, with IC_{50}'s of approximately 0.5 μM, independent of the electronic nature of the substituent. In fact, there was little difference between the 4-substituted analogues and the unsubstituted derivative **24**. In general, these compounds showed selectivities of >20 against 11β-HSD2. The most active compound in the series was **33** which was marginally more active than **9m** with respect to 11β-HSD1 and had a selectivity of >60 against 11β-HSD2. One of the most selective analogues (compound **25**) was tested at a higher concentration of 11β-HSD2. At 50 μM it showed an inhibition of 24% which is a factor of >90 relative to 11β-HSD1. This concentration is bordering on the limit of solubility of the compound in the testing medium.

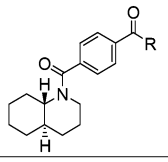
It appears that the position of the substituents on the phenyl ring does not have a dramatic effect on activity. For example, the *ortho*-, *meta*-, and *para*-fluoro analogues (**35**, **34**, and **25**) are equipotent. Both 4-chloro

Table 3. In Vitro Data of Other Decahydroquinoline Analogues[a]

No.	Structure	11β-HSD1 IC_{50} (μM)	11β-HSD2 (% Inh. at 10 μM)
72		0.014	12
76		NA	
77		0.38	79
80		3.86	
81		0.06	8
84		NA	
85		0.05	64
87		0.05	17

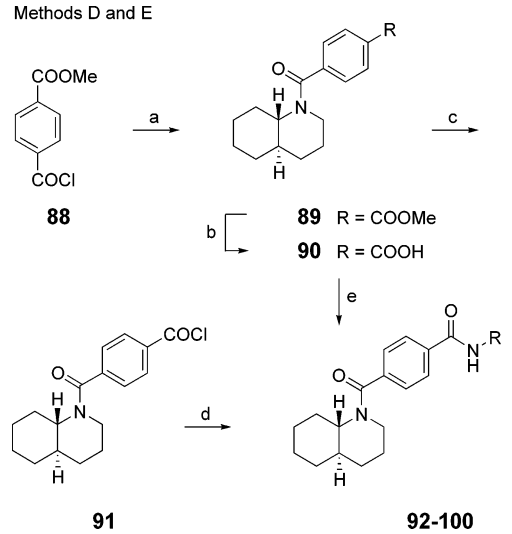
[a] NA = not active.

Table 4. In Vitro Data of Terephthalate Analogues



No.	R	11β-HSD1 IC_{50} (μM)	11β-HSD2 % Inh. at 10 μM
92	$HN(CH_2)_5CH_3$	2.21	23
93	HN-cyclohexyl	6.02	54
94	HN-isopropyl	3.19	15
95	$HNCH_2CH(CH_3)_2$	2.66	28
96	$HNCH_2Ph$	2.66	46
97		0.99	12
98		1.29	33
99		3.59	47
100		0.18	66

Scheme 10[a]



[a] Reagents: (a) *trans*-decahydroquinoline, *i*-Pr_2NEt; (b) NaOH; (c) $SOCl_2$; (d) $R-NH_2$, EDCl, HOBt.

and 2-chloro analogues **26** and **37** have IC_{50}'s greater than 1 μM for 11β-HSD1, however, the combined 2,4-dichloro derivative **9m** increased inhibition by a factor of 5 relative to either compound. The corresponding 2,4-difluoro analogue **38** was about half as active as **9m**. Since the *ortho*-methoxy derivative **36** increased 11β-HSD1 inhibition by an order of magnitude over the corresponding chloro analogue **37**, the 4-chloro-2-methoxy analogue **40** was prepared. Unfortunately this combination did not result in enhanced activity. Additionally, selectivity against 11β-HSD2 dropped dramatically. Replacing the phenyl ring with heterocycles (i.e., **50**, **51**, **52**) retained 11β-HSD1 activity relative to **24**, although, 11β-HSD2 selectivity decreased slightly.

Table 5. Cellular and Animal Data

no.	primary rat hepatocytes (% inhib at 1 μM)	ADX mouse liver corticosterone concentration (%)[b]
9e	55	NA[c]
9g	61	NA
9m	81	−70
24	84	−57
25	86	−73
26	81	−69
29	79	−18
30	23	
31	75	−34
32	57	NA
33	76	−37
39	82	−50
42	74	nd[d]
45	68	−20
46	50	−15
48	17	
49	59	−73
52	100	−67
54	79	NA
55	74	−21
72	19	
81	47	
87	45	
92	74	−23
94	34	
95	42	
96	70	−22
97	57	−47
98	79	NA
99	1	
4	66[a]	−98

[a] 2.5 μM (IC_{50} = 2 μM). [b] Dosed at 50 mg/kg. [c] NA = not active. [d] nd = not determined.

Replacing the phenyl ring with alkyl groups (i.e., **53**, **54**, **55**) resulted in consistent loss of 11β-HSD1 activity. Therefore, an aromatic ring at the secondary benzamide location seems to be important for high potency.

Substitution on the central phenyl ring (compounds **41**−**49**) produced mixed results. Those compounds with functional groups on the carbon adjacent to the amide nitrogen (**41**−**44**) were generally less active than **9m**. Only the methoxy derivative **42** retained similar potency compared to **9m** and exhibited a selectivity of >36 against 11β-HSD2. Substitution at the carbon adjacent to the amide carbonyl (**46**−**48**) produced consistent 11β-HSD1 inhibitions roughly twice that of **9m**. Comparison of methoxy-substituted analogues **42** and **47** revealed that even though **47** was twice as active as **42**, it was significantly less 11β-HSD2-selective than **42**. Replacing methoxy with *n*-propoxy (**48**) retained 11β-HSD1 activity and increased 11β-HSD2 selectivity to >80. The naphthalene derivative **49** was as potent as the chloro analogue **46** and both exhibited selectivities of >100 over 11β-HSD2.

Moving the secondary benzamide from the 4- to the 3-position (**72**) resulted in a dramatic increase in activity (IC_{50} = 14 nM), nearly 50 times the potency of **24** and with a selectivity of >700 over 11β-HSD2 (Table 3). Unfortunately, **72** did not inhibit cellular 11β-HSD1 enough (see Table 5) to warrant further investigation.

The tertiary benzamide portion of the molecule is sensitive to structural changes. Insertion of a methylene between the carbonyl and phenyl ring (compound **76**) to form a homologated version of **25** resulted in complete loss of activity. Replacing the amide carbonyl with

sulfonyl (**80**) loses nearly an order of magnitude potency relative to **25**. Conversion of the amide to thioamide (**84**) also resulted in complete loss of activity.

The secondary amide is not as sensitive to structural manipulations. Insertion of a methylene between the amide carbonyl and phenyl ring (compound **77**) resulted in a slight increase in 11β-HSD1 activity relative to **25**, however, 11β-HSD2 selectivity dropped considerably. Replacing the amide carbonyl with sulfonyl (**81**) increased 11β-HSD1 inhibition by an order of magnitude relative to **25** and with a selectivity of >166 over 11β-HSD2. Removal of the amide carbonyl oxygen (**85**) or *N*-methylation of the amide nitrogen (**87**) also increased activity by a factor of 10 relative to **25**, however, **85** was less selective against 11β-HSD2. The only deleterious change associated with the secondary amide is the transposition of the amide nitrogen and carbonyl to form a terephthalate (compounds **92**−**100**) and the results are listed in Table 4. The data indicate that, with the exception of isoquinoline amide **100**, all of the compounds were less active than their 4-aminobenzamide counterparts (i.e., **93** vs **53**, **94** vs **54**, and **98** vs **25**). Although compound **100**, which can be considered a conformationally restricted analogue of **96**, exhibited a potency enhancement of 15 over the N-benzylamide **96**, it did not meet the 11β-HSD2 selectivity requirement.

Of the 64 synthetic analogues discussed in this paper 30 compounds were screened further for cellular 11β-HSD1 inhibition (Table 5) and of these 30 compounds, 22 met the criteria for in vivo testing in the ADX mouse model.

It is well-known that the adrenal gland is the main source of circulating glucorticoids and, under normal circumstances, most of the glucocorticoid concentration within various tissues and organs is also adrenal-derived. Glucocorticoid, a class of steroid hormones, performs an important role in regulating many metabolic and homeostatic processes. It stimulates transcription of the hepatic gluconeogenic enzyme and plays a major role in the enhancement of liver glucose output.[57] Increased gluconeogenesis is a major source of increased glucose production in type 2 diabetes.[58]

To isolate and ascertain the relative contribution of liver 11β-HSD1 to liver glucocorticoid concentration, ADX mice were used to avoid the confounding influence of adrenal-derived steroids which, under the stress of sacrifice, usually increase above normal levels by several-fold. ADX mice were studied 10 days after adrenalectomy. It was found that in ADX mice circulating corticosterone was reduced to only 3% of the values measured in animals with intact adrenals. There was also a concomitant reduction in corticosterone concentration in the liver to 19% of normal values. The low levels of plasma and tissue corticosterone in the ADX mice are considered to be produced by 11β-HSD1 in liver, lung and adipose stores. These low levels are not caused by imperfectly removed adrenals because the absence of adrenal remnants was ascertained after sacrifice in all the ADX animals. Furthermore, adrenal remnants in rodents have a very high rate of cell proliferation, rapidly leading to abnormally elevated plasma steroid levels (the basis for the experimental model called "Adrenal regeneration hypertension"). Therefore, there are advantages in using ADX animals for these studies because even if very low glucocorticoid levels are present, these levels represent a uniformly low background between animals (not as those produced by the stress of sacrifice in normal animals) thus allowing the accurate determination of small changes in glucocorticoid production. Also, it has been suggested that it is possible that the availability of very disparate amounts of substrate within the tissue (as those present in stressed animals with intact adrenals) may impart large variations in the activity of the enzyme. In ADX animals, despite the reduction in liver corticosterone, 11β-HSD1 activity was unchanged compared to normal animals. Although liver corticosterone levels were significantly reduced, enough remained to be useful in determining the 11β-HSD1 inhibitory activity of test compounds. In the ADX mouse model, the known 11β-HSD inhibitor carbenoxolone (**4**) reduced the liver corticosterone level by about 98% relative to untreated controls. Carbenoxolone was administered orally at 50 mg/kg.

Conclusion

Optimization of the 11β-HSD1 screening hit **5** has led to a series of perhydroquinolylbenzamides. In general, substitution on the benzamide phenyl did not adversely affect potency, whereas, substitution on the central phenyl ring produced mixed results. Alkylation on nitrogen, removal of the amide carbonyl or replacing the benzamide with benzenesulfonamide is tolerated. The best 11β-HSD1 inhibitors of the series (IC_{50}'s between 0.6 and 0.014 μM) are about 200−9000 times more potent than initial compound **5**. The majority of these compounds show selectivity of >20 to >700-fold over 11β-HSD2. Thirty of these compounds were screened in a cellular 11β-HSD1 assay and 22 analogues which showed >50% inhibition at 1 μM were tested in vivo in the ADX mouse model. A maximal response of >70% decrease in liver corticosterone levels was observed for three compounds; **9m**, **25** and **49**. These compounds can serve as useful tools to study the effects of 11β-HSD1 inhibition in animal models of diabetes, dyslipidemia and obesity.

Experimental Section

Human 11β-HSD1 Assay. Recombinant human 11β-HSD1 is expressed in yeast *Pichia pastoris* as reported by Hult.[34] Cultures are grown at 30 °C for 3 days in the presence of methanol to induce enzyme expression. The microsomal fraction overexpressing 11β-HSD1 is prepared from the cell homogenate and used as the enzyme source for primary screening. A test compound at the desired concentration is preincubated for 10 min at room temperature with 3 μg of the microsomal protein in 50 mM sodium phosphate, pH 7.5, in a total volume of 80 μL. The enzyme reaction is initiated by adding 20 μL of a mixture containing 5 mM NADPH, 500 nM cortisone, and 80 000 dpm of [^{3}H]cortisone in the same buffer and is terminated by ethyl acetate after incubation for 90 min at 37 °C. The production of [^{3}H]cortisol is quantitated upon separation from [^{3}H]cortisone by a C_{18} column on HPLC equipped with a radioactivity detector. Glycerrhetinic acid, a known inhibitor of 11β-HSD1, is used as a standard.

Human 11β-HSD2 Assay. The SW-620 human colon carcinoma cell line is obtained from the American Type Culture Collection (ATCC). Cells are plated at a density of 8−10 × 10^4 cells/cm^2 in DMEM/F12 containing 5% BCS, 100 U/mL penicillin, 100 μg/mL streptomycin and 0.25 μg/L amphotericin B. Cultures are grown to 80−90% confluence in

a humidified atmosphere of 5% CO_2 at 37 °C. The medium is changed to serum-free, phenol red-free DMEM/F12 twenty 4 h before harvesting the cells.

After 24 h, in serum-free medium, cultured SW-620 cells are rinsed and scraped in Kreb's-Ringer buffer, pH 7.4, containing 1 mM EDTA, 2 μg/mL aprotinin, 10 μM leupeptin and 1 μM pepstatin. After sonication (30 s) and low speed centrifugation (2000 rpm, 5 min) to remove cellular debris, the supernatant is collected and used to determine enzyme activity and protein concentration (BCA, Pierce, Rockford, IL).

Dehydrogenase activity is quantified by measuring the conversion of radiolabeled cortisol to cortisone using lysates of SW-620 cells as the enzyme source. The assay is performed in tubes containing Kreb's-Ringer buffer pH 7.4, with 0.20 mM NAD and 200 000 dpm of [^{3}H]cortisol and a test compound in a total volume of 1 mL. The tubes are preincubated for 10 min at 37 °C before adding 200 μg of cell lysates to start the reaction. After incubation for 1 h at 37 °C in a shaking water bath, the mixture is extracted with 2 volumes of ethyl acetate and centrifuged for 10 min at 2000 rpm. The organic layer is collected, dried under vacuum and resuspended in methanol. The dissolved residues are quantitatively transferred to thin layer plates and developed in chloroform−methanol (90:10). Unlabeled cortisol and cortisone were used as reference markers. The TLC plates are scanned on a Bioscan radioimaging detector (Bioscan, Washington, DC), and the fractional conversion of cortisol to cortisone is calculated. Enzyme activity is expressed as pmoles of product formed per mg protein per hour. Carbenoxolone and glycyrrhetinic acid are used as standards.

Cellular Primary Rat Hepatocyte 11β-HSD1 Assay. Male Sprague−Dawley rats weighing 180−200 g are anesthetized with sodium pentobarbital (65 mg/kg). The liver is perfused in situ with calcium-free Earl's Balanced Salt Solution (EBSS) followed by EBSS containing 100−150 U/mL of collagenase, 1.8 mM $CaCl_2$ and 10 mM HEPES, pH 7.4. The perfused liver is removed and aseptically placed in warm William's Medium E containing 10% BCS. After decapsulation, the organ is transferred to fresh medium and gently shaken to facilitate tissue dissociation and cell release. Hepatocytes are separated from nonparenchymal and dead cells by repeated low speed centrifugation. Cell viability is determined by trypan blue exclusion.

Hepatocytes are plated on collagen coated dishes at a density of 1×10^5 cells/cm^2 in William's medium E containing 10% BCS, 100 U/mL penicillin, 100 μg/mL streptomycin, 0.25 μg/mL amphotericin B, 2 mM L-glutamine, 10 mM HEPES, 100 nM insulin and 1 nM dexamethasone. After 1 h the medium is changed to serum-free William's medium E supplemented as described above. Thereafter, the medium is replaced every 24 h. The cultures are maintained in a humidified atmosphere of 5% CO_2 at 37 °C.

Enzyme activity is measured in the medium of primary cultures of rat hepatocytes 48 h after plating the cells. The medium is aspirated and replaced with serum-free William's medium E containing 2 nM [^{3}H]11-dehydrocorticosterone and a test compound and is incubated for 2 h. An aliquot of culture medium is removed at the end of the incubation and the mixture is extracted with 2 volumes of ethyl acetate, dried under vacuum and resuspended in methanol. The dissolved residues are quantitatively transferred to thin layer plates and developed in chloroform-methanol (90:10). The TLC plates are scanned on a Bioscan imaging detector and the fractional conversion of 11-dehydrocorticosterone to corticosterone is calculated. The cell layer is rinsed with cold phosphate-buffered saline and dissolved in 0.1 N NaOH/5% SDS for the determination of cellular protein (BCA, Pierce, Rockford, IL). Enzyme activity is expressed as pmoles of product formed per mg protein per hour.

Inhibition of Corticosterone Production in Adrenalectomized (ADX) Mice. Bilateral adrenalectomy was performed in male mice of the CD1 strain (6 to 8 weeks of age, 25−30 g body weight) through a lumbar laparotomy. After 10 days the animals were fasted for 24 h. Compounds were administered orally at 25 mg/kg each at 4 and 2 h before sacrifice (total dose: 50 mg/kg). A second group of animals received carbenoxolone administered in the same fashion (two 25 mg/kg doses at 4 and 2 h before sacrifice), and a third group received the vehicle (cornstarch). Homogenized liver samples were used to measure corticosterone concentration which was determined by radioimmunoassay and is expressed as pg of corticosterone per mg of liver protein. The coefficient of variance for the inhibition of corticosterone production by carbenoxolone was 22% (83 ± 18% inhibition [SDM]; $n = 28$).

Chemistry. All melting points (mp) were obtained on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Bruker AC 300-MHz spectrometer. Chemical shifts in ppm (δ) are reported relative to TMS. Mass spectra were run on a Finnigan Mat 4600 spectrometer. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. and are within 0.4% of theoretical values unless otherwise indicated. Thin-layer chromatography (TLC) was carried out on Macherey-Nagel Polygram Sil G/U_{254} plates. Column chromatography purifications were performed on a Biotage Flash 40 apparatus or employing standard flash chromatography techniques[59] using Merck silica gel (230−400 mesh) in glass columns. Reagents and solvents were purchased from common suppliers and were utilized as received. All reactions were conducted under a nitrogen or argon atmosphere. Yields stated are of purified product and were not optimized.

Preparation of Aminobenzamides 9. Method A. To a solution of 1 mmol of the appropriate amine and 1.5 mmol of triethylamine in 2 mL of methylene chloride was added dropwise a solution of 1.1 mmol of 4-nitrobenzoyl chloride. The mixture was stirred at room temperature for 18 h then was washed with 2 N HCl followed by 10% $NaHCO_3$. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The product was purified by crystallization or flash chromatography to give **7**.

A solution of **7** in 10 mL of ethanol was hydrogenated over 10% Pd/C for 3−5 h. The catalyst was filtered through Celite and the solvent removed under reduced pressure to furnish the desired product **8**. This generally was used without further purification.

To a solution of 1 mmol of **8** and 1.5 mmol of triethylamine or diisopropylethylamine in 10 mL of methylene chloride was added dropwise a solution of 1 mmol of the appropriately substituted benzoyl chloride in 5 mL methylene chloride. The solution was stirred at room temperature for 4−18 h then was washed with 2 N HCl followed by 10% $NaHCO_3$. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The product was purified by crystallization or flash chromatography to give **9**.

Method A (Multiparallel Synthesis Using Autochem). Automated parallel solution-phase synthesis/HPLC purification was performed according to the method described by Tommasi.[60] Stock solutions (0.5 M) of **8** (R_1, R_2 = piperidine[61] and $R_1 = CH_2C_6H_{11}$, R_2 = Me), **58**, **59** or **60** in DMF, *N*-methylmorpholine (1.0 M in THF) and the appropriate acid chloride (1.0 M in THF) were used and the ratio of reactants was 1:1.5:1.5 equivalents. The chemistry was performed directly on the HPLC setup and the reaction mixtures were quenched and purified automatically after the preprogrammed reaction time had elapsed (typically 18 h). The product from each reaction was collected as a single component in one easily traceable fraction using dual wavelength UV detection at 210 and 254 nm. The molecular weight of each compound was confirmed by API-MS. Using this method, the following compounds were obtained; **9a**, MS (ES^+) *m/z* 399 $(M + 1)^+$; **9b**, MS (ES^+) *m/z* 327 $(M + 1)^+$; **9c**, MS (ES^+) *m/z* 377 $(M + 1)^+$; **9j**, MS (ES^+) *m/z* 419 $(M + 1)^+$; **46**, (ES^+) *m/z* 465 $(M + 1)^+$; **47**, (ES^+) *m/z* 461 $(M + 1)^+$; **48**, (ES^+) *m/z* 489 $(M + 1)^+$.

4-(2,4-Dichlorobenzoylamino)benzoic Acid Ethyl Ester (11). To a solution of 2.5 g (15.1 mmol) of ethyl 4-aminobenzoate (**10**) and 1.97 g (15.1 mmol) of diisopropylethylamine in 75 mL of methylene chloride was added dropwise a solution

of 3.17 g (15.1 mmol) of 2,4-dichlorobenzoyl chloride in 5 mL of methylene chloride. The mixture was stirred at room temperature for 16 h then was washed successively with 50 mL portions of H_2O, 1 N HCl, H_2O and saturated NaCl solution. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The resulting solid was triturated with ether to give 4.09 g (80%) of **11**; mp = 133−134 °C; IR (KBr), ν (cm^{-1}): 3349, 1710; ^1H NMR (DMSO-d_6): δ 10.90 (s, 1H), 7.97 (d, J = 8.46 Hz, 2H), 7.88−7.77 (m, 3H), 7.67 (d, J = 8.09 Hz, 1H), 7.61−7.55 (m, 1H), 4.30 (q, 2H), 1.32 (t, 3H); MS (ES^-) *m/z* 336 $(M - 1)^-$. Anal. ($C_{16}H_{13}Cl_2NO_3$) C, H, N.

4-(2,4-Dichlorobenzoylamino)benzoic Acid. To a suspension of 4.9 g (14.5 mmol) of **11** in 200 mL of H_2O/EtOH (1:1) was added 15 mL of 1 N NaOH. The mixture was refluxed for 1 h then the solvent was removed until precipitation occurred. Water was added and the resulting solution was washed with ether and the aqueous phase acidified with 1 N HCl. The resulting precipitate was filtered, washed with H_2O and dried to give 3.6 g (97%) of product as a white solid; mp = 274−275 °C; IR (KBr), ν (cm^{-1}): 1665, 1592, 769; ^1H NMR (DMSO-d_6): δ 12.80 (s, 1H), 10.87 (s, 1H), 7.94 (d, J = 8.67 Hz, 2H), 7.86−7.78 (m, 3H), 7.67 (d, J = 8.29 Hz, 1H), 7.62−7.55 (m, 1H); MS (ES^-) *m/z* 308 $(M - 1)^-$. Anal. ($C_{14}H_9NO_3Cl_2$) C, H, N.

4-(2,4-Dichlorobenzoylamino)benzoyl Chloride (12a). A mixture of 250 mg (0.81 mmol) of the above acid, 407 mg (3.2 mmol) of oxalyl chloride and 2 drops of DMF in 5 mL of methylene chloride was stirred at room temperature for 90 min. The solvent was removed under reduced pressure. Methylene chloride was added and the solvent was removed under reduced pressure (3x) to give 260 mg (97%) of **12a** as a white solid, mp = 95−99 °C; IR (KBr), ν (cm^{-1}): 3230, 3095, 1770, 1743, 1672; ^1H NMR ($CDCl_3$): δ 8.49 (s, broad, 1H), 8.13 (d, J = 8.82 Hz, 2H), 7.82 (d, J = 8.82, 2H), 7.71 (d, J = 8.45 Hz, 1H), 7.48 (m, 1H), 7.43−7.34 (m, 1H); Anal. ($C_{14}H_8NO_2Cl_3$) C, H, N.

4-(2,4-Dichlorobenzoylamino)-3-methoxybenzoyl Chloride (12b). To a solution of 270 mg (1.49 mmol) of 4-amino-3-methoxybenzoic acid methyl ester and 386 mg (2.99 mmol) of diisopropylethylamine in 10 mL of methylene chloride was added 312 mg (1.49 mmol) of 2,4,-dichlorobenzoyl chloride. The mixture was stirred at room temperature for 18 h then was washed with 1 N HCl followed by 8% $NaHCO_3$ solution. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to give 385 mg (72%) of 4-(2,4-dichlorobenzoylamino)-3-methoxybenzoic acid methyl ester. This ester was dissolved in 30 mL of THF/H_2O (2:1) and 91 mg of LiOH was added. The mixture was stirred at room temperature for 18 h then was poured into EtOAc. The mixture was acidified with 1 N HCl and any insoluble material was filtered. The organic phase was dried over sodium sulfate and the solvent evaporated to give 295 mg (81%) of 4-(2,4-dichlorobenzoylamino)-3-methoxybenzoic acid. A mixture of the benzoic acid and 441 mg of oxalyl chloride and one drop of DMF in 10 mL of methylene chloride was stirred at room temperature for 18 h. The solvent was removed under reduced pressure then methylene chloride was added and the solvent was removed again. This process was repeated three times to give 311 mg (100%) of **12b**. This material was used directly in subsequent steps.

Method B (Multiparallel Synthesis). On an argonaut Quest 210 apparatus, each tube was charged with 0.5 mmol of the appropriate amine (R_1NHR_2), 200 mg of PS-DIEA resin (3.75 mmol/g) and 10 mL of methylene chloride. To this was added 182 mg (0.55 mmol) of **12a**. After agitation for 18 h, 100 mg of PS-Trisamine resin (3.75 mmol/g) was added and agitation was continued for an additional 3 h. The tubes were drained and the resin was washed with methylene chloride. The solvent was removed to afford the desired product. The following compounds were prepared by this method: **9d**, MS (ES^+) *m/z* 391 $(M + 1)^+$; **9e**, MS (ES^+) *m/z* 405 $(M + 1)^+$; **9f**, MS (ES^+) *m/z* 405 $(M + 1)^+$; **9g**, MS (ES^+) *m/z* 405 $(M + 1)^+$; **9h**, MS (ES^+) *m/z* 399 $(M + 1)^+$; **9i**, MS (ES^+) *m/z* 473 $(M + 1)^+$.

Method B (Preparative). The following procedure is an illustrative example of using Method B for the preparation of **2,4-Dichloro-*N*-[4-((4a*R**,8a*S**)-octahydroquinoline-1-carbonyl)phenyl]benzamide (9m).** To a solution of 1.39 g (10 mmol) of *trans*-decahydroquinoline and 1.2 g (9 mmol) of diisopropylethylamine in 45 mL of methylene chloride was added dropwise a solution of 3.0 g (9 mmol) of **12a** in 10 mL of methylene chloride. After stirring the mixture at room temperature for 18 h, it was washed with H_2O and the organic phase was dried over sodium sulfate. The solvent was removed under reduced pressure and the residual solid was crystallized from EtOH to give 2.73 g (69%) of **9m**, mp = 213−214 °C; IR (KBr), ν (cm^{-1}): 1740, 1707; ^1H NMR (DMSO-d_6): δ 10.69 (s, 1H), 7.79 (d, 1H, J = 1.8 Hz), 7.73 (d, 2H, J = 8.4 Hz), 7.65 (d, 1H, J = 8.4 Hz), 7.57 (m, 1H), 7.36 (d, 2H, J = 8.40 Hz), 3.34 (m, 3H), 2.10 (m, 1H), 1.77−0.98 (m, 12H); MS (ES^+) *m/z* 431 $(M + 1)^+$; Anal. ($C_{23}H_{24}N_2O_2Cl_2$) C, H, N.

***N*-Bicyclo[2.2.1]hept-2-yl-4-nitrobenzamide (14).** To a solution of 1.0 g (9 mmol) of *exo*-norbornylamine and 1.4 g (14 mmol) of triethylamine in 20 mL of methylene chloride was added dropwise a solution of 1.7 g (9.2 mmol) of 4-nitrobenzoyl chloride in 5 mL methylene chloride. The mixture was stirred at room temperature for 18 h then was washed with 2 N HCl followed by 10% $NaHCO_3$. The organic phase was dried over sodium sulfate and the solvent was concentrated to approximately one-fourth volume at which point crystallization occurred. Some MTBE was added and the solid was filtered to give 1.55 gm (66%) of **14**, mp = 163−165 °C; ^1H NMR ($CDCl_3$): δ 8.27 (d, J = 8.8, 2H), 7.89 (d, J = 8.8 Hz, 2H), 6.00 (m, broad, 1H), 3.94 (m, 1H), 2.36 (s, 2H), 1.98−1.88 (m, 1H), 1.66−1.45 (m, 2H), 1.44−1.14 (m, 5H); Anal. ($C_{14}H_{16}N_2O_3$) C, H, N.

***N*-Bicyclo[2.2.1]hept-2-yl-*N*-methyl-4-nitrobenzamide (15).** To a solution of 1.5 g (5.8 mmol) of **14** in 25 mL of DMF was added 0.22 g (5.8 mmol) of sodium hydride (60% in mineral oil). The mixture was stirred at room temperature for 90 min. To the resulting orange solution was added 1.3 g (9.2 mmol) of methyl iodide. The mixture was stirred at room temperature for 18 h then an additional 100 mg of sodium hydride and 400 mg of methyl iodide were added. After stirring the mixture for 24 h the solvent was removed under reduced pressure. Water was added and the mixture was extracted with methylene chloride. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The resulting oil was passed through a plug of silica gel using 2% MeOH/methylene chloride to elute the product, 1.5 g (95%) of **15** as an oil; MS (ES^+) *m/z* 275 $(M + 1)^+$. This material was used directly in the next step.

4-Amino-*N*-bicyclo[2.2.1]hept-2-yl-*N*-methylbenzamide (16). A solution of 1.5 g (5.5 mmol) of **15** in 50 mL of ethanol was hydrogenated over 150 mg of 10% Pd/C at 40 psi for 3 h. The catalyst was filtered through Celite and the solvent was evaporated. The residue was filtered through a pad of silica gel using 2% MeOH/methylene chloride to elute the product, 1.3 g (99%) of **16** as an off-white solid, mp = 178−181 °C; IR (CH_2Cl_2), ν (cm^{-1}): 3682, 3596, 1610; ^1H NMR ($CDCl_3$): δ 8.27 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 2.98 (s, broad, 3H), 2.33 (d, broad, J = 12.5 Hz, 2H), 1.74−0.77 (m, 11H); MS (ES^+) *m/z* 245 $(M + 1)^+$; Anal. ($C_{15}H_{20}N_2O$?0.4 H_2O) C, H, N.

***N*-((1S*,2S*)-2-Methyl-cyclohexyl)-4-nitrobenzamide (18).** To a solution of 2.26 g (20 mmol) of 2-methylcyclohexylamine and 2.2 g (22 mmol) of triethylamine in 70 mL of methylene chloride was added dropwise a solution of 3.72 g (20 mmol) of 4-nitrobenzoyl chloride in 5 mL methylene chloride. The mixture was stirred at room temperature for 4 h then the solvent was removed under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The residual solid was crystallized from methylene chloride/MTBE

to give 2.4 g (46%) of **18**, mp = 172−174 °C; ^{1}H NMR ($CDCl_3$): δ 8.28 (d, J = 9 Hz, 2H), 7.91 (d, J = 9.2 Hz, 2H), 5.91 (d, broad, J = 8.8 Hz, 1H), 3.80−3.65 (m, 1H), 2.13−2.02 (m, 1H), 1.86−1.68 (m, 3H), 1.39 (m, 2H), 1.29−1.13 (m, 3H), 1.00 (d, J = 6.5 Hz, 3H); Anal. ($C_{14}H_{18}N_2O_3$) C, H, N.

***N*-Methyl-*N*-((1*S**,2*S**)-2-methyl-cyclohexyl)-4-nitrobenzamide (19).** To a solution of 1.7 g (6.5 mmol) of **18** in 25 mL of DMF was added 0.25 g (6.6 mmol) of sodium hydride (60% in mineral oil). The mixture was stirred at room temperature for 90 min. To the resulting orange solution was added 1.2 g (8.4 mmol) of methyl iodide. The mixture was stirred at room temperature for 18 h then an additional 100 mg of sodium hydride and 500 mg of methyl iodide were added. After stirring the mixture for 24 h the solvent was removed under reduced pressure. Water was added and the mixture was extracted with methylene chloride. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The resulting oil was passed through a plug of silica gel using 2% MeOH/methylene chloride to elute the product, 1.7 g (95%) of **19** as an oil which solidifies to a waxy solid on standing, mp = 75−79 °C; ^{1}H NMR ($CDCl_3$): δ 8.27 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 0.75H), 7.49 (d, J = 8.8 Hz, 1.25 H), 2.97 (s, 2H), 2.96−2.86 (m, 1H), 2.74 (s, 1H), 1.90−1.44 (m, 7H), 1.30−1.00 (m, 2H), 0.96 (d, J = 6.6 Hz, 1H), 0.80 (d, J = 6.6 Hz, 2H); MS (ES$^+$) *m/z* 277 (M + 1)$^+$; Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

4-Amino-*N*-methyl-*N*-((1*S,2*S**)-2-methylcyclohexyl)-benzamide (20).** A solution of 1.6 g (5.8 mmol) of **19** in 40 mL of ethanol was hydrogenated over 160 mg of 10% Pd/C at 50 psi for 18 h. The catalyst was filtered through Celite and the solvent evaporated to give 1.2 g (85%) of **20**, mp = 151−153 °C; MS (ES$^+$) *m/z* 247 (M + 1)$^+$. The material was used directly in the next step.

Preparation of 4-Aminobenzamide Derivatives 24−55 (Method C). (4-Nitrophenyl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (22).** To a solution of 10.0 g (71.8 mmol) of *trans*-decahydroquinoline (**21**) and 18.6 g (144 mmol) of diisopropylethylamine in 150 mL of methylene chloride cooled in an ice bath was added dropwise a solution of 13.33 g (71.8 mmol) of 4-nitrobenzoyl chloride in 25 mL of methylene chloride. The mixture was stirred at room temperature for 18 h then was washed twice with 1 N HCl. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was crystallized three times from ether/hexane and once from ether to give 10.47 g (51%) of **22**; mp = 84−87 °C; ^{1}H NMR ($CDCl_3$): δ 8.26 (d, 2H, J = 7 Hz), 7.55 (d, 2H, J = 7 Hz), 3.55−3.45 (m, 1H), 3.43−3.24 (m, 2H), 2.27 (m, 1H), 1.87−1.04 (m, 12H); MS (ES$^+$) *m/z* 289 (M + 1)$^+$; Anal. ($C_{16}H_{20}N_2O_3$) C, H, N.

4-Aminophenyl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (23).** A mixture of 2.0 g of **22** and 200 mg of 10% Pd/C in 100 mL ethanol was hydrogenated at 1 atm for 18 h. The catalyst was filtered through Celite and the filtrate was evaporated to give 1.8 g (100%) of **23**. This material was used directly in subsequent steps.

Method C (Multiparallel Synthesis). On an argonaut Quest 210 apparatus, each tube was charged with 0.25 mmol of **23**, 100 mg of PS-DIEA resin (3.75 mmol/g) and 4 mL of methylene chloride. To this was added 0.28 mmol of the appropriate acid chloride. After agitation for 18 h, 75 mg of PS-Trisamine resin (3.75 mmol/g) was added and agitation was continued for an additional 3 h. The tubes were drained and the resin was washed with methylene chloride. The solvent was removed to afford the desired product. The following compounds were prepared by this method: **24**, mp = 216−219 °C; MS (ES$^+$) *m/z* 363 (M + 1)$^+$; **26**, mp = 269−270 °C; MS (ES$^+$) *m/z* 397 (M + 1)$^+$; **36**, MS (ES$^+$) *m/z* 393 (M + 1)$^+$; **72** (from **71**), MS (ES$^+$) *m/z* 363 (M + 1)$^+$.

Method C (Preparative, General Procedure). To a solution of 1 mmol of **23** and 1.5 mmol of diisopropylethylamine in 10 mL of methylene chloride was added dropwise a solution of 1 mmol of the appropriate acid chloride in 5 mL of methylene chloride. After stirring the mixture at room temperature for 18 h, it was washed sequentially with 1 N HCl, 8% aqueous $NaHCO_3$ and saturated NaCl. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified either by crystallization or flash chromatography.

***N*-[4-((4a*R**,8a*S**)-Octahydroquinoline-1-carbonyl)phenyl]-4-sulfamoylbenzamide (32).** To a solution of 100 mg (0.39 mmol) of **23** and 78 mg (0.39 mmol) of 4-sulfamoylbenzoic acid and 75 mg (0.39 mmol) of EDCI in 10 mL of DMF was added 58 mg 0.43 mmol) of HOBt. The mixture was stirred at 50 °C for 18 h. After cooling the mixture to room temperature, EtOAc was added then the mixture was washed with 1 N HCl and 8% $NaHCO_3$ solution. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The residual solid was crystallized from EtOH to give 65 mg (38%) of **32**, mp = >250 °C; ^{1}H NMR (DMSO-d_6): δ 10.57 (s, 1H), 8.11 (d, J = 8.46 Hz, 2H), 7.97 (d, J = 8.45 Hz, 2H), 7.83 Hz (d, J = 8.83 Hz, 2H), 7.54 (s, 2H), 7.37 (d, J = 8.45 Hz, 2H), 3.49−3.25 (m, 3H), 2.15−2.04 (m, 1H), 1.78−0.96 (m, 12H); MS (ES$^+$) *m/z* 442 (M + 1)$^+$; Anal. ($C_{23}H_{27}N_3O_4S$) C, H, N.

2-Fluoro-*N*-[4-((4a*R,8a*S**)-octahydroquinoline-1-carbonyl)phenyl]benzamide (35).** Prepared in 99% yield from **23** and 2-fluorobenzoyl chloride according to Method A (step c), mp = 198−204 °C; ^{1}H NMR ($CDCl_3$): δ 8.57 (d, J = 15.44 Hz, 1H), 8.17 (t, 1H), 7.70 (d, J = 8.46 Hz, 2H), 7.60−7.50 (m, 1H), 7.43 (d, J = 8.46 Hz, 1H), 7.37−7.14 (m, 3H), 3.58−3.30 (m, 3H), 2.37−2.19 (m, 1H), 1.86−1.01 (m, 12H); MS (ES$^+$) *m/z* 381 (M + 1)$^+$; Anal. ($C_{23}H_{25}N_2O_2F$) C, H, N.

2-Chloro-*N*-[4-((4a*R,8a*S**)-octahydroquinoline-1-carbonyl)phenyl]benzamide (37).** Prepared in 42% yield from **23** and 2-chlorobenzoyl chloride according to Method A (step c), mp = 204−205 °C; ^{1}H NMR ($CDCl_3$): δ 8.02 (s, broad, 1H), 7.81−7.75 (m, 1H), 7.65 (d, J = 8.66 Hz, 2H), 7.50−7.36 (m, 5H), 3.56−3.29 (m, 3H), 2.32−2.23 (m, 1H), 1.86−1.02 (m, 12H); MS (ES$^+$) *m/z* 397 (M + 1)$^+$; Anal. ($C_{23}H_{25}N_2O_2Cl$) C, H, N.

2,4-Difluoro-*N*-[4-((4a*R,8a*S**)-octahydroquinoline-1-carbonyl)phenyl]benzamide (38).** Prepared in 79% yield from **23** and 2,4-difluorobenzoyl chloride according to Method A (step c), mp = 226−228 °C; IR (KBr), ν (cm^{-1}): 3448, 3308, 3190, 3119, 1677, 1603; ^{1}H NMR (DMSO-d_6): δ 10.57 (s, 1H), 7.82−7.71 (m, 2H), 7.74 (d, J = 8.45 Hz, 1H), 7.49−7.39 (m, 1H), 7.35 (d, J = 8.46 Hz, 2H), 7.29−7.21 (m, 1H), 3.45−3.25 (m, 3H), 2.14−2.04 (m, 1H), 1.77−0.96 (m, 12H); MS (ES$^+$) *m/z* 399 (M + 1)$^+$; Anal. ($C_{23}H_{24}N_2O_2F_2$) C, H, N.

4-Chloro-2-methyl-*N*-[4-((4a*R,8a*S**)-octahydroquinoline-1-carbonyl)phenyl]benzamide (39).** Prepared in 64% yield from **23** and 4-chloro-2-methylbenzoyl chloride according to Method A (step c), mp = 204−207 °C; IR (KBr), ν (cm^{-1}): 3433, 3308, 1675, 1596; ^{1}H NMR ($CDCl_3$): δ 8.02 (s, 1H), 7.56 (d, J = 8.09 Hz, 2H), 7.44 (d, J = 8.09 Hz, 1H), 7.34 (d, J = 8.09 Hz, 2H), 7.26−7.21 (m, 2H), 3.51−3.30 (m, 3H), 2.49 (s, 3H), 2.27−2.18 (m, 1H), 1.83−1.53 (m, 6H), 1.47−1.00 (m, 6H); MS (ES$^+$) *m/z* 411 (M + 1)$^+$; Anal. ($C_{24}H_{27}N_2O_2Cl$) C, H, N.

4-Chloro-2-methoxy-*N*-[4-((4a*R,8a*S**)-octahydroquinoline-1-carbonyl)phenyl]benzamide (40).** Prepared in 67% yield from **23** and 4-chloro-2-methoxybenzoyl chloride according to Method A (step c), mp = 145−153 °C; ^{1}H NMR ($CDCl_3$): δ 9.72 (s, 1H), 8.22 (d, J = 8.45 Hz, 1H), 7.67 (d, J = 8.46 Hz, 2H), 7.42 (d, J = 8.46 Hz, 2H), 7.13 (dd, J = 8.46 and 1.84 Hz, 1H), 7.04 (m, 1H), 4.08 (s, 3H), 3.57−3.33 (m, 3H), 2.35−2.24 (m, 1H), 1.87−1.56 (m, 6H), 1.52−1.04 (m, 6H); MS (ES$^+$) *m/z* 427 (M + 1)$^+$; Anal. ($C_{24}H_{27}N_2O_3Cl$) C, H, N.

***N*-[2-Amino-4-((4a*R**,8a*S**)-octahydroquinoline-1-carbonyl)phenyl]-2,4-dichlorobenzamide (43).** To a solution of 6.06 g (20 mmol) of **57** and 700 mg (5.7 mmol) of DMAP in 70 mL of pyridine was added 4.5 g (21 mmol) of 2,4-dichlorobenzoyl chloride. The mixture was stirred at 85 °C for 16 h then the pyridine was removed under reduced pressure. The resulting solid was washed with H_2O and dried. This was purified by flash chromatography (CH_2Cl_2 as eluent) and the product crystallized from ether/hexane to give 5.0 g (52%) of 2,4-dichloro-*N*-[2-nitro-4-((4a*R**,8a*S**)-octahydroquinoline-1-carbonyl)phenyl]benzamide as a pale-yellow solid, mp = 165−

167 °C; ^{1}H NMR ($CDCl_3$): δ 10.95 (s, 1H), 8.96 (d, J = 8.82 Hz, 1H), 8.33 (d, J = 1.84 Hz, 1H), 7.76 (dd, J = 8.45 and 1.83 Hz, 1H), 7.69 (d, J = 8.09 Hz, 1H), 7.53 (d, J = 1.84 Hz, 1H), 7.41 (dd, J = 8.46 and 1.84 Hz, 1H), 3.55−3.33 (m, 3H), 2.32−2.23 (m, 1H), 1.88−1.59 (m, 7H), 1.53−1.02 (m, 5H).

A solution of 2.4 g (5 mmol) of the above material in 150 mL of MeOH/CH_2Cl_2 (1:1) was hydrogenated at 50 psi over 700 mg of sulfided 5% Pt/C for 3.25 h. The catalyst was filtered through Celite and the solvent was removed under reduced pressure. The residual foam was crystallized from ether to give 1.94 g (86%) of **43** as an off-white solid, mp = 208−210 °C; ^{1}H NMR ($CDCl_3$): δ 9.56 (s, 1H), 7.67 (d, J = 8.29 Hz, 1H), 7.46 (d, J = 1.51 Hz, 1H), 7.35 (dd, J = 8.29 and 1.88 Hz, 1H), 7.03 (d, J = 8.29 Hz, 1H), 6.66 (s, 1H), 6.58−6.51 (m, 1H), 3.40−3.15 (m, 3H, 2.03−1.92 (m, 1H), 1.82−1.49 (m, 9H), 1.35−0.99 (6H); MS (ES$^+$) m/z 447 (M + 1)$^+$; Anal. ($C_{23}H_{25}N_3O_2Cl_2$) C, H, N.

***N*-[2-Acetylamino-4-((4a*R**,8a*S**)-octahydroquinoline-1-carbonyl)phenyl]-2,4-dichlorobenzamide (44).** To a solution of 178 mg (0.4 mmol) of **43** and 111 mg (1.1 mmol) of triethylamine in 4 mL of CH_2Cl_2 was added 102 mg (1 mmol) of acetic anhydride. After stirring the mixture for 16 h, it was washed with H_2O and the organic phase was dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (2% MeOH/CH_2Cl_2 as eluent). The product was crystallized from ether to give 90 mg (46%) of **44** as an off-white solid, mp = 187−188 °C; ^{1}H NMR ($CDCl_3$): δ 9.96 (s, 1H), 8.53 (s, 1H), 7.63 (d, J = 8.29 Hz, 1H), 7.50−7.45 (m, 2H), 7.37 (dd, J = 8.29 and 1.88 Hz, 1H), 7.27 (d, J = 7.92 Hz, 1H), 6.87 (dd, J = 7.91 and 1.51 Hz, 1H), 3.36−3.17 (m, 3H), 2.17 (s, 3H), 2.05−1.94 (m, 1H), 1.85−1.48 (m, 7H), 1.37−0.97 (m, 5H); Anal. ($C_{25}H_{27}N_3O_3Cl_2$) C, H, N.

2,4-Dichloro-*N*-[5-((4a*R,8a*S**)-octahydroquinoline-1-carbonyl)-pyridin-2-yl]benzamide (45).** To a stirred solution of 1.1 g (3.54 mmol) of **69** in 25 mL of methylene chloride was added 545 mg (3.9 mmol) of **21** followed by 50 mg (0.41 mmol) of DMAP. To this was added 1.2 g (6.28 mmol) of EDCI. After stirring the mixture at room temperature for 18 h, it was poured into H_2O. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed successively with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$ solution, H_2O and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue is triturated with ether to give 230 mg (15%) of **45** as a white solid: mp 202−203 °C; IR (KBr), ν (cm^{-1}): 2925, 1678, 1613, 1587, 1310, 855, 796;^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.38 (s, 2H), 7.86−7.69 (m, 2H), 7.51 (s, 1H), 7.42−7.36 (m, 1H), 3.56−3.36 (m, 3H), 2.33−2.21 (m,1H), 1.94−1.00 (m, 12H); MS (ES$^+$) m/z 432 (M + 1)$^+$; MS (ES$^+$) m/z 489 (M + 1)$^+$; Anal. ($C_{22}H_{23}N_3O_2Cl_2 \cdot 0.25\ H_2O$) C, H, N.

(4-Amino-3-methylphenyl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (56).** To a solution of 3.84 g (27.6 mmol) of *trans*-decahydroquinoline (**21**) and 7.1 g (55 mmol) of diisopropylethylamine in 50 mL of methylene chloride was added dropwise a solution of 5.5 g (27.6 mmol) of 3-methyl-4-nitrobenzoyl chloride in 5 mL of methylene chloride. After stirring at room temperature for 18 h, the mixture was poured into EtOAc. The solution was washed with 1 N HCl (2x) and saturated NaCl solution. The solution was dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was stirred with ether for 18 h and the solid filtered to give 4.0 g (48%) of (3-methyl-4-nitrophenyl)-(4a*R**,8a*S**)-octahydroquinolin-1-yl-methanone, mp = 93−95 °C; IR (KBr), ν (cm^{-1}): 3435, 1633; ^{1}H NMR ($CDCl_3$): δ 7.99 (d, J = 8.46 Hz, 1H), 7.40−7.26 (m, 2H), 3.57−3.23 (m,3H), 2.62 (s, 3H), 2.33−2.22 (m,1H), 1.91−1.00 (m, 12H); Anal. ($C_{17}H_{22}N_2O_3$) C, H, N.

A solution of 500 mg (1.65 mmol) of the above compound in 50 mL of EtOH was hydrogenated over 50 mg of 10% Pd/C at 1 atm for 16 h. The catalyst was removed by vacuum filtration through Celite and the solvent removed under reduced pressure to give 450 mg (100%) of **56**. This was used directly in subsequent reactions.

(4-Amino-3-nitrophenyl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (57).** To a solution of 8.5 g (59.2 mmol) of **21**, 10.8 g (59.2 mmol) of 4-amino-3-nitrobenzoic acid and 8.0 g (59.2 mmol) of HOBt in 100 mL DMF was added 11.4 g (59.2 mmol) of EDCI. After stirring the mixture at room temperature for 18 h, H_2O was added. The resulting solid was filtered, washed with H_2O, dried under reduced pressure and recrystallized from MeOH/CH_2Cl_2 to give 11.7 g (65%) of **57** as yellow crystals, mp = 212−215 °C; ^{1}H NMR (DMSO-d_6) δ 7.97 (s, 1H), 7.69 (s, 2H), 7.43 (dd, J = 8.67, 1.88 Hz, 1H), 7.03 (d, J = 9.04 Hz, 1H), 3.53−3.14 (m, 3H), 2.12−2.01 (m, 1H), 1.78−0.93 (m, 12H); MS (ES$^+$) m/z 304 (M + 1)$^+$; Anal. ($C_{16}H_{21}N_3O_3 \cdot 0.2\ H_2O$) C, H, N.

(4-Amino-2-chlorophenyl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (58).** To a solution of 2.01 g (10 mmol) of 2-chloro-4-nitrobenzoic acid in 20 mL of DMF was added 2.75 mL (25 mmol) of *N*-methylmorpholine and 5.56 g (12 mmol) of TPTU. After stirring the reddish mixture for 15 min, 1.67 g (12 mmol) of **21** was added. The mixture was stirred at room temperature for 18 h then was partitioned between H_2O and EtOAc. The organic phase was washed sequentially with saturated aqueous lithium chloride and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded 1.1 g (34%) of (2-chloro-4-nitrophenyl)-(4a*R**,8a*S**)-octahydroquinolin-1-yl-methanone as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.19−8.16 (m,1H), 8.32−8.27 (m, 1H), 7.54−7.42 (m, 1H), 2.62−3.43 (m, 3H), 1.84−1.15 (m, 13H).

A solution of 844 mg (2.62 mmol) of the above compound in 40 mL of EtOAc/EtOH (1:3) was hydrogenated over 50 mg of 10% Pd/C at 1 atm for 16 h. The catalyst was removed by vacuum filtration through Celite and the residue was purified by flash chromatography (60% EtOAc/hexane) to afford 700 mg (92%) of **58** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.70−6.93 (m, 1H), 6.56−6.52 (m, 1H), 6.69−6.62 (m, 1H), 3.84 (s, broad, 2H), 3.54−3.15 (m, 3H), 1.81−1.04 (m, 13H).

(4-Amino-2-methoxyphenyl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (59).** To a solution of 2.22 g (11.26 mmol) of 2-methoxy-4-nitrobenzoic acid and 0.5 mL of DMF in 25 mL of methylene chloride was added dropwise 1.47 mL (16.9 mmol) of oxalyl chloride. The mixture was stirred at room temperature for 1 h, then 2.48 mL (22.54 mmol) of *N*-methylmorpholine was added followed by a dropwise addition of 2.35 g (16.9 mmol) of **21** in 10 mL of methylene chloride. The mixture was stirred at room temperature for 18 h then was quenched with 1 N HCl. The mixture was extracted with ether and the organic phase was washed sequentially with 1 N NaOH, H_2O and brine. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was flash chromatographed (20% EtOAc/hexane) to give 2.35 g (44%) of (2-Methoxy-4-nitrophenyl)-(4a*R**,8a*S**)-octahydroquinolin-1-yl-methanone: ^{1}H NMR ($CDCl_3$) δ 7.87 (dd, J = 8.29 and 1.88 Hz, 1H), 7.76 (s, 1H), 7.44−7.29 (m, 1H), 3.93 (s, 3H), 3.71−2.86 (m, 3H), 2.53−2.27 (m, 1H), 2.01−0.96 (m, 12H).

A solution of the above material in 75 mL of EtOH/EtOAc (1:1) was hydrogenated over 150 mg of 10% Pd/C at 1 atm for 24 h. The catalyst was filtered through Celite and the filtrate evaporated under reduced pressure to give 2.25 g (100%) of **59** as a foam: ^{1}H NMR (DMSO-d_6) δ 6.74 (s, 1H), 6.19 (s, 1H), 6.12 (dd, J = 7.72 and 1.84 Hz, 1H), 5.31 (s, 2H), 3.66 (s, 3H), 3.50−3.08 (m, 3H), 2.14−1.93 (m, 1H), 1.80−1.43 (m, 7H), 1.38−0.92 (m, 5H).

(4-Amino-2-propoxyphenyl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (60).** To a solution of 1.937 g (10.58 mmol) of 2-hydroxy-4-nitrobenzoic acid in 40 mL of DMF was added 931 mg (23.28 mmol) of sodium hydride. After stirring the mixture at room temperature for 20 min, 2.61 mL (23.28 mmol) of allyl bromide was added and the reaction was strirred at room temperature for 16 h. The reaction was quenched with 1 N HCl and the mixture was extracted with EtOAc. The organic layer was washed sequentially with saturated aqueous lithium chloride and brine, dried over Na_2SO_4, and the solvent

was removed under reduced pressure. Purification by flash chromatography (10% EtOAc/hexane) afforded 1.49 g (76%) of 2-allyloxy-4-nitrobenzoic acid allyl ester as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.80−7.94 (m, 3H), 5.97−6.13 (m, 2H), 5.29−5.57 (m, 4H), 4.83−4.86 (m, 2H), 4.72−4.74 (m, 2H).

A solution of 1.13 g (28.23 mmol) of sodium hydroxide dissolved in 10 mL of H_2O was added to a solution of 1.49 g (5.65 mmol) of the above allyl ester in 40 mL THF. The reaction was stirred at room temperature for 16 h then acidified with 1 N HCl. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford 1.12 g (89%) of 2-allyloxy-4-nitrobenzoic acid as a pale yellow solid. This was used directly in the following step; ^{1}H NMR ($CDCl_3$) δ 8.29−8.33 (m, 1H), 7.84−7.98 (m, 2H), 6.05−6.18 (m, 1H), 5.48−5.61 (m, 2H), 4.89 (d, J = 5.3 Hz, 2H).

Oxalyl chloride (0.65 mL, 7.47 mmol) was added dropwise to a solution of 1.11 g (4.98 mmol) of the above benzoic acid in 40 mL CH_2Cl_2 and 0.5 mL DMF at 0 °C. The reaction was stirred at 0 °C for 1 h then 1.37 mL (12.45 mmol) of *N*-methylmorpholine and 832 mg (5.97 mmol) of *trans*-decahydroquinoline (**21**) were added sequentially. The reaction was warmed to room temperature and stirred for 3 h. The mixture was partitioned between EtOAc and 1 N NaOH. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (25% EtOAc/hexane) to give 1.2 g (76%) of (2-allyloxy-4-nitrophenyl)-(4a*R**,8a*S**)-octahydroquinolin-1-yl-methanone as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.73−7.89 (m, 2H), 7.33−7.42 (m, 1H), 5.96−5.99 (m, 1H), 5.38 (dd, 2H), 4.64 (s, broad, 2H), 3.01−3.58 (m, 2H), 2.42 (br s, 1H), 1.24−1.76 (m, 13H); MS (ES^+) *m/z* 345 $(M + 1)^+$.

A solution of 1.15 g (3.43 mmol) of the above compound in 30 mL of EtOAc/EtOH (1:1) was hydrogenated over 50 mg of 10% Pd/C at 1 atm for 16 h. The catalyst was removed by vacuum filtration through Celite and the residue was purified by flash chromatography (50% EtOAc/hexane) to afford 730 mg (69%) of **60** as a yellow foam: ^{1}H NMR (DMSO-d_6) δ 6.71−6.79 (m, 1H), 6.10−6.17 (m, 2H), 5.31 (s, broad, 2H), 3.80 (t, 2H), 3.20 s, broad, 3H), 1.15−1.72 (m, 15H), 0.95 (t, 3H): MS (ES^+) *m/z* 317 $(M + 1)^+$.

(4-Nitronaphthalen-1-yl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (61).** To a solution of 1.12 g (5.2 mmol) of 4-nitronaphthalene-1-carboxylic acid[64] and 1.45 g (10.4 mmol) of **21** in 40 mL of DMF was added 0.8 g (5.2 mmol) of HOBt followed by 1.5 g (7.8 mmol) of EDCI. Within 5 min a suspension formed. The mixture was stirred at room temperature for 18 h then was poured into H_2O. The mixture was extracted with ether (3 × 120 mL) and the organic solution was washed with H_2O and saturated NaCl. The organic phase was dried over magnesium sulfate and the solvent was removed under reduced pressure and the residue was triturated with hexane to give 1.32 g (75%) of **61** as a solid, mp = 129−135 °C; IR (KBr), ν (cm^{-1}): 3439, 1630; ^{1}H NMR (DMSO-d_6): δ 8.17 (d, J = 8.09 Hz, 1H), 8.10 (d, J = 7.72 Hz, 1H), 7.77−7.62 (m, 3H), 7.48−7.29 (m, 1H), 3.42−2.93 (m, 3H), 2.25−2.16 (m, 1H), 1.85−0.75 (m, 12H); MS (ES^+) *m/z* 339 $(M + 1)^+$; Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

(4-Aminonaphthalen-1-yl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (62).** To a solution of 340 mg (1 mmol) of **61** in 40 mL of EtOH (under nitrogen) was added 1.8 mL of hydrazine hydrate followed by 70 mg of 10% Pd/C. The mixture was refluxed for 30 min then was allowed to cool. The catalyst was filtered from the reaction mixture through Celite and the solvent was removed under reduced pressure. Hexane was added to the residue and was removed under reduced pressure (3x) to give 335 mg (100%) of **62** as an orange foam. This was used directly in subsequent reactions. ^{1}H NMR (DMSO-d_6): δ 8.19 (d, J = 8.09 Hz, 1H), 7.80−7.67 (m 1H), 7.60−7.41 (m, 2H), 7.26−7.11 (m, 1H), 6.72 (d, J = 7.72 Hz, 1H), 6.06 (s, 2H), 3.65−3.09 (m, 3H), 2.39−2.16 (m, 1H), 2.03−0.92 (m, 12H).

(4-Nitrophenyl)-(4a*R,8a*S**)-octahydroisoquinolin-2-yl-methanone (63).** To a solution of 695 mg (5 mmol) of *trans*-decahydroisoquinoline and 750 mg (7.4 mmol) of triethylethylamine in 30 mL of methylene chloride was added dropwise a solution of 930 mg (5 mmol) of 4-nitrobenzoyl chloride in 10 mL of methylene chloride. The mixture was stirred at room temperature for 4 h then was washed with 2 N HCl followed by 10% $NaHCO_3$. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The residual solid was crystallized from CH_2Cl_2/MTBE to give 950 mg (66%) of **63** as a white solid, mp = 137−139 °C; IR (KBr), ν (cm^{-1}): 1631; ^{1}H NMR ($CDCl_3$): δ 8.27 (d, J = 8.82 Hz, 2H), 7.55 (d, J = 8.46 Hz, 2H), 4.79 (d, J = 13.61 Hz, 0.5 H), 4.61 (d, J = 12.50 Hz, 0.5H), 3.58 (d, J = 12.50 Hz, 0.5H), 3.38 (d, J = 13.97 Hz, 0.5H), 3.05 (t, 0.5H), 2.83−2.61 (m, 1H), 2.39 (t, 0.5H), 1.85−0.87 (m, 12H); Anal. ($C_{16}H_{20}N_2O_3$) C, H, N.

(4-Aminophenyl)-(4a*R,8a*S**)-octahydroisoquinolin-2-yl-methanone (64).** A mixture of 940 mg of **63** and 100 mg of 10% Pd/C in 50 mL ethanol was hydrogenated at 50 psi For 18 h. The catalyst was filtered through Celite and the filtrate was evaporated to give 810 mg (96%) of **64** as a gray solid, mp = 143−146 °C; IR (KBr), ν (cm^{-1}): 3459, 3359, 1607; ^{1}H NMR ($CDCl_3$): δ 7.24 (d, J = 8.46 Hz, 2H), 6.65 (d, J = 8.46 Hz, 2H), 4.90−3.93 (m, broad, 1H), 3.85 (s, broad, 3H), 3.03−3.21 (m, 2H), 1.84−0.81 (m, 12H); MS (ES^+) *m/z* 259 $(M + 1)^+$. Anal. ($C_{16}H_{22}N_2O$) C, H, N.

(4-Nitrophenyl)-(4a*S,8a*S**)-octahydrobenzo[1,4]oxazin-4-yl-methanone (65).** To a solution of 700 mg (5 mmol) of (4a*S**,8a*S**)-octahydrobenzo[1,4]oxazine[66] and 600 mg (6 mmol) of triethylamine in 10 mL of methylene chloride was added dropwise a solution of 930 mg (5 mmol) of 4-nitrobenzoyl chloride in 10 mL of methylene chloride. After stirring the mixture at room temperature for 18 h, the solvent was removed under reduced pressure. Ethyl acetate was added to the residue and the mixture was washed with H_2O. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The residual solid was crystallized from MTBE/hexane to give 1.25 g (86%) of **65**, mp = 115−118 °C; ^{1}H NMR ($CDCl_3$): δ 8.27 (d, J = 8.82 Hz, 2H), 7.62 (d, J = 8.83 Hz, 2H), 3.95−3.49 (m, 5H), 3.44−3.33 (m, 1H), 2.47 (d, broad, J = 15.44 Hz, 1H), 2.07−1.96 (m, 1H), 1.86−1.70 (m, 2H), 1.55−1.25 (m, 4H); MS (ES^+) *m/z* 290 $(M + 1)^+$; Anal. ($C_{15}H_{18}N_2O_4$) C, H, N.

(4-Aminophenyl)-(4a*S,8a*S**)-octahydrobenzo[1,4]-oxazin-4-yl-methanone (66).** A mixture of 1.1 g of **65** and 100 mg of 10% Pd/C in 35 mL ethanol was hydrogenated at 50 psi for 4 h. Methylene chloride was added to dissolve some precipitated product then the catalyst was filtered through Celite. The solvent was concentrated until crystallization occurred. On cooling, the solid was filtered and washed with MTBE to give 840 mg (85%) of **66** as a white solid, mp = 196−198 °C; IR (KBr), ν (cm^{-1}): 3434, 3349, 2936, 2863, 1619; ^{1}H NMR ($CDCl_3$): δ 7.34 (d, J = 8.83 Hz, 2H), 6.64 (d, J = 8.46 Hz, 2H), 3.94−3.74 (m, 5H), 3.68−3.56 (m, 1H), 3.54−3.41 (m, 2H), 2.60−2.51 (m, 1H), 2.03−1.94 (m, 1H), 1.82−1.66 (m, 2H), 1.49−1.28 (m, 4H); MS (ES^+) *m/z* 261 $(M + 1)^+$.

6-(2,4-Dichlorobenzoylamino)-nicotinic Acid methyl ester (68). To a stirred solution of 1.0 g (5.31 mmol) of **67**[65] and 1.4 g (13.3 mmol) of triethylamine in 20 mL of methylene chloride at 0 °C was added 1.67 g (7.97 mmol) of 2,4-dichlorobenzoyl chloride. After the mixture was stirred at room temperature for 4 h, 50 mL of ether was added. The solids were filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography using hexane/EtOAc (3:1) to provide1.65 g (96%) of **68**. The material was used directly in the next step; MS (ES^+) *m/z* 325 $(M + 1)^+$.

6-(2,4-Dichlorobenzoylamino)-nicotinic Acid (69). To a solution of 1.2 g (3.68 mmol) of **68** in 6 mL THF/MeOH (2:1) was added 3 mL of 4 N NaOH (12 mmol). After stirring the mixture for 10 h, it was poured into 25 mL of H_2O and the mixture was washed with ether. The aqueous layer was acidified with 6 N HCl and extracted with EtOAc. The organic

phase was dried over $MgSO_4$, and solvent was removed under reduced pressure. The resulting solid is collected and dried under high vaccum to give 81% of **69**; ^{1}H NMR (DMSO-d_6) δ 11.47 (s, 1H), 8.86 (s, 1H), 8.31 (q, 2H), 7.83−7.72 (m, 2H), 7.64 (d, J = 8.29 Hz, 1H), 7.57−7.49 (m, 2H); MS (ES$^+$) *m/z* 311 (M + 1)$^+$.

(3-Nitrophenyl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (70).** To a solution of 1.39 g (10 mmol) of *trans*-decahydroquinoline (**21**) and 1.5 g (15 mmol) of triethylamine in 50 mL of methylene chloride was added dropwise a solution of 1.85 g (10 mmol) of 3-nitrobenzoyl chloride in 20 mL of methylene chloride. The mixture was stirred at room temperature for 18 h then was washed with 2 N HCl followed by 10% $NaHCO_3$. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to give 2.3 g (80%) of **70** as a thick oil; ^{1}H NMR ($CDCl_3$): δ 8.25 (s, 2H), 7.74 (d, J = 7.53 Hz, 1H),7.65−7.57 (m, 1H), 3.57−3.28 (m, 3H), 2.33−2.23 (m, 1H), 1.91−0.86 (m, 12H); MS (ES$^+$) *m/z* 289 (M + 1)$^+$.

(3-Aminophenyl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (71).** A mixture of 0.9 g of **70** and 100 mg of 10% Pd/C in 200 mL ethanol was hydrogenated at 50 psi For 18 h. The catalyst was filtered through Celite and the filtrate was evaporated to give 0.71 g (88%) of **71**. mp = 108−109 °C; MS (ES$^+$) *m/z* 259 (M + 1)$^+$; Anal. ($C_{16}H_{22}N_2O$) C, H, N.

2-(4-Nitrophenyl)-1-(4a*R,8a*S**)-octahydroquinolin-1-yl-ethanone (74).** To a solution of 7.7 g (55 mmol) of of *trans*-decahydroquinoline (**21**) and 8.4 g (83 mmol) of triethylethylamine in 200 mL of methylene chloride was added dropwise a solution of 10.9 g (55 mmol) of 4-nitrophenylacetyl chloride (**73**) in 50 mL of methylene chloride. The mixture was stirred at room temperature for 18 h then was washed with 1 N HCl followed by 10% $NaHCO_3$. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography to give 6.5 g (39%) of **74**; ^{1}H NMR ($CDCl_3$): δ 8.19 (d, J = 8.29 Hz, 2H), 7.43 (d, J = 8.67 Hz, 2H), 3.84−3.73 (m, 1H), 3.78 (d, J = 3.39 Hz, 2H), 3.44−3.13 (m, 2H), 2.18−2.07 (m, 1H), 1.84−0.97 (m, 12H).

2-(4-Aminophenyl)-1-(4a*R,8a*S**)-octahydroquinolin-1-yl-ethanone (75).** A mixture of 6.5 g of **74** and 650 mg of 10% Pd/C in 300 mL ethanol was hydrogenated at 50 psi For 18 h. The catalyst was filtered through Celite and the filtrate was evaporated to give 5.7 g (97%) of **75** as an oil; ^{1}H NMR ($CDCl_3$): δ 7.03 (d, J = 7.92 Hz, 2H), 6.63 (d, J = 8.29 Hz, 2H), 3.68−3.53 (m, 1H), 3.58 (s, 2H), 3.43−3.30 (m, 1H), 3.19−3.02 (m, 1H), 2.20−2.09 (m, 1H), 1.83−0.94 (m, 12H); MS (ES$^+$) *m/z* 273 (M + 1)$^+$.

(4a*R,8a*S**)-1-(4-Nitrobenzenesulfonyl)-decahydroquinoline (78).** To a solution of 1.4 g (10 mmol) of **21** and 1.3 g (13 mmol) of triethylamine in 15 mL of methylene chloride was added dropwise a solution of 2.2 g (10 mmol) of 4-nitrobenzenesulfonyl chloride in 15 mL of methylene chloride. A precipitate initially formed and after stirring the mixture for 18 h a solution resulted. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and H_2O. The organic phase was washed twice with H_2O and was dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was crystallized from MTBE/hexane to give 1.9 g (59%) of **78** as a tan solid; mp = 106−109 °C; ^{1}H NMR ($CDCl_3$): δ 8.34 (d, J = 8.82 Hz, 2H), 7.98 (d, J = 9.19 Hz, 2H), 4.19−4.09 (m, 1H), 2.94−2.84 (m, 1H), 2.69−2.55 (m, 1H), 2.11−2.00 (m, 1H), 1.83−0.88 (m, 12H); Anal. ($C_{15}H_{20}N_2O_4S$) C, H, N, S.

4-[(4a*R,8a*S**)-(Octahydroquinolin-1-yl)sulfonyl]-phenylamine (79).** A mixture of 1.5 g (4.6 mmol) of **78** and 150 mg of PtO_2 in 150 mL of EtOH was hydrogenated at 50 psi for 4 h. The catalyst was filtered through Celite and the filtrate evaporated under reduced pressure to give an oil. This was filtered through a pad of silica gel (CH_2Cl_2 as eluent) to give 1.3 g (96%) of **79** as a glass; MS (ES$^+$) *m/z* 295 (M + 1)$^+$. This material was used directly in the next step.

4-Fluoro-*N*-{4-[(4a*R,8a*S**)-(octahydroquinolin-1-yl)-sulfonyl]-phenyl}-benzamide (80).** Prepared in 55% yield from **79** and 4-fluorobenzoyl chloride according to Method B (multiparallel); product isolated as a foam; IR (KBr), ν (cm^{-1}): 3373, 1682, 1505, 1320, 1150; ^{1}H NMR ($CDCl_3$): δ 7.94 (s, 1H), 7.96−7.88 (m, 2H), 7.78 (s, 4H), 7.20 (t, 2H), 4.14−4.03 (m, 1H), 2.84−2.69 (m, 1H), 2.28−2.17 (m, 1H), 1.81−0.85 (m, 12H); MS (ES$^-$) *m/z* 415 (M−1)$^-$; Anal. ($C_{22}H_{25}N_2O_3SF$) C, H, N, S.

4-Fluoro-*N*-[4-((4a*R,8a*S**)-octahydroquinoline-1-carbonyl)phenyl]benzenesulfonamide (81).** To a solution of 258 mg (1 mmol) of **23** and 150 mg (1.5 mmol) of triethylamine in 15 mL of CH_2Cl_2 was added 210 mg (1.07 mmol) of 4-fluorobenzenesulfonyl chloride. The mixture was stirred at room temperature for 48 h then 100 mg of PS-Trisamine resin was added and stirring was continued for 18 h. The resin was filtered and the organic solution was washed with 2 N HCl. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The residual oil was flash chromatographed using 2% MeOH/CH_2Cl_2 to give 259 mg (62%) of **81** as a gum; ^{1}H NMR ($CDCl_3$): δ 7.84−7.76 (m, 2H), 7.46 (s, 1H), 7.26 (d, J = 8.45 Hz, 2H), 7.14−7.02 (m, 4H), 3.52−3.41 (m, 1H), 3.40−3.31 (m, 2H), 2.27−2.18 (m, 1H), 1.83−1.00 (m, 12H); MS (ES$^+$) *m/z* 417 (M + 1)$^+$.

(4-Nitrophenyl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanethione (82).** A mixture of 200 mg (0.69 mmol) of **22** and 140 mg (0.35 mmol) of Lawesson's reagent in 25 mL of toluene was refluxed for 2.5 h. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride. The solution was washed with 8% aqueous $NaHCO_3$ and was dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue flash chromatographed using hexane/ethyl acetate (75:25) to furnish 200 mg (95%) of **82**; mp = 147−150 °C; ^{1}H NMR ($CDCl_3$): δ 8.26 (d, J = 9.2 Hz, 2H), 7.53−7.23 (m, 2H), 4.47−4.19 (m, 1H), 3.61−3.34 (m, 2H), 2.84−2.57 (m, 1H), 1.94−1.60 (m, 7H), 1.45−1.08 (m, 5H); MS (ES$^+$) *m/z* 305 (M + 1)$^+$; Anal. ($C_{16}H_{20}N_2O_2S$) C, H, N.

(4-Aminophenyl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanethione (83).** A solution of 190 mg (0.62 mmol) of **82** in 100 mL of ethanol was hydrogenated at 50 psi over 50 mg of 10% Pd/C for 24 h. The catalyst was filtered through Celite and the solvent removed under reduced pressure. The residue was filtered through a pad of silica gel using ethyl acetate to elute the product, 135 mg (79%) of **83** as a solid, mp = 197−200 °C; ^{1}H NMR ($CDCl_3$): δ 7.09 (d, J = 8.09 Hz, 2H), 6.61 (d, J = 7.73 Hz, 2H), 4.33 (t, 1H), 4.04−3.91 (m, 1H), 3.76 (s, broad, 2H), 3.43−3.29 (m, 1H), 2.69 (d, broad, J = 11.4 Hz, 1H), 1.91−1.11 (m, 12H); MS (ES$^+$) *m/z* 275 (M + 1)$^+$, 316 (base, MH+MeCN); Anal. ($C_{16}H_{22}N_2S$?0.2 EtOAc) C, H, N.

4-Fluoro-*N*-[4-((4a*R,8a*S**)-octahydroquinoline-1-carbothioyl)phenyl]benzamide (84).** To a mixture of 107 mg (0.39 mmol) of **83** and 100 mg (0.78 mmol) of diisopropylethylamine in 9 mL of methylene chloride was added dropwise a solution of 62 mg (0.39 mmol) of 4-fluorobenzoyl chloride in 1 mL of methylene chloride. The mixture was stirred at room temperature for 18 h then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and was washed with 1 N HCl and saturated sodium chloride solution. The solution was filtered through a pad of silica gel and the solvent was removed under reduced pressure. The residual solid was triturated with ether to give 128 mg (82%) of **84**, mp = 239−243 °C; ^{1}H NMR ($CDCl_3$): δ 10.38 (s, 1H), 8.09−8.00 (m, 2H), 7.76 (d, J = 8.82 Hz, 2H), 7.38 (t, 2H), 7.20 (d, broad, J = 7.72 Hz, 2H), 4.20−4.04 (m, 1H), 3.55−3.27 (m, 3H), 1.92−1.54 (m, 7H), 1.44−1.01 (m, 5H); MS (ES$^+$) *m/z* 397 (M + 1)$^+$; Anal. ($C_{23}H_{25}N_2OFS$) C, H, N.

[4-(4-Fluoro-benzylamino)phenyl]-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (85).** A mixture of 150 mg (0.58 mmol) of **23**, 73 mg (0.59 mmol) of 4-fluorobenzaldehyde and 5 mg of *p*-toluenesulfonic acid in 40 mL of toluene was refluxed under Dean−Stark conditions for 16 h. The solvent was removed under reduced pressure and the residue dissolved in 20 mL of EtOH. To this was added 22 mg (0.58 mmol) of $NaBH_4$ and the mixture was stirred at room temperature for 16 h. Water was added and the mixture was extracted with

EtOAc. The organic phase was washed with brine and was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using CH_2Cl_2/EtOH (99:1) to elute the product, 154 mg (72%) of **85**, mp = 161−164 °C; ^{1}H NMR ($CDCl_3$): δ 7.39−7.22 (m, 5H), 7.02 (t, 2H), 6.57 (d, J = 8.45 Hz, 2H), 4.32 (s, 2H), 3.59−3.34 (m, 3H), 2.30−2.20 (m, 1H), 1.84−0.98 (m, 12H); MS (ES^+) m/z 367 $(M + 1)^+$; Anal. ($C_{23}H_{27}N_2OF$) C, H, N.

(4-Methylamino-phenyl)-(4a*R,8a*S**)-octahydroquinolin-1-yl-methanone (86).** Reaction using **21**, 4-methylaminobenzoic acid, HOBt and EDCI was performed similar to the preparation of **32** to give **86** in 8% yield. ^{1}H NMR ($CDCl_3$): δ 7.30 (d, J = 8.67 Hz, 2H), 6.56 (d, J = 8.67 Hz, 2H), 3.96−3.87 (m, 1H), 3.59−3.38 (m 3H), 2.85 (d, J = 4.90 Hz, 3H), 2.31−2.22 (m, 1H), 1.81−1.00 (m, 12H).

4-Fluoro-*N*-methyl-*N*-[4-((4a*R,8a*S**)-octahydroquinoline-1-carbonyl)phenyl]benzamide (87).** To a solution of 130 mg (0.48 mmol) of **86** and 180 mg (0.96 mmol) of diisopropylethylamine in 5 mL of methylene chloride was added 60 mg (0.048 mmol) of 4-fluorobenzoyl chloride. The mixture was stirred at room temperature for 18 h then was washed with water. The organic phase was dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was flash chromatographed using hexane/EtOAc (3:2) to elute the product, 70 mg (37%) of **87** as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.36−7.24 (m, 4H), 7.04 (d, J = 8.29 Hz, 2H), 6.86 (t, 2H), 3.50 (s, 3H), 3.49−3.38 (m, 1H), 3.36−3.27 (m, 2H), 2.24−2.15 (m, 1H), 1.82−1.02 (m, 12H); MS (ES^+) m/z 395 $(M + 1)^+$.

4-((4a*R,8a*S**)-Octahydroquinoline-1-carbonyl)benzoic Acid Methyl Ester (89).** To a solution of 2.8 g (20 mmol) of **21** and 2.25 g (22 mmol) of triethylamine in 100 mL of methylene chloride was added dropwise a solution of 4.0 g (20 mmol) of 4-carbomethoxybenzoyl chloride (**88**) in 10 mL methylene chloride. After stirring the mixture at room temperature for 18 h, it was washed sequentially with 1 N HCl, 1 N NaOH, and water. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was flash chromatographed using hexane/ethyl acetate (3:2) to elute the product, 4.1 gm (68%) of **89** as a white solid, mp = 109−110 °C; ^{1}H NMR ($CDCl_3$): δ 8.06 (d, 2H, J = 8.4 Hz), 7.45 (d, 2H, J = 8.4 Hz), 3.93 (s, 3H), 3.49 (m, 1H), 3.36−3.30 (m, 2H), 2.28 (m, 1H), 1.87−1.00 (m,12H); Anal. ($C_{18}H_{23}NO_3$) C, H, N.

4-((4a*R,8a*S**)-Octahydroquinoline-1-carbonyl)benzoic Acid (90).** To a solution of 3.0 g (10 mmol) of **89** in 50 mL of methanol was added 30 mL (30 mmol) of 1 N NaOH. After stirring the mixture at room temperature for 18 h, the methanol was removed under reduced pressure. The aqueous solution was acidified with 1 N HCl and was extracted with ethyl acetate. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to give 2.4 g (84%) of **90**, mp = 194−195°; ^{1}H NMR ($CDCl_3$): δ 8.12 (d, 2H, J = 8.1 Hz), 7.48 (d, 2H, J = 8.1 Hz), 4.29 (s, 1H, broad), 3.52 (m, 1H), 3.40−3.30 (m, 2H), 2.30 (m, 1H), 1.85−1.00 (m, 12H); MS (ES^-) m/z 286 $(M-1)^-$; Anal. ($C_{17}H_{21}NO_3$) C, H, N.

4-((4a*R,8a*S**)-Octahydroquinoline-1-carbonyl)benzoyl chloride (91).** To a solution of 2.0 g (6.96 mmol) of **90** in 100 mL of methylene chloride was added 3.3 g (28 mmol) of oxalyl chloride and 4 drops of DMF. The mixture was stirred at room temperature for 18 h then the solvent was removed under reduced pressure. Methylene chloride was added to the residue and the solvent was removed under reduced pressure. This was repeated three times. The resulting material was used directly in the next reaction.

Preparation of Terephthalate Derivatives 92−100. Method D. To a solution of 1 mmol of the appropriate amine and 2 mmol of diisopropylethylamine in 10 mL of methylene chloride was added dropwise a solution of 1 mmol of **91** in 2 mL of methylene chloride. After stirring the mixture at room temperature for 18 h, it was washed with 1 N HCl followed by aqueous $NaHCO_3$. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The residual solid was purified by crystallization or flash chromatography to furnish the product.

Method E. To a solution of 1 mmol of **90**, 1 mmol of EDCI and 1.1 mmol HOBt in 10 mL of methylene chloride was added 1 mmol of the appropriate amine and the resultant mixture was stirred at room temperature for 18 h. Ethyl acetate was added then the mixture was washed with 1 N HCl. The organic phase was dried over magnesium sulfate, the solvent was removed under reduced pressure and the residue was purified by flash chromatography.

4-((4a*R,8a*S**)-Octahydroquinoline-1-carbonyl)-*N*-pentylbenzamide (92).** Prepared in 46% yield from **90** and *n*-hexylamine according to Method E, mp = 94−95 °C; ^{1}H NMR ($CDCl_3$): δ 7.76 (d, J = 8.29 Hz, 2H), 7.42 (d, J = 8.29 Hz, 2H), 6.16 (s, broad, 1H), 3.55−3.39 (m, 3H), 3.38−3.29 (m, 2H), 2.33−2.19 (m, 1H), 1.84−1.02 (m, 20H), 0.90 (t, 3H); MS (ES^+) m/z 371 $(M + 1)^+$; Anal. ($C_{23}H_{34}N_2O_2$) C, H, N.

Supporting Information Available: Spectral data for compounds **9k**, **9l**, **9n**, **25**, **27**−**31**, **33**, **34**, **41**, **42**, **49**−**55**, **76**, **77**, **93**−**100** and table of elemental analyses for purified products described in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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