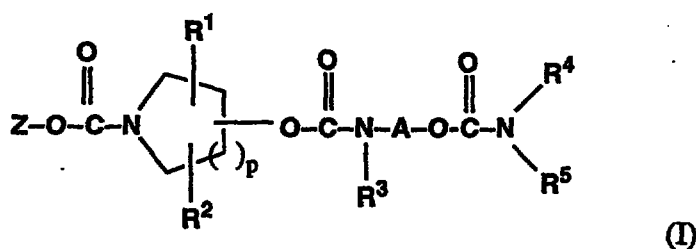


TRIS CARBAMIC ACID ESTERS: INHIBITORS OF CHOLESTEROL ABSORPTION

This invention relates to tris carbamic acid esters, processes for preparing them and
5 pharmaceutical compositions containing them.

Cholesterol ester hydrolase and acyl-CoA cholesterol acyltransferase have been implicated in the reesterification and absorption of exogenous cholesterol. It has been demonstrated that removal of CEH from pancreatic juice results in an 80% reduction in the uptake of cholesterol into the bloodstream in rats [Hoisie, J. Biol. Chem. 262, 260-264 (1987).] Furthermore, several lines of investigation have indicated that ACAT may play a key role in the intestinal absorption of cholesterol [DeVries *et al.*, J. Med. Chem. 29, 1131(1985)]. The association between high serum cholesterol levels and coronary vascular disease is well documented; consequently compounds of this invention may be useful for treating atherosclerosis, familial hypercholesterolemia, hyperlipidemia, and like diseases.

20 This invention relates to novel carbamic acid esters of 4 to 8 membered azacycloalkanols, particularly 4-piperidinol, which inhibit absorption of cholesterol from the intestinal tract and have been shown to inhibit the enzymes, cholesterol ester hydrolase (CEH) and/or acyl-CoA cholesterol acyltransferase (ACAT). The novel CEH/ACAT inhibitors of this invention have the formula:



25 wherein

p is 0, 1, 2, 3, or 4;

$$Z \text{ is } -\text{Ar}^1, -\text{Ar}^1-\text{Ar}^2, -\text{Ar}^1-\text{O}-\text{Ar}^2, -\text{Ar}^1-\text{S}-\text{Ar}^2, -\text{Ar}^1-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Ar}^2,$$
$$-\text{Ar}^1-\overset{\text{O}}{\parallel}\text{C}-\text{O}-\text{Ar}^2, -\text{Ar}^1-\overset{\text{O}}{\parallel}\text{C}-\text{Ar}^2, -\text{Ar}^1-(\text{CH}_2)_{1-20}-\text{Ar}^2,$$
$$-\text{Ar}^1-(\text{CH}_2)_{1-20}-\text{O}-\text{Ar}^2, -\text{Ar}^1-\text{O}-(\text{CH}_2)_{1-20}-\text{Ar}^2,$$

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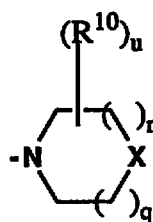


$-\text{Ar}^1-(\text{CR}^6=\text{CR}^6)_{1-3}-\text{Ar}^2$ or $-\text{Ar}^1-\text{NR}^7-\text{Ar}^2$; where R^6 is hydrogen or C_1-C_8 alkyl and R^7 is hydrogen, C_1-C_8 alkyl, C_1-C_8 alkylcarbonyl or C_1-C_8 alkoxycarbonyl;

and Ar^1 and Ar^2 are, independently, selected from phenyl, naphthyl, furanyl, benzofuranyl, dibenzofuranyl, pyridinyl, pyrimidinyl, pyrazinyl, thienyl, benzothienyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, benzthiazolyl, isoxazolyl, benzisoxazolyl, indenyl, indolyl, quinolinyl, isoquinolinyl, benzotriazolyl, carbazolyl, benzimidazolyl, or fluorenyl,

and Ar^1 and Ar^2 , independently, are optionally substituted by fluorine, chlorine, bromine, iodine, cyano, nitro, $-\text{CO}_2\text{H}$, C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_8 cycloalkyl, C_1-C_{20} alkoxy, C_1-C_{20} alkyl- $\text{O}-(\text{C}_1-\text{C}_{20}$ alkyl)-, C_1-C_{20} alkyl- $\text{O}-(\text{C}_1-\text{C}_{20}$ alkyl)- $\text{O}-$, trifluoromethyl, C_1-C_{20} alkylcarbonyl, C_3-C_8 cycloalkyloxy, C_1-C_{20} alkylcarbonyloxy, C_1-C_{20} alkoxycarbonyl, mono or di C_1-C_{20} alkylaminocarbonyl, tetrazolyl, $-\text{OH}$, $-(\text{CH}_2)_{1-6}-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$ or $-(\text{CH}_2)_{1-6}-\text{NR}^8\text{R}^9$

where R^8 is C_1-C_{20} alkyl, C_1-C_{20} alkylcarbonyl, C_1-C_{20} alkoxycarbonyl and R^9 is hydrogen or C_1-C_{20} alkyl or R^8 and R^9 together with the interposed nitrogen atom form a heterocyclic ring of the formula:



where q is 0, 1 or 2, r is 1 or 2, u is 0, 1 or 2, R^{10} is C_1-C_8 alkyl and X is $-\text{O}-$, $-\text{S}-$, $-\text{NR}^{11}-$ where R^{11} is H, C_1-C_{20} alkyl or benzyl or $-\text{CR}^{12}\text{R}^{13}-$ where R^{12} is H, OH, C_1-C_{20} alkyl, C_1-C_{20} alkoxy, C_1-C_{20} alkylcarbonyloxy, Ar^1 or $-(\text{CH}_2)_{1-10}-\text{Ar}^1$, R^{13} is H, C_1-C_{20} alkyl, or R^{12} and R^{13} together with the interposed carbon forms a 3 to 8 membered carbocyclic ring;

A is a bridging group selected from:

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a saturated or unsaturated, straight or branched hydrocarbon chain of 1 to 20 carbons and which may have 1 to 6 sites of olefinic and/or acetylenic unsaturation;

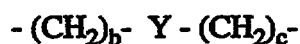
5 a group of the formula:



10 where m and n are 1 to 19, m+n is 2 to 20 and W is a group selected from -O-, -S-, or -NR¹⁴- where R¹⁴ is hydrogen, C₁-C₂₀ alkyl, C₁-C₂₀ alkylcarbonyl, C₁-C₂₀ alkoxy carbonyl, or benzyl;

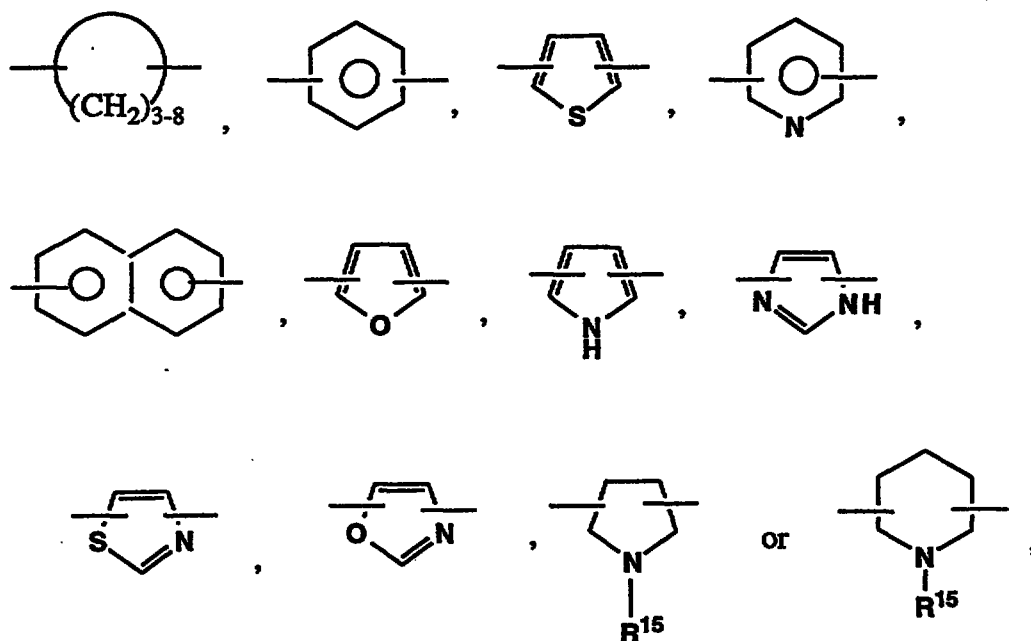
a group of the formula:

15



where b and c are 0 to 20, b+c is 1 to 20 and Y is selected from the group consisting of:

20



where R¹⁵ is H, C₁-C₈ alkyl, C₁-C₂₀ alkylcarbonyl.

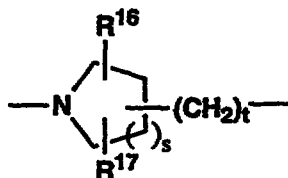
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C₁-C₂₀ alkoxy carbonyl, or benzyl; or

A together with R³ and the interposed nitrogen form a heterocyclic moiety of the formula:

5



10

where s is 0, 1, 2, 3 or 4, t is 0 to 15, and R¹⁶ and R¹⁷ are, independently, hydrogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkyl carbonyl, hydroxy, cyano, C₁-C₈ alkyl carbonyloxy, or -(CH₂)₀₋₆-NR¹⁸R¹⁹ where R¹⁸ is C₁-C₈ alkyl, C₁-C₈ alkoxy carbonyl, or C₁-C₈ alkyl carbonyl and R¹⁹ is hydrogen or C₁-C₈ alkyl;

15

R¹ and R² are independently hydrogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkyl carbonyl, hydroxy, cyano, C₁-C₈ alkyl carbonyloxy, or -(CH₂)₀₋₆-NR¹⁸R¹⁹ where R¹⁸ is C₁-C₈ alkyl, C₁-C₈ alkoxy carbonyl, or C₁-C₈ alkyl carbonyl and R¹⁹ is hydrogen or C₁-C₈ alkyl;

20

R³ is H, C₁-C₈ alkyl or C₇-C₁₅ aryl alkyl where aryl is phenyl optionally substituted with a C₁-C₆ alkyl group or is combined with A to form a heterocyclic ring as described above;

25

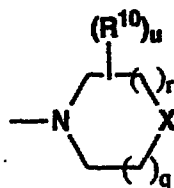
R⁴ and R⁵ are independently hydrogen, C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, -(CH₂)₁₋₂₀(C₃₋₁₀ cycloalkyl), -(CH₂)₁₋₂₀Ar¹, or -(CH₂)₁₋₂₀NR²⁰R²¹ where R²⁰ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₁-C₂₀ alkyl carbonyl, C₁-C₂₀ alkoxy carbonyl or benzyl; and R²¹ is hydrogen or C₁-C₂₀ alkyl, wherein Ar¹ is defined above, or

30

R⁴ and R⁵ together with the interposed nitrogen form a heterocyclic moiety of the formula:

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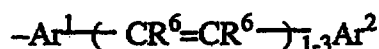
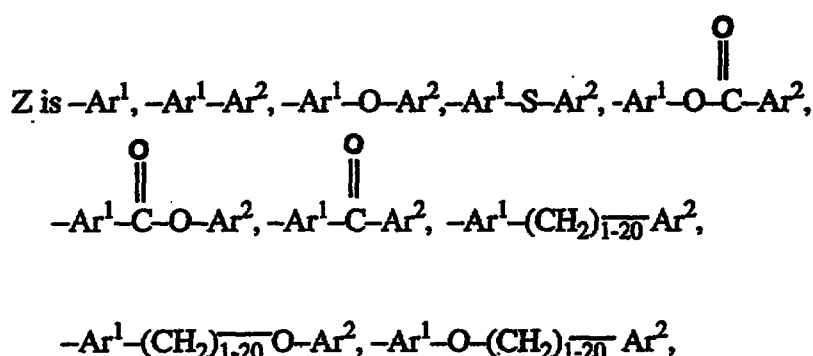
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where r , q , u , R^{10} and X are as defined above,
or a pharmaceutically acceptable salt thereof.

5

In the preceding group of compounds, the preferred values for Z are:



where R^6 is H or C_1 - C_8 alkyl, or $-Ar^1-NR^7-Ar^2$ where R^7 is hydrogen, C_1 - C_8 alkyl, C_1 - C_8 alkylcarbonyl or C_1 - C_8 alkoxy carbonyl and Ar^1 and Ar^2 are selected from phenyl, naphthyl, furanyl, benzofuranyl, dibenzofuranyl, pyridinyl, thienyl, benzothienyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, benzthiazolyl, isoxazolyl, benzisoxazolyl, indenyl, indolyl, quinoliny, isoquinoliny, carbazolyl, benzimidazolyl or fluorenyl; and Ar^1 and Ar^2 may be optionally substituted by fluorine, chlorine, bromine, iodine, cyano, nitro, $-CO_2H$, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, C_2 - C_8 alkenyl, trifluoromethyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkyloxy, C_1 - C_8 alkylcarbonyl, C_1 - C_8 alkoxy carbonyl, C_1 - C_8 alkylcarbonyloxy, $-NH_2$, $-(CH_2)_{1-6}-NR^8R^9$ where R^8 is C_1 - C_8 alkyl, C_1 - C_8 alkylcarbonyl or C_1 - C_8 alkoxy carbonyl, and R^9 is hydrogen or C_1 - C_8 alkyl.

The preferred values for A in the generic description of the compounds of this invention is:

A is a bridging group selected from:

a saturated or unsaturated, straight or branched hydrocarbon chain of 1 to 20 carbon atoms which may have 1 to 6 sites of olefinic and/or acetylenic unsaturation;

a group of the formula:



where m and n are 1 to 19, m+n is 2 to 20 and W is a group selected from

-O-, -S-, or -NR¹⁴- where R¹⁴ is hydrogen, C₁-C₈ alkyl,

5

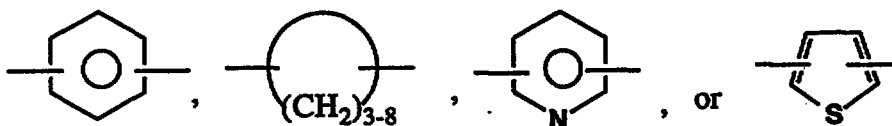
C₁-C₈ alkylcarbonyl, C₁-C₈ alkoxy carbonyl or benzyl;

a group of the formula:



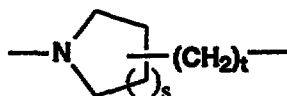
10

where b and c are each 0 to 20, b+c is 1 to 20, and Y is selected from the group consisting of:



15

or A together with R³ and the interposed nitrogen form a heterocyclic moiety of the formula:



20

where s is 0, 1, 2 or 3 and t is 0 to 15.

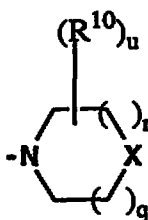
In addition, the preferred values for R⁴ and R⁵ are, independently, hydrogen, C₁-C₁₂ alkyl, C₂-C₈ alkenyl, C₃-C₈ cycloalkyl, -(CH₂)₁₋₁₀-(C₃-C₁₀ cycloalkyl),

-(CH₂)₁₋₁₀Ar¹, -(CH₂)₁₋₁₀-NR²⁰R²¹ where R²⁰ is C₁-C₈ alkyl, C₂-C₈ alkenyl,

25

C₁-C₈ alkylcarbonyl, C₁-C₈ alkoxy carbonyl or benzyl, and R²¹ is hydrogen or

C₁-C₈ alkyl, or R⁴ and R⁵ together with the interposed nitrogen forms a heterocyclic moiety of the formula:



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10

25

a) reacting a compound of formula:



30

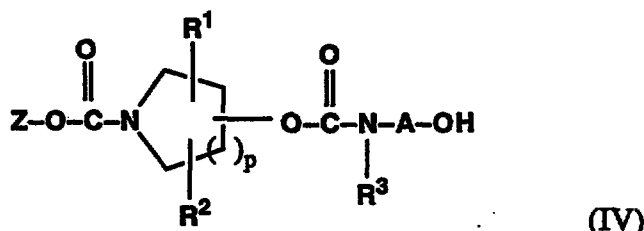


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wherein R^4 and R^5 are as defined above, to give a compound of formula I as defined above,

or

b) reacting a compound of formula:



wherein p , R^1 , R^2 , R^3 , A and Z are as defined above, with an isocyanate of formula:

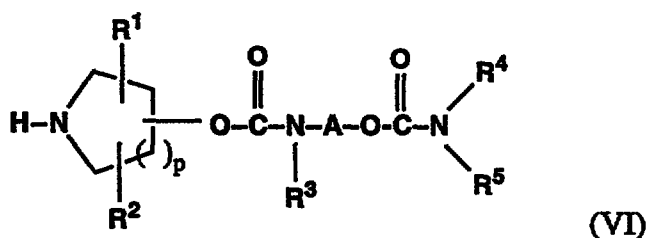


(V)

wherein R^4 is as defined above excepting hydrogen, to give a corresponding compound of formula I where R^4 is as defined in connection with formula V and R^5 is hydrogen,

or

c) reacting a compound of formula:



20 wherein p , R^{1-5} and A are as defined above with a compound of formula:



25 wherein Z is as defined above and B is a leaving group, e.g. p -nitrophenyl, chlorine or imidazolyl.

After any of the aforementioned processes the compound of formula I may be isolated as a pharmaceutically acceptable salt or as the free base.



In the processes above reactive substituent groups may be protected during the reaction and the protecting groups removed thereafter. Starting compounds of formula II, III, IV, V, VI and VII are either known compounds, analogous to known compounds or can be prepared by methods as described hereinafter.

5

With regard to processes (a) and (c) the reaction can be conveniently carried out in an inert solvent in the presence of an acid acceptor.

Process (b) can be conveniently carried out in an inert solvent if required with heating.

10

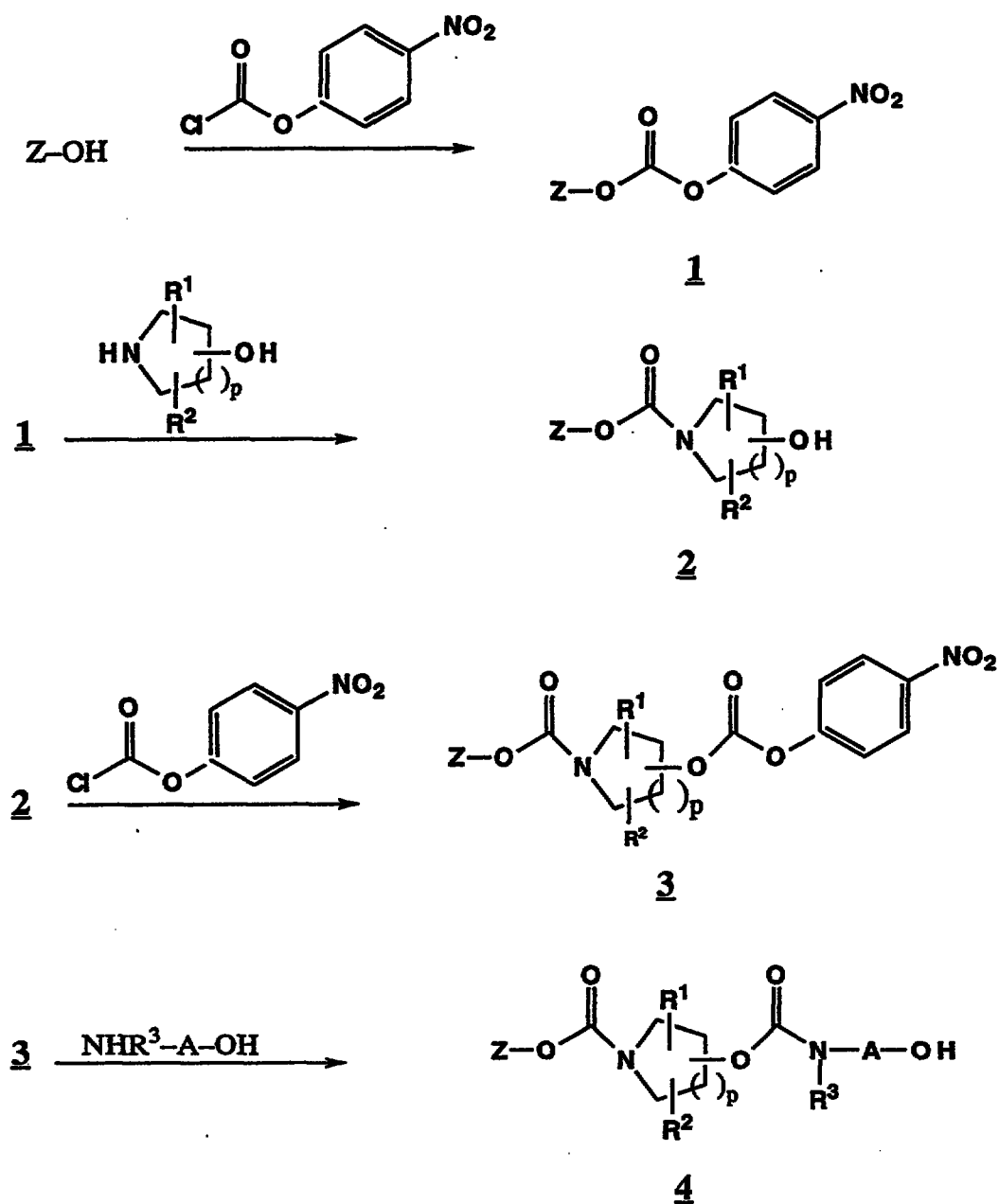
The compounds of this invention are most conveniently prepared by reacting an intermediate hydroxy compound with phosgene or a phosgene equivalent followed by adding an appropriate amine or amine hydrochloride in the presence of a base in a suitable solvent. The preferred phosgene equivalent is 4-nitrophenyl chloroformate and the most suitable solvents are methylene chloride, chloroform and dimethylformamide. When convenient, an isocyanate or carbamoyl chloride can be prepared and reacted directly with the alcohol to give the desired carbamates ($R^4 \neq H$) outlined in Scheme II. The preferred synthetic route is illustrated in Scheme I.

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Scheme I

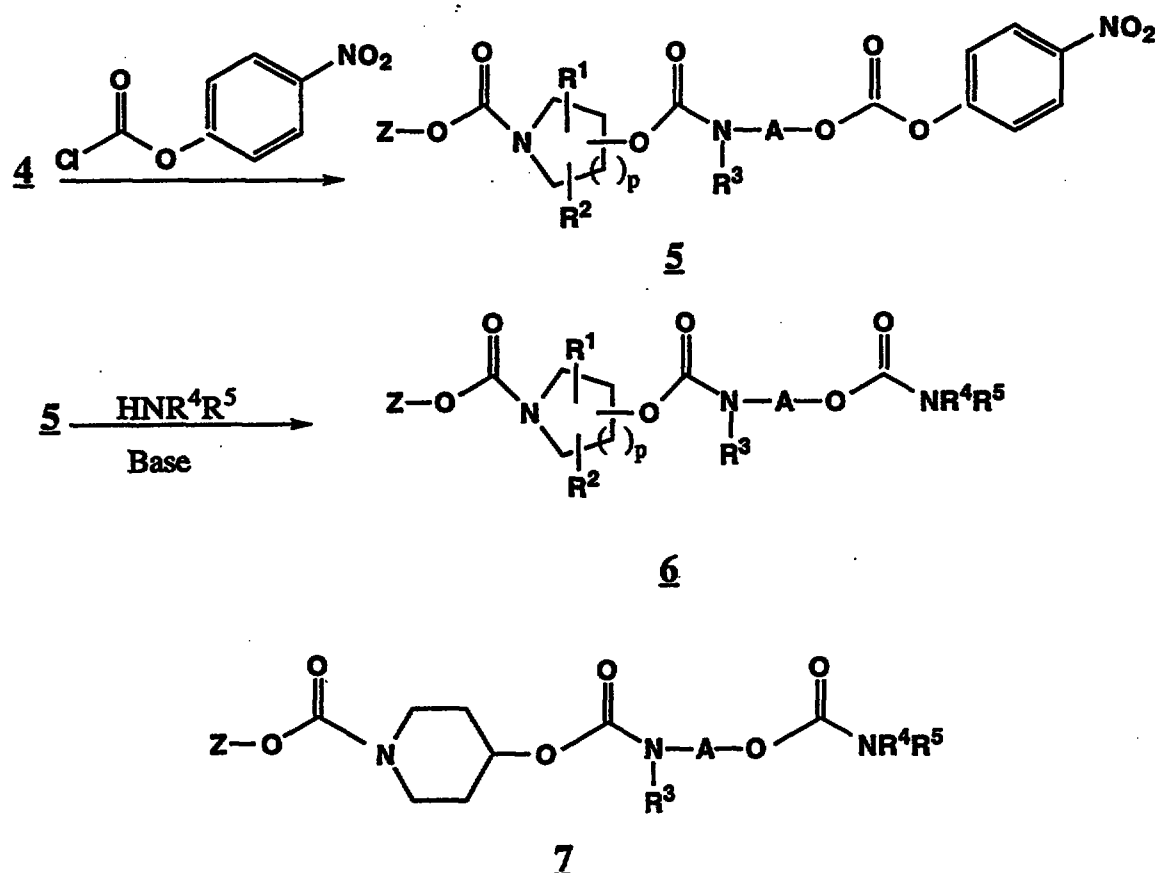


5

Preferred compounds of this invention are of formula 6 where p is 2, R^1 and R^2 are H, and the preferred compounds therefore have the following formula:

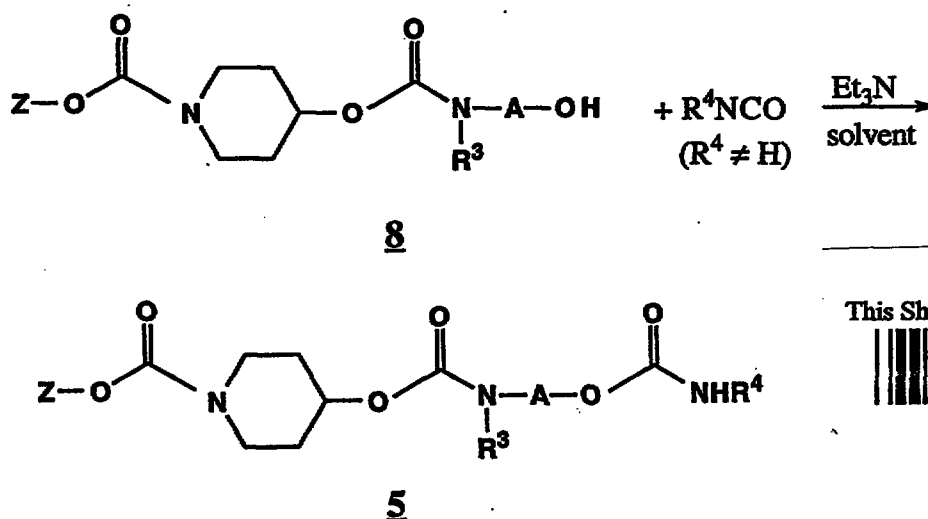
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- 5 The preferred piperidine dicarbamate structure 8 is used to illustrate the use of an isocyanate to make the compounds of this invention.

Scheme II



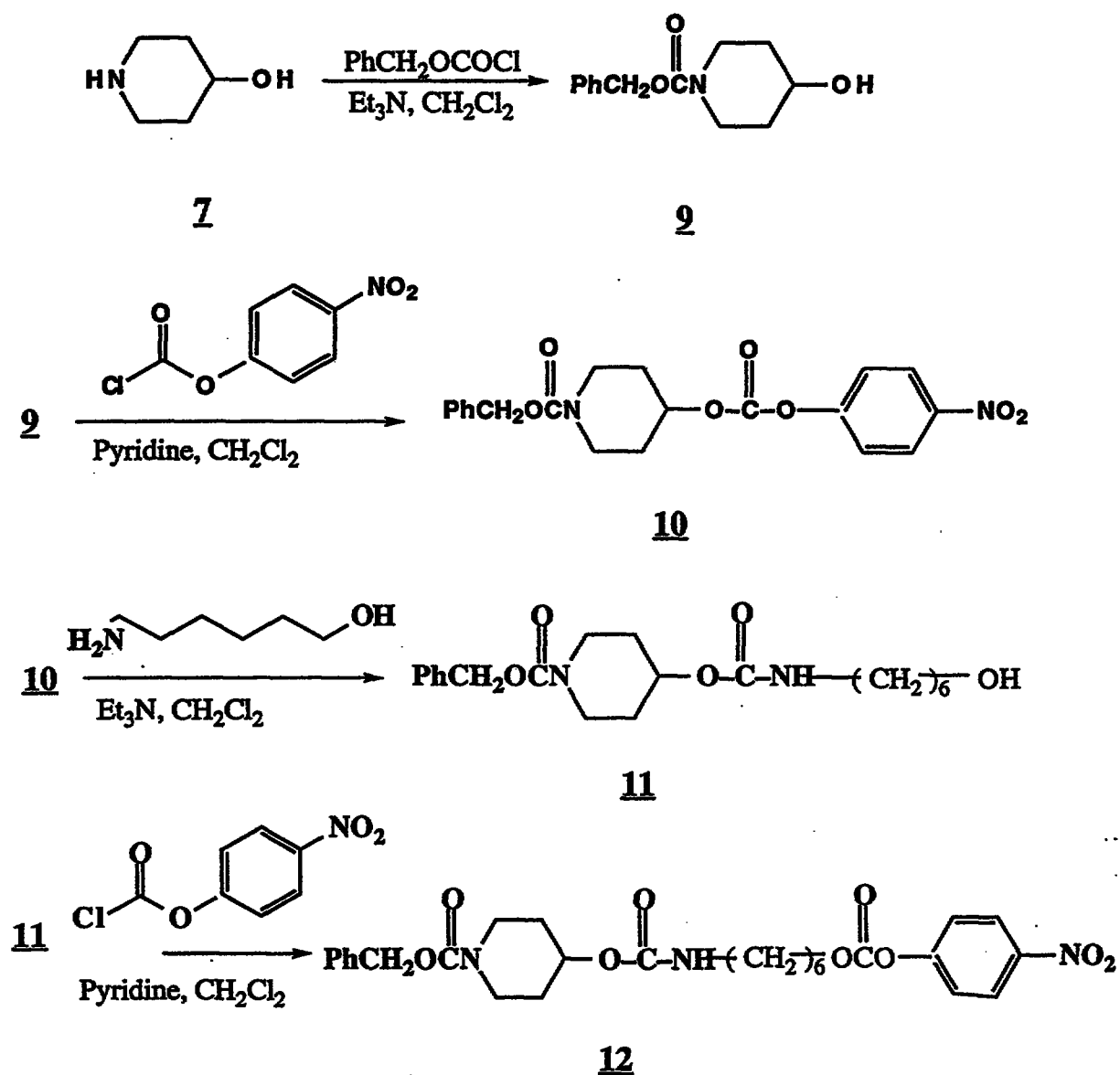
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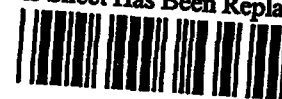
- 10 Scheme III outlines a convenient synthetic method for preparing invention compounds 7 from a prepared common intermediate 14 where the moiety Z is to be varied. For illustrative purposes in Scheme III, A is $-(\text{CH}_2)_6-$ and NR^4R^5 is 8-

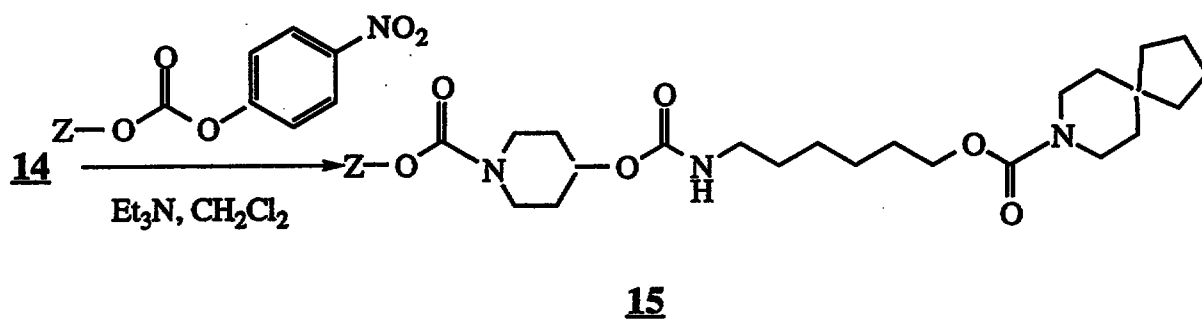
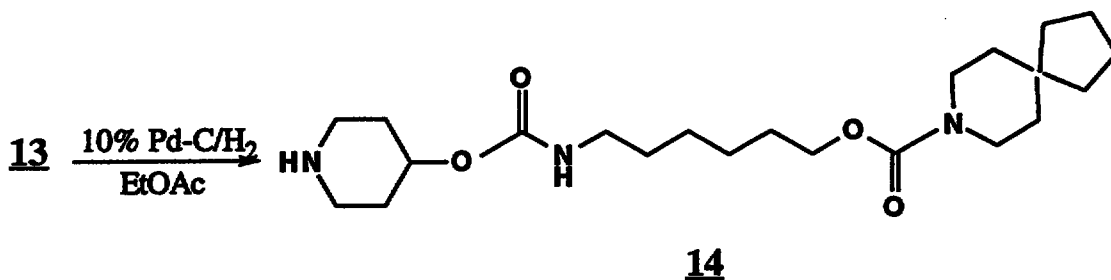
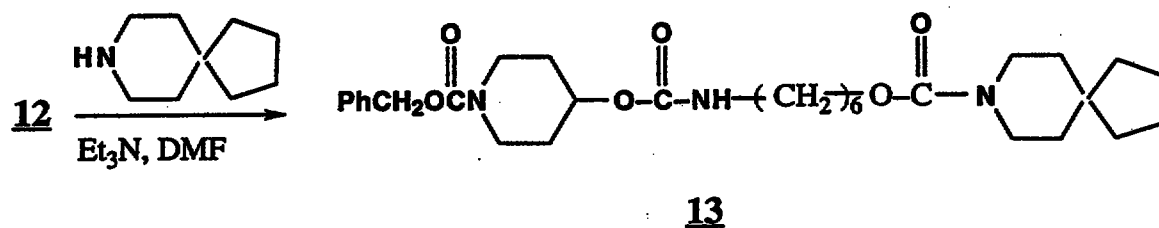
azaspiro[4.5]decane-8-yl. Z may be activated by a variety of methods known in the art of organic synthesis. One such method is illustrated in Scheme III. Another method of activating Z is as its chloroformate as illustrated in Example 26.

Scheme III



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5

In the above outlined synthetic procedures of Schemes I-III where a hydroxyl, amino, or carboxyl substituent is present and not utilized in the carbamate forming reactions, the hydroxyl, amino, or carboxyl group may be protected by a removable protecting group. The protected form is recommended where the hydroxyl, amino, or carboxyl group may otherwise undergo an undesired reaction. Protecting groups for hydroxyl, amino, or carboxyl groups are given in J. F. W. McOmie, *Protective Groups in Organic Chemistry* (Plenum Press, 1973) and T. W. Greene, *Protective Groups in Organic Chemistry* (John Wiley and Sons, 1981). The protecting group may be removed at a suitable later stage in the synthetic scheme during the course of synthesis of end products.

15

The following specific examples for the synthesis of intermediates and invention compounds are included for illustrative purposes only and are not to be construed as limiting to this disclosure in any way. Those skilled in the art will be aware of other methods of preparing compounds of this invention. The starting materials or intermediates are available commercially or can be prepared following standard literature procedures.

20

Example 1**Carbonic Acid (4-nitrophenyl) ester (4-phenoxyphenyl) ester**

5 A solution of 4-phenoxyphenol (50 g, 0.27 mol) and pyridine (22 mL, 0.27 mol) in 500 mL of methylene chloride was added under nitrogen dropwise over 1.5 hours to a solution of 4-nitrophenyl chloroformate (54 g, 0.27 mol) in 500 mL of methylene chloride at room temperature. After the addition the reaction was stirred overnight at room temperature. The reaction was extracted two times with 1N HCl, multiple times
10 with saturated Na_2CO_3 , dried (MgSO_4) and the solvent removed under reduced pressure to give 94.86 g of a light yellow crystalline solid. Recrystallization from methylene chloride-diisopropyl ether gave 69.13 g (73%) of the title compound as a light tan crystalline solid, mp 113-115°C.

15 Analysis Calc'd for $\text{C}_{19}\text{H}_{13}\text{NO}_6$: C, 64.96; H, 3.73; N, 3.99
 Found: C, 64.63; H, 3.89; N, 3.93

Example 2

20 **4-Hydroxy-1-piperidinecarboxylic acid 4-phenoxyphenyl ester**

 A solution of the carbonate (45 g, 0.13 mol) produced in Example 1 in 250 mL of methylene chloride was added dropwise under nitrogen over three hours to a solution of 4-hydroxypiperidine (14.3 g, 0.14 mol) and triethylamine (19.7 mL, 0.14 mol) in 250 mL of methylene chloride at ice bath temperature. After the addition the reaction was
25 stirred at ice bath temperature for 4 hours and at room temperature overnight. The reaction was extracted one time with 1N HCl and then multiple times with saturated Na_2CO_3 , dried (MgSO_4) and the solvent removed under reduced pressure to give 39.27 g of a light yellow solid. Recrystallization from diisopropyl ether-methanol gave 31.78 g (79%) of the title compound as an off-white crystalline solid, mp 130-133°C.

30 Analysis Calc'd for $\text{C}_{18}\text{H}_{19}\text{NO}_4$: C, 69.00; H, 6.11; N, 4.47
 Found: C, 68.90; H, 6.18; N, 4.45

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Example 3**4-(4-Nitro-phenoxy-carbonyloxy)-piperidine-1-carboxylic acid 4-phenoxyphenyl ester**

5 A solution of the alcohol (25 g, 80 mmol) produced in Example 2 and pyridine (6.4 mL, 80 mmol) in 300 mL of methylene chloride was added under nitrogen dropwise over one hour to a solution of 4-nitrophenyl chloroformate (16.1 g, 80 mmol) in 200 mL of methylene chloride at ice bath temperature. The reaction was stirred at
10 ice bath temperature for two hours and then overnight at room temperature. The reaction was extracted one time with 1N HCl, two times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 37.3 g of an off-white solid. Recrystallization from 1:1 ethyl acetate: hexane gave 26.4 g (69%) of the title compound as an off-white solid, mp 108-109°C.

15

Analysis Calc'd for C₂₅H₂₂N₂O₈: C, 62.76; H, 4.63; N, 5.86
Found: C, 62.99; H, 4.53; N, 5.85

Example 4

20

4-[[[(6-Hydroxyhexyl)aminol-carbonylloxy]-1-piperidinecarboxylic acid 4-phenoxyphenyl ester

25 A solution of triethylamine (65.5 mL, 0.47 mol) and 6-aminohexanol (13.2 g, 0.11 mol) in 300 mL of methylene chloride was added dropwise under nitrogen to a solution of the carbonate (45.0 g, 0.09 mol) produced in Example 3 in 500 mL of methylene chloride at room temperature. After the addition the solution was stirred at room temperature overnight. The reaction was extracted one time with 1N HCl and then multiple times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under
30 reduced pressure to give 47.0 g of an off-white solid. Recrystallization from methylene chloride-diisopropyl ether gave 35.5 g (83%) of the title compound as a white crystalline solid, mp 69-72°C.

Analysis Calc'd for C₂₅H₃₂N₂O₆: C, 65.77; H, 7.07; N, 6.14
35 Found: C, 65.49; H, 7.05; N, 5.85

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Example 5**4-[6-(4-Nitro-phenoxy-carbonyloxy)-hexyl-carbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester**

5

A solution of the alcohol (40.0 g, 88 mmol) produced in Example 4 and pyridine (7.1 ml, 88 mmol) in 300 ml of methylene chloride was added under nitrogen dropwise over one hour to a solution of 4-nitrophenyl chloroformate (17.7 g, 88 mmol) in 300 ml of methylene chloride at ice bath temperature. The reaction was stirred at ice bath
10 temperature for two hours and overnight at room temperature. The reaction was extracted one time with 1N HCl, multiple times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 54.9 g of an off-white solid. Recrystallization from 1:1 ethyl acetate-hexane gave 51.6 g (95%) of the title compound as a white crystalline solid, mp 117-120°C.

15

Analysis Calc'd for C ₃₂ H ₃₅ N ₃ O ₁₀ :	C, 61.83; H, 5.68; N, 6.76
Found:	C, 61.01; H, 5.65; N, 6.66

Example 6

20

4-[6-(Hexyl-carbamoyloxy)-hexyl-carbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester

A solution of the carbonate (35.0 g, 56 mmol) produced in Example 5 in 400 mL
25 of methylene chloride was added dropwise under nitrogen to a solution of hexylamine (8.9 mL, 67 mmol) and triethylamine (39.2 mL, 281 mmol) in 400 mL of methylene chloride at ice bath temperature. After the addition the reaction was stirred at room temperature until it was judged complete by thin layer chromatographic analysis (TLC). If necessary, additional quantities of hexylamine and triethylamine can be
30 added to drive the reaction to completion. The reaction was extracted one time with 1N HCl, multiple times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 30.9 g of a white solid. Recrystallization from methylene chloride-diisopropyl ether gave 27.6 g (84%) of the title compound as a white crystalline solid, mp 79-80°C.

35

Analysis Calc'd for C ₃₂ H ₄₅ N ₃ O ₇ :	C, 65.84; H, 7.77; N, 7.20
Found:	C, 65.83; H, 7.80; N, 7.13



Example 7**4-[6-(Dihexyl-carbamoyloxy)-hexylcarbamoyloxy-piperidine-1-carboxylic acid 4-phenoxyphenyl ester**

5

A solution of the carbonate (2.0 g, 3.2 mmol) produced in Example 5 in 30 ml of methylene chloride was added dropwise under nitrogen to a solution of dihexylamine (900 μ l, 3.9 mmol) and triethylamine (2.7 ml, 16 mmol) in 30 ml of methylene chloride at ice bath temperature. The reaction was stirred at ice bath temperature for approximately one hour and then overnight at room temperature. The reaction was extracted one time with 1N HCl, multiple times with saturated Na_2CO_3 , dried (MgSO_4) and the solvent removed under reduced pressure to give 2.35 g of a yellow oil. Purification of the oil by chromatography on 230 g of silica gel (230-400 mesh) using 10% ethyl acetate-methylene chloride as the eluent gave 1.90 g (88%) of the title compound as a clear oil, MS m/e 668 ($\text{M}+\text{H}$)⁺.

15

Analysis Calc'd for $\text{C}_{38}\text{H}_{57}\text{N}_3\text{O}_7$:

C, 68.34; H, 8.60; N, 6.29

Found:

C, 68.63; H, 8.69; N, 6.30

20

Example 8**4-[6-(Piperidine-1-carbonyloxy)-hexylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester**

25

A solution of the carbonate (2.0 g, 3.2 mmol) produced in Example 5, piperidine (0.38 mL, 3.9 mmol) and triethylamine (2.2 mL, 16 mmol) in 30 mL of anhydrous dimethylformamide was stirred under nitrogen at room temperature overnight. The reaction was diluted with methylene chloride, extracted one time with 1N HCl, multiple times with saturated Na_2CO_3 , dried (MgSO_4) and the solvent removed under reduced pressure to give 1.76 g of a white solid. Recrystallization from methylene chloride-diisopropyl ether gave 0.85 g (46%) of the title compound as a white crystalline solid, mp 92-93°C.

30

Analysis Calc'd for $\text{C}_{31}\text{H}_{41}\text{N}_3\text{O}_7$:

C, 65.59; H, 7.28; N, 7.40

35

Found:

C, 65.49; H, 7.32; N, 7.11

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Example 94-[6-Dibenzyl-carbamoyloxy]-hexyl-carbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester

5

A solution of the carbonate (2.0 g, 3.2 mmol) produced in Example 5 in 50 mL of chloroform (free of ethanol) was added dropwise under nitrogen to a solution of dibenzylamine (0.74 mL, 3.9 mmol) and triethylamine (2.2 mL, 16 mmol) in 50 mL of chloroform at ice bath temperature. After the addition the solution was heated to reflux and the reaction monitored by TLC. The reaction was extracted one time with 1N HCl, multiple times with saturated Na_2CO_3 , dried (MgSO_4) and the solvent removed under reduced pressure to give 2.30 g of a brown oil. Purification on 250 g of silica gel (230-400 mesh) using ethyl acetate - methylene chloride as an eluent gave 1.56 g of an oil. Crystallization of the oil from diisopropyl ether gave 1.16 g (53%) of the diisopropyl etherate of the title compound as a white crystalline solid, mp 68-70°C.

15

Analysis Calc'd $\text{C}_{40}\text{H}_{45}\text{N}_3\text{O}_7 \cdot 0.1$ mole diisopropyl ether: C, 70.68; H, 6.78;
N, 6.09

Found: C, 70.85; H, 6.71;
N, 5.87

20

Example 104-[12-(Hexylcarbamoyloxy)-dodecylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester

25

A mixture of the carbonate (11.0 g, 23 mmol) produced in Example 3, 12-aminododecanoic acid (5.9 g, 28 mmol) and triethylamine (16.0 mL, 110 mmol) in 300 mL of anhydrous dimethylformamide was stirred under nitrogen at approximately 70°C for 3 hours. The reaction was diluted with ethyl acetate, extracted two times with 1N HCl, multiple times with water, dried (MgSO_4) and the solvent removed under reduced pressure to give 16.3 g of an off-white solid. Purification on 400 g of silica gel (230-400 mesh) using 10% EtOAc- CH_2Cl_2 to remove the nitrophenol and then 5% MeOH- CH_2Cl_2 to remove the desired product gave, after removal of the solvent under reduced pressure, 4-(11-carboxy-undecylcarbamoyloxy)-piperidine-1-carboxylic acid 4-phenoxyphenyl ester (11.2 g, 88%) as a white crystalline solid, mp 88-90°C.

35

Analysis Calc'd for $\text{C}_{31}\text{H}_{42}\text{N}_2\text{O}_7$: C, 67.12; H, 7.63; N, 5.05

Found: C, 67.28; H, 7.60; N, 4.80



A 1M solution of $\text{BH}_3 \cdot \text{THF}$ in THF (14.4 mL, 14.4 mmol) was added under nitrogen dropwise over 30 minutes to a solution of the acid (8.0 g, 14.4 mmol) produced in the previous step in 250 mL of anhydrous THF at ice bath temperature. The reaction was stirred at ice bath temperature for 1 hour and overnight at room temperature. By TLC analysis the reaction was not complete. An additional 21.6 mL (21.6 mmol) of the $\text{BH}_3 \cdot \text{THF}$ was added and the solution stirred at room temperature until the reaction was complete by TLC. The reaction was quenched by the addition of 60 mL of 1N HCl. After stirring at room temperature for 15 minutes the THF was removed under reduced pressure and the residue partitioned between 1N HCl and EtOAc. The organic layer was separated, washed one additional time with 1N HCl, dried (MgSO_4) and the solvent removed under reduced pressure to give 7.43 g of a white solid. Purification on 800 g of silica gel (230-400 mesh) using hexane - ethyl acetate as an eluent and recrystallization from diisopropyl ether - methylene chloride gave 4-(12-hydroxy-dodecylcarbamoyloxy)-piperidine-1-carboxylic acid 4-phenoxyphenyl ester (3.88 g, 50%) as a white crystalline solid, mp 75-76°C.

Analysis Calc'd for $\text{C}_{31}\text{H}_{44}\text{N}_2\text{O}_6$:

C, 68.86; H, 8.20; N, 5.18

Found:

C, 68.65; H, 8.24; N, 5.09

A solution of the alcohol (1.00 g, 1.86 mmol) produced in the previous step and pyridine (150 μL , 1.85 mmol) in 30 ml of methylene chloride was added under nitrogen dropwise over one hour to a solution of 4-nitrophenyl chloroformate (0.37 g, 1.85 mmol) in 10 ml of methylene chloride at ice bath temperature. The reaction was stirred at ice bath temperature for 3.5 hours and then overnight at room temperature. The reaction was extracted one time with 1N HCl, multiple times with saturated Na_2CO_3 , dried (MgSO_4) and the solvent removed under reduced pressure to give 1.26 g of a white crystalline solid. Purification of the solid on 300 g of silica gel (230-400 mesh) using 25% ethyl acetate-hexane as the eluent gave 979 mg (75%) of 4-[12-(4-nitrophenoxy-carbonyloxy)-dodecylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester as a white crystalline solid, mp 96-98°C.

Analysis Calc'd for $\text{C}_{38}\text{H}_{47}\text{N}_3\text{O}_7$:

C, 64.67; H, 6.71; N, 5.95

Found:

C, 64.74; H, 6.67; N, 5.77

A solution of triethylamine (882 μL , 6.33 mmol) and 6-hexylamine (200 μL , 1.51 mmol) in 20 ml of methylene chloride was added dropwise under nitrogen to a solution of the carbonate (893 mg, 1.27 mmol), produced in the previous step, in 20 ml of methylene chloride at ice bath temperature. After the addition, the reaction was stirred at ice bath temperature for two hours and at room temperature for approximately three



days. The reaction was extracted one time with 1N HCl, multiple times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 799 mg of a white crystalline solid. Purification of this solid by recrystallization from methylene chloride-diisopropyl ether gave 734 mg (87%) of the title compound as a
5 white crystalline solid, mp 98-100°C.

Analysis Calc'd for C₃₈H₅₇N₃O₇:

C, 68.34; H, 8.60; N, 6.29

Found:

C, 68.33; H, 8.59; N, 6.21

10

Example 11

4-{6-[4-(2,2-Dimethyl-propyl)-benzyl]-heptyl-carbamoyloxy]-hexyl-carbamoyloxy}-piperidine-1-carboxylic acid 4-phenoxyphenyl ester

15 A solution of the carbonate (2.0 g, 3.2 mmol) produced in Example 5, 4-(2,2-dimethyl-propyl)-benzyl-heptylamine (1.1 g, 3.9 mmol) and triethylamine (2.2 ml, 16 mmol) in 30 ml of anhydrous dimethylformamide was stirred under nitrogen at room temperature overnight. The reaction was diluted with methylene chloride, extracted one time with 1N HCl, multiple times with saturated Na₂CO₃, dried (MgSO₄) and the
20 solvent removed under reduced pressure to give 2.73 g of a light brown oil. Purification of this oil by chromatography on silica gel (230-400 mesh) using 10% ethyl acetate-methylene chloride as the eluent gave 2.11 g (87%) of the title compound as a clear oil, MS m/e 758 (M+H)⁺.

25 Analysis Calc'd for C₄₅H₆₃N₃O₇:

C, 71.30; H, 8.38; N, 5.54

Found:

C, 71.01; H, 8.34; N, 5.14

Example 12

8-Aza-spiro[4,5]decane-8-carboxylic acid 6-[1-(4-phenoxy-phenoxy-carbonyl)-piperidine-4-oxycarbonylamino]-hexyl ester

30 A solution of the carbonate (2.0 g, 3.2 mmol) produced in Example 5, 8-aza-spiro[4,5]-decane hydrochloride (680 mg, 3.9 mmol) and triethylamine (2.7 ml, 19 mmol) in
35 30 ml of anhydrous dimethylformamide was stirred under nitrogen at room temperature for 5 hours. The reaction was diluted with methylene chloride, extracted one time with 1N HCl, multiple times with saturated Na₂CO₃, dried (MgSO₄), and the solvent removed under reduced pressure to give 1.85 g of a white solid. Recrystallization of



this solid from methylene chloride-diisopropyl ether gave 1.0 g (50%) of the title compound as a white crystalline solid, mp 83-85°C.

Analysis Calc'd for $C_{35}H_{47}N_3O_7$: C, 67.61; H, 7.62; N, 6.76
5 Found: C, 67.83; H, 7.70; N, 6.48

Example 13

10 (Z)-4-[6-(octadec-9-enylcarbamoyloxy)-hexylcarbamoyloxy]-piperidine-1-
carboxylic acid 4-phenoxyphenyl ester

A solution of the carbonate (2.0 g, 3.2 mmol), produced in Example 5, in 30 ml of methylene chloride was added dropwise under nitrogen to a solution of oleylamine (1.6 ml, 3.9 mmol) and triethylamine (2.2 ml, 16 mmol) in 30 ml of methylene chloride at
15 ice bath temperature. After the addition, the reaction was stirred at ice bath temperature for approximately one hour and then overnight at room temperature. The reaction was extracted one time with 1N HCl, multiple time with saturated Na_2CO_3 , dried ($MgSO_4$) and the solvent removed under reduced pressure to give 2.65 g of a light yellow solid. Purification of this solid on 300 g of silica gel (230-400 mesh) using 10% EtOAc-
20 CH_2Cl_2 as the eluent gave 2.02 g (84%) of the title compound as a white crystalline solid, mp 74-76°C.

Analysis Calc'd for $C_{44}H_{67}N_3O_7$: C, 70.46; H, 9.00; N, 5.60
25 Found: C, 70.01; H, 8.91; N, 5.75

Example 14

30 (Z)-4-[12-(Octadec-9-enylcarbamoyloxy)-dodecylcarbamoyloxy]-piperidine-1-
carboxylic acid 4-phenoxyphenyl ester

A solution of the carbonate (1.5 g, 2.1 mmol) produced in Example 10, in 30 ml of methylene chloride was added dropwise under nitrogen to a solution of oleylamine (1.0 ml, 2.6 mmol) and triethylamine (1.5 ml, 11 mmol) in 30 ml of methylene chloride at ice bath temperature. After the addition, the reaction was stirred at ice bath
35 temperature for approximately one hour and then overnight at room temperature. The reaction was extracted one time with 1N HCl, multiple times with saturated Na_2CO_3 , dried ($MgSO_4$) and the solvent removed under reduced pressure to give 2.19 g of a yellow solid. Recrystallization of the solid from diisopropyl ether gave 1.47 g (83%) of the title compound as a crystalline solid, mp 83-84°C.

Analysis Calc'd for $C_{50}H_{79}N_3O_7$:

C, 71.99; H, 9.55; N, 5.04

Found:

C, 72.25; H, 9.70; N, 4.98

5

Example 15**4-[[[(3-Hydroxypropyl)amino]carbonyloxy]-1-piperidinecarboxylic acid 4-phenoxyphenyl ester**

10 A solution of the carbonate (10.0 g, 21 mmol) produced in Example 3 in 50 mL of methylene chloride was added dropwise over 1 hr under nitrogen to a solution of triethylamine (14.6 mL, 100 mmol) and 3-aminopropanol (1.9 mL, 25 mmol) in 25 mL of methylene chloride at ice bath temperature. After the addition the solution was stirred at ice bath temperature for 1 hr and then at room temperature overnight. The

15 reaction was extracted one time with 1N HCl and then multiple times with saturated Na_2CO_3 , dried ($MgSO_4$) and the solvent removed under reduced pressure to give 8.23 g of a white solid. Trituration with hot diisopropyl ether gave 7.56 g (87%) of the title compound as a white crystalline solid, mp 81-83°C.

20 Analysis Calc'd for $C_{22}H_{36}N_2O_6$:

C, 63.76; H, 6.32; N, 6.76

Found:

C, 63.80; H, 6.40; N, 6.98

Example 16

25 **4-[6-(Hexylcarbamoyloxy)-propylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester**

A solution of the alcohol (2.0 g, 4.8 mmol) produced in Example 15, triethylamine (540 μ L, 3.9 mmol) and hexyl isocyanate (740 mg, 5.8 mmol) in 20 mL of

30 $CHCl_3$ (EtOH free) was stirred under nitrogen at room temperature overnight. By TLC the reaction was not complete. An additional 610 mg (4.8 mmol) of hexyl isocyanate was added and the solution refluxed. The reaction was monitored by TLC. At the end of the reaction the solution was extracted two times with 1N HCl, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 2.70 g of a white solid.

35 Recrystallization from diisopropyl ether gave 2.10 g (80%) of the title compound as a white crystalline solid, mp 90-92°C.

Analysis Calc'd for $C_{29}H_{39}N_3O_7$:

C, 64.31; H, 7.26; N, 7.76

Found:

C, 64.38; H, 7.28; N, 7.67

**Example 17****4-[3-(4-Nitro-phenoxy-carbamoyloxy)-propyl-carbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester**

5

A solution of the alcohol (4.96 g, 12 mmol) produced in Example 15, and pyridine (970 μ l, 12 mmol) in 50 ml of methylene chloride was added under nitrogen dropwise over thirty minutes to a solution of 4-nitrophenyl chloroformate (2.4 g, 12 mmol) in 30 ml of methylene chloride at ice bath temperature. After the addition, the reaction was stirred at ice bath temperature for one hour and overnight at room temperature. The reaction was extracted one time with 1N HCl, multiple times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 6.80 g of a white solid. Recrystallization of the solid from methylene chloride-diisopropyl ether gave 2.76 g (40%) of the title compound as a white crystalline solid. Recrystallization of the mother liquor from methylene chloride-diisopropyl ether gave an additional 2.02 g (29%) of the title compound, mp 97-100°C.

10

15

Analysis Calc'd for C₂₉H₂₉N₃O₁₀: C, 60.10; H, 5.04; N, 7.25
Found: C, 59.92; H, 4.92; N, 7.22

20

Example 18**4-[9-(Nonyl-carbamoyloxy)-propyl-carbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester**

25

A solution of the carbonate (2.0 g, 3.4 mmol) produced in Example 17 in 20 mL of anhydrous dimethylformamide was added dropwise under nitrogen to a solution of nonylamine (760 μ l, 4.1 mmol) and triethylamine (2.4 mL, 17 mmol) in 20 mL of anhydrous dimethylformamide at ice bath temperature. After the addition the solution was stirred at ice bath temperature for 2 hrs and at room temperature overnight. The reaction was diluted with ethyl acetate, extracted five times with water, one time with 1N HCl, five times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 1.94 g of an off-white solid. Recrystallization from diisopropyl ether gave 1.55 g (77%) of the title compound as a white crystalline solid, mp 89-91°C.

30

35

Analysis Calc'd for C₃₂H₄₅N₂O₇: C, 65.84; H, 7.77; N, 7.20
Found: C, 65.72; H, 7.84; N, 7.22

**Example 19****5 8-Aza-spiro[4.5]decane-8-carboxylic acid 6-[[1-(4-phenoxy-phenoxy-carbonyl)-piperidine-4-oxycarbonyl]-amino]-propyl ester**

10 A solution of the carbonate (2.0 g, 3.5 mmol) produced in Example 17 in 20 ml of anhydrous dimethylformamide was added dropwise under nitrogen to a solution of 8-aza-spiro[4.5]decane (750 mg, 4.9 mmol) and triethylamine (2.9 ml, 21 mmol) in 20 ml of anhydrous dimethylformamide at ice bath temperature. After the addition, the reaction was stirred at ice bath temperature for approximately 2 hours and at room temperature overnight. The reaction was diluted with ethyl acetate, extracted four times with water, one time with 1N HCl, five times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 1.93 g of a yellow oil. The oil
15 was chromatographed on 200 g of silica gel (230-400 mesh) using 30%-40% EtOAc-hexane as the eluent. The material isolated was then recrystallized from EtOAc-hexane to give 667 mg (33%) of the title compound as white crystalline solid, mp 92-93°C.

20 Analysis Calc'd for C₃₂H₄₁N₃O₇: C, 66.30; H, 7.13; N, 7.25
Found: C, 66.35; H, 7.23; N, 7.33

Example 20**25 4-Hydroxy-piperidine-1-carboxylic acid benzyl ester**

A solution of benzyl chloroformate (35.3 ml, 0.25 moles) in 25 ml of methylene chloride was added dropwise under nitrogen over three hours to a solution of 4-hydroxypiperidine (25 g, 0.25 moles) and triethylamine (34.5 ml, 0.25 moles) in 500 ml of methylene chloride at ice bath temperature. After the addition the reaction was
30 stirred at ice bath temperature for four hours and at room temperature overnight. The reaction was then extracted two times with 1N HCl, dried (MgSO₄) and the solvent removed under reduced pressure to give 53.1 g (90%) of the title compound as a light yellow oil.

35 Analysis Calc'd for C₁₃H₁₇NO₃: C, 66.36; H, 7.28; N, 5.95
Found: C, 65.77; H, 7.18; N, 5.35

**Example 21****4-(4-Nitro-phenoxy-carbonyloxy)-piperidine-1-carboxylic acid benzyl ester**

5 A solution of the alcohol (72.3 g, 0.31 moles) produced in Example 20 and
pyridine (37.3 ml, 0.46 moles) in 300 ml of methylene chloride was added dropwise
under nitrogen over two hours to a solution of 4-nitrophenyl chloroformate (92.8 g,
0.46 moles) in 600 ml of methylene chloride at room temperature. After the addition
the reaction was stirred for two days at room temperature. The reaction was then
10 extracted two times with 1N HCl, multiple times with saturated Na₂CO₃, dried
(MgSO₄) and the solvent removed under reduced pressure. Recrystallization of the
crude product from methylene chloride-diisopropyl ether gave the title compound as a
crystalline solid, mp 118-120°C.

15 Analysis Calc'd for C₂₀H₂₀N₂O₇: C, 60.00; H, 5.03; N, 7.00
Found: C, 59.82; H, 4.93; N, 7.00

Example 22**4-(6-Hydroxy-hexyl-carbamoyloxy)-piperidine-1-carboxylic acid benzyl ester**

A solution of the carbonate (128.826 g, 0.322 moles) produced in Example 21 in
450 ml of methylene chloride was added dropwise under nitrogen to a solution of 6-
amino-1-hexanol (56.6 g, 0.483 moles) and triethylamine (224.2 ml, 1.61 moles) in 2 L
25 of methylene chloride at room temperature. After the addition the reaction was stirred
overnight at room temperature. By TLC the reaction was not complete. An additional
37.7 g (0.322 moles) of 6-amino-1-hexanol and 224.2 ml (1.61 moles) of triethylamine
were added and the stirring continued overnight. By TLC the reaction was complete.
The reaction was extracted two times with 1N HCl, multiple times with saturated
30 Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 95.0 g
(78%) of a yellow oil which crystallized on standing, mp 50-52°C.

Analysis Calc'd for C₂₀H₃₀N₂O₅: C, 63.47; H, 7.99; N, 7.40
Found: C, 63.68; H, 8.07; N, 7.42

Example 23**4-[6-(4-Nitro-phenoxy-carbonyloxy)-hexyl-carbamoyloxy]-piperidine-1-carboxylic acid benzyl ester**

5

A solution of the alcohol (50 g, 0.13 moles) produced in Example 22 and pyridine (10.7 ml, 0.13 moles) in 500 ml of methylene chloride was added dropwise under nitrogen to a solution of 4-nitrophenyl chloroformate (26.64 g, 0.13 mol) in 500 ml of methylene chloride at room temperature. After the addition, the reaction was stirred overnight at room temperature. A solid had formed which was removed by filtration. The filtrate was extracted two times with 1N HCl, multiple times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure. Recrystallization of the crude reaction product from hexane gave 27.9 g (39%) of the title compound as a light yellow crystalline solid, mp 78-80°C.

15

Analysis Calc'd for C ₂₉ H ₃₃ N ₃ O ₉ :	C, 59.66; H, 6.12; N, 7.73
Found:	C, 59.32; H, 6.14; N, 7.74

Example 24

20

8-Aza-spiro[4.5]decane-8-carboxylic acid 6-[2-(1-benzyloxycarbonyl-piperidin-4-yl)-oxycarbonylamino]-hexyl ester

25

A solution of the carbonate (29.2 g, 54 mmol) produced in Example 23 in 300 ml of anhydrous dimethylformamide was added dropwise under nitrogen to a solution of 8-aza-spiro[4.5]decane (11.53 g, 83 mmol) and triethylamine (37.49 ml, 269 mmol) in 300 ml of anhydrous dimethylformamide at room temperature. After the addition the reaction was heated at 80°C for 5 hrs. The reaction was diluted with methylene chloride, extracted one time with 1N HCl, multiple times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 26.11 g of a yellow oil. Purification on silica gel (230-400 mesh) using ethyl acetate-methylene chloride as an eluent gave a light yellow solid. Trituration of the solid one time with hexane gave 14.75 g (50%) of the title compound as a white crystalline solid, mp 76-79°C.

30

35 Analysis Calc'd for C ₃₀ H ₄₅ N ₃ O ₆ :	C, 66.27; H, 8.34; N, 7.73
Found:	C, 66.16; H, 8.41; N, 7.69

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Example 258-Aza-spiro[4.5]decane-8-carboxylic acid 6-(2-piperidin-4-yl-oxycarbonylamino)-hexyl ester

5

A mixture of the carbamate (10.00 g, 18.4 mmol) produced in Example 24 and 2.0 g of 10% Pd-C in 150 ml of ethyl acetate was hydrogenated at room temperature and 45-50 psi for 18 hrs. The catalyst was removed by filtration through celite and the filtrate concentrated under reduced pressure to give 7.57 g of a light yellow oil. The oil was used in subsequent reactions without further purification.

10

Analysis Calc'd for $C_{22}H_{39}N_3O_4$:

C, 64.52; H, 9.60; N, 10.26

Found:

C, 63.43; H, 9.96; N, 10.13

15

Example 268-Aza-spiro[4.5]decane-8-carboxylic acid 6-[[1-(4-nitro-phenoxy-carbonyl)-piperidine-4-oxycarbonyl]-amino]-hexyl ester

20

A solution of 4-nitrophenyl chloroformate (1.48 g, 7.32 mmol) in 25 ml of methylene chloride was added dropwise under nitrogen to a solution of the amine (3.00 g, 7.32 mmol) produced in Example 25 and triethylamine (5.10 ml, 36.6 mmol) in 50 ml of methylene chloride at room temperature. The reaction was stirred 3 hours at room temperature and then extracted one time with 1N HCl, multiple times with saturated Na_2CO_3 , dried ($MgSO_4$) and the solvent removed under reduced pressure to give 3.844 g of yellow crystals. Purification on silica gel (230-400 mesh) using 30% ethyl acetate-methylene chloride as an eluent gave 2.195 g (52%) of the title compound as a white crystalline solid, mp 113-114°C.

25

30 Analysis Calc'd for $C_{29}H_{42}N_4O_8$:

C, 60.61; H, 7.37; N, 9.75

Found:

C, 60.61; H, 7.47; N, 9.67

Example 27

35

Carbonic Acid (4-nitrophenyl)ester (2-dibenzofuranyl) ester

A solution of 2-hydroxydibenzofuran (25 g, 0.136 mol) and pyridine (11 ml, 0.136 mol) in 300 ml of methylene chloride was added under nitrogen dropwise over five hours to a solution of 4-nitrophenyl chloroformate (27.4 g, 0.136 mol) in 300 ml of



methylen chloride at ice bath temperature. After the addition the reaction was stirred at room temperature overnight. The solid formed was collected by filtration to give 33.08 g of a light tan solid. The filtrate was extracted one time with 1N HCl, one time with saturated Na₂CO₃ (emulsion formed), dried (MgSO₄) and the solvent removed under reduced pressure to give an additional 14.30 g of a light tan solid. This solid was triturated two times with methylen chloride to give 7.39 g of a light tan solid which was combined with the original 33.08 g of solid. Recrystallization of the combined material from ethyl acetate gave 20.23 g (43%) of the title compound as a light tan crystalline solid, mp 183-185°C.

10

Analysis Calc'd for C ₁₉ H ₁₁ NO ₆ :	C, 65.33; H, 3.17; N, 4.01
Found:	C, 65.11; H, 3.32; N, 3.94

Example 28

15

8-Aza-spiro[4.5]decane-8-carboxylic acid 6-[[1-(dibenzofuran-2-yloxy)carbonyl]piperidin-4-yl]-oxycarbonylamino}-hexyl ester

A solution of the carbonate (1.706 g, 4.88 mmol) produced in Example 27 in 30 ml of chloroform (EtOH free) was added under nitrogen dropwise to a solution of the amine (2.00 g, 4.88 mmol) produced in Example 25 and triethylamine (3.40 ml, 24.4 mmol) in 30 ml of chloroform at room temperature. After the addition the reaction was stirred overnight at room temperature. The reaction was extracted one time with 1N HCl, multiple times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 3.03 g of off-white crystals. Purification on silica (230-400 mesh) using ethyl acetate-methylen chloride as an eluent gave a white solid. Recrystallization of this solid from hexane-ethyl acetate gave 1.3979 g (46%) of the title compound as a white crystalline solid, mp 100-102°C.

30 Analysis Calc'd for C ₃₅ H ₄₅ N ₃ O ₇ :	C, 67.83; H, 7.32; N, 6.78
Found:	C, 67.73; H, 7.29; N, 6.78

Example 29**Carbonic acid (4-nitrophenyl)ester (4-phenylphenyl)ester**

5 A solution of 4-phenylphenol (25.0 g, 0.15 mol) and pyridine (11.89 ml, 0.15 mol) in 250 ml of methylene chloride were added dropwise under nitrogen to a solution of 4-nitrophenyl chloroformate (29.65 g, 0.15 mol) in 200 ml of methylene chloride at ice bath temperature. The reaction was stirred at ice bath temperature for approximately two hours and then overnight at room temperature. The reaction was
10 extracted one time with 1N HCl, multiple times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 46.05 g of light yellow crystals. Recrystallization from methylene chloride-diisopropyl ether gave the title compound as light yellow crystals, mp 138-140°C.

15 Analysis Calc'd for C₁₉H₁₃NO₅: C, 68.06; H, 3.91; N, 4.18
Found: C, 67.99; H, 3.70; N, 4.03

Example 30

20 **8-Aza-spiro[4.5]decane-8-carboxylic acid 6-[[1-(4-phenyl-phenoxy-carbonyl)-piperidine-4-oxycarbonyl]-amino]-hexyl ester**

A solution of the carbonate (0.941 g, 2.8 mmol) produced in Example 29 in 10 ml of anhydrous DMF was added dropwise under nitrogen to a solution of the amine
25 (1.153 g, 2.8 mmol) produced in Example 25 and triethylamine (1.95 ml, 14.0 mmol) in 20 ml of anhydrous DMF at approximately -40°C. The reaction was stirred at -40° for approximately 5 hours and then at room temperature overnight. The reaction was diluted with methylene chloride, extracted one time with 1N HCl, multiple times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to
30 give 1.2066 g of a yellow crystalline solid. Recrystallization from ethyl acetate gave the title compound as a white crystalline solid, mp 110-111°C.

Analysis Calc'd for C₃₅H₄₇N₃O₆: C, 69.40; H, 7.82; N, 6.94
Found: C, 69.36; H, 7.95; N, 6.94

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Example 31**Carbonic acid (4-nitrophenyl)ester (4-pentylphenyl) ester**

5 A solution of 4-pentylphenol (20.1 g, 0.13 mol) and pyridine (10 ml, 0.13 mol) in 300 ml of methylene chloride was added under nitrogen dropwise over 45 minutes to a solution of 4-nitrophenyl chloroformate (25.28 g, 0.13 mol) in 200 ml of methylene chloride at room temperature. After the addition, the reaction was stirred overnight at room temperature. The reaction was extracted one time with 1N HCl, four times with
10 saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 36.97 g of a yellow crystalline solid. Purification of the solid on 450 g of silica gel (230-400 mesh) using 50-60% CH₂Cl₂-hexane as the eluent gave 11.58 g (28%) of the title compound as a yellow crystalline solid, mp 67-69°C.

15 Analysis Calc'd for C₁₈H₁₉NO₅: C, 65.64; H, 5.82; N, 4.25
 Found: C, 65.90; H, 5.85; N, 4.18

Example 32

20 **8-Aza-spiro[4.5]decane-8-carboxylic acid 6-[[1-(4-pentyl-phenoxy)carbonyl]-piperidine-4-oxycarbonyl]-amino}-hexyl ester**

 Analysis Calc'd for C₃₄H₅₃N₃O₆: C, 68.08; H, 8.91; N, 7.00
 Found: C, 68.17; H, 9.08; N, 7.03

25

 A solution of the carbonate (2.21 g, 6.72 mmol) produced in Example 31 in 50 ml of methylene chloride was added dropwise under nitrogen over 45 minutes to a solution of the amine (3.0 g, 6.72 mmol; HCl salt) produced in Example 25, and triethylamine (4.68 ml, 33.6 mmol) in 75 ml of methylene chloride at ice bath temperature. After the
30 addition, the reaction was stirred at ice bath temperature for one hour and then for two days at room temperature. The reaction was extracted one time with 1N HCl, four times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 3.79 g of a light yellow crystalline solid. The solid was chromatographed on 400 g of silica gel (230-400 mesh) using 1:1 EtOAc-hexane as the
35 eluent. The title compound (3.07 g, 76%) was isolated as a white crystalline solid, mp 100-102°C.

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**Example 33**

5 **4-[4-(Hexylcarbamoyloxymethyl)-benzylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester**

A mixture of the carbonate (15.0 g, 31 mmol) produced in Example 3, 4-(aminomethyl)benzoic acid (5.7 g, 38 mmol), and triethylamine (21.8 ml, 160 mmol) in 100 ml of anhydrous dimethylformamide was stirred under nitrogen at 70°C for two
10 hours. The reaction was diluted with ethyl acetate, extracted with 1N HCl, multiple times with water, dried (MgSO₄) and the solvent removed under reduced pressure to give 18.5 g of a light tan solid. Recrystallization of the solid from ethyl acetate gave 9.08 g (59%) of the desired acid compound as a white crystalline solid, mp 165-167°C.

15 Analysis Calc'd for C₂₇H₂₆N₂O₇: C, 66.11; H, 5.34; N, 5.71
Found: C, 65.94; H, 5.31; N, 5.76

Diisopropylcarbodiimide (1.3 ml, 9.0 mmol) in 10 ml of methylene chloride was added under nitrogen dropwise to a solution of the acid (4.4 g, 9.0 mmol) produced in
20 the previous step, N-hydroxysuccinimide (1.0 g, 9.0 mmol) and dimethylaminopyridine (1.1 g, 9.0 mmol) in 50 ml of methylene chloride at ice bath temperature. After the addition the reaction was stirred at ice bath temperature for 1 hour and at room temperature for 2 hours. The solid formed was removed by filtration. The filtrate was extracted with 1N HCl, 5% NaHCO₃, dried (MgSO₄) and the solvent removed under
25 reduced pressure to give 6.92 g of a white solid. Purification of the solid on 400 g of silica gel (230-400 mesh) using ethyl acetate-methylene chloride as the eluent gave the desired succinimide ester (2.88 g, 55%) as a white crystalline solid, mp 141-145°C.

Analysis Calc'd for C₃₁H₂₉N₃O₉: C, 63.37; H, 4.97; N, 7.15
30 Found: C, 63.36; H, 5.08; N, 6.79

Sodium borohydride (420 mg, 11 mmol) was added under nitrogen to a solution of the ester (2.6 g, 4.4 mmol) produced in the previous step in 50 ml of THF at room temperature. The reaction was then stirred overnight. The excess sodium borohydride
35 was destroyed with 1N HCl. The THF was removed under reduced pressure and the residue partitioned between 1N HCl and methylene chloride. The organic layer was separated. The aqueous layer was extracted two times with methylene chloride. The combined extracts were dried (MgSO₄) and the solvent removed under reduced pressure to give 2.14 g of a white foam. Purification of the foam on 200 g of silica gel



(230-400 mesh) using ethyl acetate-methylene chloride as the eluent gave the desired alcohol (991 mg, 47%) as a white crystalline solid, mp 97-101°C.

Analysis Calc'd for $C_{27}H_{28}N_2O_6$: C, 68.05; H, 5.92; N, 5.88
5 Found: C, 67.87; H, 5.84; N, 5.76

A solution of the alcohol (900 mg, 1.89 mmol) produced in the previous step, triethylamine (210 μ l, 1.51 mmol) and hexyl isocyanate (528 mg, 4.15 mmol) in 20 ml of $CHCl_3$ (EtOH free) was refluxed under nitrogen overnight. By TLC starting
10 material remained. An additional 240 mg (1.89 mmol) of hexyl isocyanate was added and the reaction was refluxed overnight. The reaction was extracted two times with 1N HCl, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 1.58 g of a white solid. Recrystallization of the solid from EtOAc-diisopropyl ether gave the title compound as a white crystalline solid, mp 116-118°C.

15 Analysis Calc'd for $C_{34}H_{41}N_3O_7$: C, 67.64; H, 6.85; N, 6.96
Found: C, 67.84; H, 6.71; N, 6.92

Example 34

20

8-Aza-spiro[4.5]decane-8-carboxylic acid 6-[[1-(3-phenoxy-phenoxy-carbonyl)-piperidine-4-oxycarbonyl]-amino]-hexyl ester

A solution of 3-phenoxyphenol (18.3 g, 98 mmol) and pyridine (7.9 ml, 98 mmol)
25 in 300 ml of methylene chloride was added dropwise under nitrogen to a solution of 4-nitrophenyl chloroformate (19.75 g, 98 mmol) in 200 ml of methylene chloride at ice bath temperature. The reaction was stirred at ice bath temperature approximately two hours and then overnight at room temperature. The reaction was extracted one time
30 removed under reduced pressure to give 33.37 g of a brown solid. Five recrystallizations from EtOAc-diisopropyl ether gave 8.6 g (25%) of the desired carbonate as a light tan crystalline solid, mp 105-107°C.

Analysis Calc'd for $C_{19}H_{13}NO_6$: C, 64.96; H, 3.73; N, 3.99
35 Found: C, 65.12; H, 3.57; N, 4.11

A solution of the carbonate (2.36 g, 6.72 mmol), produced in the preceding step, in 50 ml of methylene chloride was added dropwise under nitrogen to a solution of the amine (HCl salt; 3.0 g, 6.72 mmol), produced in Example 25, and triethylamine (4.68
40 ml, 33.6 mmol) in 75 ml of methylene chloride at approximately -70°C. The reaction



was stirred at -70°C for 5 hr and dried at room temperature overnight. The reaction was extracted one time with 1N HCl, multiple times with saturated Na_2CO_3 , dried (MgSO_4) and the solvent removed under reduced pressure to give 3.90 g of an oil. Purification of the oil on 400 g of silica gel (230-400 mesh) using hexane-ethyl acetate as the eluent and then recrystallizing the material isolated from hexane gave the title compound (2.53 g, 61%) as a white crystalline solid, mp $72-120^{\circ}\text{C}$ (Note: material is a single component by TLC).

Analysis Calc'd for $\text{C}_{35}\text{H}_{47}\text{N}_3\text{O}_7$: C, 67.61; H, 7.62; N, 6.76
10 Found: C, 67.59; H, 7.47; N, 6.79

Example 35

15 8-Aza-spiro[4.5]decane-8-carboxylic acid 6-([1-(4-benzyl-phenoxy-carbonyl)-piperidin-4-yl-oxycarbonyl]-amino)-hexyl ester

A solution of 4-hydroxydiphenylmethane (20.0 g, 0.11 mol) and pyridine (8.8 ml, 11 mol) in 300 ml of methylene chloride was added dropwise under nitrogen to a solution of 4-nitrophenyl chloroformate (21.88 g, 11 mol) in 200 ml of methylene chloride at ice bath temperature. The reaction was stirred at ice bath temperature for approximately two hours and at room temperature overnight. The reaction was extracted one time with 1N HCl, four times with saturated Na_2CO_3 , dried (MgSO_4) and the solvent removed under reduced pressure to give 37.71 g of a brown crystalline solid. One recrystallization from EtOAc-diisopropyl ether and then repeated recrystallizations from EtOAc gave 17.64 g (47%) of the desired carbonate as a light yellow crystalline solid, mp $100-102^{\circ}\text{C}$.

Analysis Calc'd for $\text{C}_{20}\text{H}_{15}\text{NO}_5$: C, 68.77; H, 4.33; N, 4.01
30 Found: C, 68.65; H, 4.13; N, 3.91

A solution of the carbonate (2.35 g, 6.72 mmol) produced in the previous step in 50 ml of methylene chloride was added dropwise under nitrogen to a solution of the amine (3.0 g, 6.72 mmol; HCl salt) produced in Example 25, and triethylamine (4.68 ml, 33.6 mmol) in 75 ml of methylene chloride at ice bath temperature. After the addition, the reaction was stirred at ice bath temperature for four hours and at room temperature overnight. The reaction was extracted one time with 1N HCl, four times with saturated Na_2CO_3 , dried (MgSO_4) and the solvent removed under reduced pressure to give 3.34 g of a yellow crystalline solid. Chromatography of the solid on 100 g of silica gel (230-400 mesh) using 1:1 EtOAc-hexane as the eluent gave 0.537 g



(13%) of the title compound as a white crystalline solid, mp 78-130°C (Note: the material is a single component on TLC).

Analysis Calc'd for $C_{30}H_{49}N_3O_6$: C, 69.76; H, 7.97; N, 6.78

5 Found: C, 69.73; H, 7.83; N, 6.78

Example 36

10 8-Aza-spiro[4.5]decane-8-carboxylic acid 1-[1-(4-phenoxy-phenoxy-carbonyl)-piperidin-4-yl-oxycarbonyl]-piperidin-4-yl ester

A solution of the carbonate (13.0 g, 27 mmol) produced in Example 3 in 100 ml of methylene chloride was added under nitrogen dropwise to a solution of 4-hydroxypiperidine (3.0 g, 30 mmol) and triethylamine (3.8 ml, 30 mmol) in 100 ml of methylene chloride at approximately -5°C. The reaction was stirred at -5°C for 2 hours and at room temperature overnight. The reaction was extracted one time with 1N HCl, multiple times with saturated Na_2CO_3 , dried ($MgSO_4$) and the solvent removed under reduced pressure to give 11.4 g of a white solid. Recrystallization of the solid from ethyl acetate-diisopropyl ether gave the desired alcohol (9.73 g, 81%) as a white crystalline solid, mp 122-123°C.

Analysis Calc'd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36

Found: C, 65.46; H, 6.42; N, 6.60

A solution of the alcohol (6.5 g, 14 mmol) produced in the previous step and pyridine (0.93 ml, 11 mmol) in 50 ml of methylene chloride was added dropwise under nitrogen over thirty minutes to a solution of 4-nitrophenyl chloroformate (2.3 g, 11 mmol) in 30 ml of methylene chloride at ice bath temperature. The reaction was stirred at ice bath temperature for two hours and at room temperature overnight. The reaction was extracted one time with 1N HCl, five times with saturated Na_2CO_3 , dried ($MgSO_4$) and the solvent removed under reduced pressure to give 8.10 g of a white foam. Chromatography of the foam on 400 g of silica gel (230-400 mesh) using 1:1 EtOAc-hexane as the eluent gave 5.56 g (62%) of the desired carbonate as a white crystalline solid, mp 140-142°C.

Analysis Calc'd for $C_{31}H_{31}N_3O_{10}$: C, 61.48; H, 5.16; N, 6.94

35 Found: C, 61.64; H, 5.18; N, 6.74

A solution of the carbonate (2.0 g, 3.3 mmol) produced in the previous step in 30 ml of anhydrous dimethylformamide was added dropwise under nitrogen to a solution of 8-aza-spiro[4.5]decane-8-carboxylic acid hydrochloride (670 mg, 3.8 mmol) and



- triethylamine (0.91 ml, 6.6 mmol) in 20 ml of anhydrous dimethylformamide at ice bath temperature. After the addition, the reaction was stirred at ice bath temperature for two hours and at room temperature overnight. The reaction was diluted with ethyl acetate, extracted five times with water, one time with 1N HCl, five times with saturated
- 5 Na_2CO_3 , dried (MgSO_4) and the solvent removed under reduced pressure to give 1.93 g of a white foam. Chromatography on the foam on 100 g of silica gel (230-400 mesh) using 1:1 EtOAc-hexane as the eluent gave 1.18 g (91%) of the title compound as a white solid foam, mp 48-63°C (Note: the compound is a single component by TLC).
- 10 Analysis Calc'd for $\text{C}_{34}\text{H}_{43}\text{N}_3\text{O}_7$: C, 67.42; H, 7.16; N, 6.94
Found: C, 67.05; H, 7.09; N, 6.83

Example 37

- 15 4-[4-(4-Phenyl-butyl)carbamoyloxy]-piperidine-1-carbonyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester

- A solution of the carbonate (2.0 g, 3.3 mmol) produced in step 2 of Example 36 in 30 ml of anhydrous dimethylformamide was added dropwise under nitrogen to a
- 20 solution of 4-phenylbutylamine (0.63 ml, 4.0 mmol) and triethylamine (0.56 ml, 4.0 mmol) in 20 ml of anhydrous dimethylformamide at ice bath temperature. After the addition, the reaction was stirred at ice bath temperature for two hours and overnight at room temperature. The reaction was diluted with ethyl acetate, extracted five times with water, one time with 1N HCl, five times with saturated Na_2CO_3 , dried (MgSO_4),
- 25 and the solvent removed under reduced pressure to give 2.03 g of a clear oil. Chromatography of the oil on 100 g of silica gel (230-400 mesh) using 10% EtOAc- CH_2Cl_2 as the eluent gave 1.72 g (85%) of the title compound as a white solid foam, mp 50-60°C (Note: the compound is a single component by TLC).

- 30 Analysis Calc'd for $\text{C}_{35}\text{H}_{41}\text{N}_3\text{O}_7$: C, 68.27; H, 6.71; N, 6.82
Found: C, 67.87; H, 6.69; N, 6.76

**Example 38****4-(4-Hexylcarbamoyl-cyclohexylcarbamoyloxy)-piperidine-1-carboxylic acid 4-phenoxyphenyl ester**

5

A solution of the carbonate (10.0 g, 21 mmol), produced in Example 3, in 100 ml of anhydrous dimethylformamide was added dropwise under nitrogen to a solution of trans-4-aminocyclohexanol hydrochloride (3.5 g, 23 mmol) and triethylamine (6.4 ml, 46 mmol) in 50 ml of anhydrous dimethylformamide at ice bath temperature. After the addition, the reaction was stirred at ice bath temperature for two hours and overnight at room temperature. The reaction was diluted with ethyl acetate, extracted five times with water, one time with 1N HCl, five times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 8.39 g of a white solid. Recrystallization of the solid from EtOAc-hexane gave 6.45 g (68%) of the desired alcohol as a white crystalline solid, mp 155-156°C.

15

Analysis Calc'd for C₂₅H₃₀N₃O₆: C, 66.06; H, 6.65; N, 6.16
Found: C, 66.08; H, 6.67; N, 6.01

20

A solution of the alcohol (2.0 g, 4.4 mmol) produced in the previous step, triethylamine (0.49 ml, 3.5 mmol) and hexyl isocyanate (1.2 g, 9.7 mmol) in 20 ml of chloroform (EtOH free) was refluxed under nitrogen until the reaction was complete by TLC. The reaction was extracted two times with 1N HCl, dried (MgSO₄) and the solvent removed under reduced pressure to give 2.80 g of a white solid. Recrystallization of the solid from ethyl acetate gave 2.06 g (81%) of the title compound as a white crystalline solid, mp 190-191°C.

25

Analysis Calc'd for C₃₂H₄₃N₃O₇: C, 66.07; H, 7.45; N, 7.22
Found: C, 66.10; H, 7.50; N, 7.27

30

Example 39**4-[6-(Hexylcarbamoyloxy)-hexylcarbamoyloxy]-piperidine-1-carboxylic acid 4-cyclohexyl-phenyl ester**

35

A solution of 4-cyclohexylphenol (20.0 g, 0.11 mol) and pyridine (9.2 ml, 0.11 mol) in 300 ml of methylene chloride was added dropwise under nitrogen to a solution of 4-nitrophenyl chloroformate (22.88 g, 11 mmol) in 200 ml of methylene chloride at ice bath temperature. The reaction was stirred at ice bath temperature for



approximately two hours and at room temperature overnight. The reaction was extracted one time with 1N HCl, four times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 37.23 g of a yellow solid. Chromatography of the solid on 500 g of silica gel (230-400 mesh) using 40% CH₂Cl₂-hexane as the eluent and then recrystallization of the material isolated from diisopropyl ether gave 18.9 g (49%) of the desired carbonate as a white solid, mp 93-94°C.

Analysis Calc'd for C₁₉H₁₉NO₅: C, 66.85; H, 5.61; N, 4.10

Found: C, 66.85; H, 5.56; N, 4.16

10

A solution of the carbonate (2.76 g, 8.08 mmol) produced in the previous step in 50 ml of methylene chloride was added dropwise under nitrogen to a solution of (6-hexylcarbamoyloxy-hexyl)carbamic acid piperidin-4-yl ester (3.0 g, 8.08 mmol) and triethylamine (3.38 ml, 24.2 mmol) in 75 ml of methylene chloride at ice bath temperature. After the addition, the reaction was stirred at ice bath temperature for 3 hours and overnight at room temperature. The reaction was extracted one time with 1N HCl, four times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 4.27 g of a solid. Recrystallization of the solid from EtOAc-diisopropyl ether gave 2.69 g (58%) of the title compound as a white crystalline compound, mp 94-96°C.

20

Analysis Calc'd for C₃₂H₅₁N₃O₆: C, 66.99; H, 8.96; N, 7.32

Found: C, 66.70; H, 8.96; N, 7.36

25

Example 40

8-Aza-spiro[4.5]decane-8-carboxylic acid 4-([1-(4-phenoxy-phenoxy-carbonyl)-piperidine-4-carbonyl]amino)-cyclohexyl ester

A solution of the alcohol (3.30 g, 7.3 mmol) produced in step 1 of Example 38 and pyridine (0.59 ml, 7.3 mmol) in 50 ml of methylene chloride was added dropwise under nitrogen to a solution of 4-nitrophenyl chloroformate (1.5 g, 7.3 mmol) in 30 ml of methylene chloride at ice bath temperature. The reaction was stirred at ice bath temperature for 2 hours and then overnight at room temperature. The reaction was extracted one time with 1N HCl, five times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 4.42 g of an off-white solid. Recrystallization of the solid from EtOAc-diisopropyl ether gave 2.36 g (52%) of the desired carbonate as a white crystalline solid, mp 152-155°C.

30

35



Analysis Calc'd for $C_{32}H_{33}N_3O_{10}$: C, 62.03; H, 5.37; N, 6.78
Found: C, 62.42; H, 5.45; N, 6.78

5 A solution of the carbonate (2.0 g, 3.2 mmol) produced in the previous step in 30 ml of anhydrous dimethylformamide was added dropwise under nitrogen to a solution of 8-aza-spiro-[4.5]-decane-8-carboxylic acid hydrochloride (680 mg, 3.9 mmol) and triethylamine (1.0 ml, 7.1 mmol) in 20 ml of anhydrous dimethylformamide at ice bath temperature. After the addition, the reaction was stirred at ice bath temperature for two hours and overnight at room temperature. The reaction was diluted with ethyl acetate, 10 extracted five times with water, one time with 1N HCl, five times with saturated Na_2CO_3 , dried ($MgSO_4$) and the solvent removed under reduced pressure to give 2.12 g of an off-white solid. Recrystallization of the solid from EtOAc gave 1.42 g (71%) of the title compound as a white crystalline solid, mp 230-231°C.

15 Analysis Calc'd for $C_{35}H_{45}N_3O_7$: C, 67.83; H, 7.32; N, 6.78
Found: C, 67.74; H, 7.36; N, 6.74

Example 41

20 4-(4-Hexylcarbamoyl-piperidine-1-carboxyloxy)-piperidine-1-carboxylic acid 4-phenoxyphenyl ester

A solution of the alcohol (2.0 g, 4.54 mmol) produced in step 1 of Example 36, triethylamine (0.51 ml, 3.36 mmol) and hexyl isocyanate (690 mg, 5.45 mmol) in 20 ml 25 of $CHCl_3$ (EtOH free) was refluxed under nitrogen for approximately 24 hours. An additional 580 mg (4.56 mmol) of hexyl isocyanate was added and the reaction refluxed for 6 hours and at room temperature for 48 hours. One more equivalent of hexyl isocyanate was added and the reaction refluxed for approximately 24 hours. The reaction was extracted two times with 1N HCl, dried ($MgSO_4$) and the solvent removed 30 under reduced pressure to give 2.92 g of a clear oil. Purification of the oil by chromatography on silica gel (230-400 mesh) using 1:1 EtOAc-hexane as the eluent gave 1.98 g (77%) of the title compound as a clear oil, MS m/e 567 (M^+).

35 Analysis Calc'd for $C_{31}H_{41}N_3O_7$: C, 65.59; H, 7.28; N, 7.40
Found: C, 65.05; H, 7.40; N, 7.44

**Example 42****4-{4-[(Hexylcarbamoyloxy)methyl]-(cyclohexylmethylcarbamoyloxy)-piperidine-1-carboxylic acid 4-phenoxyphenyl ester**

5

A solution of the carbonate (1.95 g, 4.1 mmol) produced in Example 3 in 20 ml of anhydrous dimethylformamide was added dropwise under nitrogen to a solution of 4-(aminomethyl)-cyclohexanemethanol (700 mg, 4.9 mmol) and triethylamine (0.68 ml, 4.9 mmol) in 10 ml of anhydrous dimethylformamide at ice bath temperature. The reaction was stirred at ice bath temperature for approximately two hours and at room temperature overnight. The reaction was diluted with ethyl acetate, extracted five times with water, one time with 1N HCl, five times with saturated Na₂CO₃, dried (MgSO₄) and the solvent removed under reduced pressure to give 1.89 g of a yellow oil. Chromatography on the oil on 200 g of silica gel (230-400 mesh) using 20% EtOAc-CH₂Cl₂ as the eluent gave 775 mg (39%) of the desired alcohol as a white crystalline solid, mp 97-110°C (Note: the compound is a single component by TLC).

Analysis Calc'd for C₂₇H₃₄N₂O₆: C, 67.20; H, 7.10; N, 5.81
Found: C, 66.92; H, 7.09; N, 5.76

20

A solution of the alcohol (700 mg, 1.45 mmol) produced in the previous step, triethylamine (0.16 ml, 1.16 mmol) and hexyl isocyanate (406 mg, 3.19 mmol) in 10 ml of CHCl₃ (EtOH free) was refluxed under nitrogen for 55 hours. The reaction was extracted two times with 1N HCl, dried (MgSO₄) and the solvent removed under reduced pressure to give 987 mg of an off-white solid. Recrystallization of the solid from EtOAc-diisopropyl ether gave 642 mg (73%) of the title compound as a white crystalline solid, mp 99-102°C.

Analysis Calc'd for C₃₄H₄₇N₃O₇: C, 66.97; H, 7.77; N, 6.89
Found: C, 66.91; H, 7.74; N, 7.05

30

In-Vitro and In-Vivo Pharmacological Procedures

- 35 1. The ability of the compounds of this invention to inhibit acyl-coenzyme A: cholesterol acyltransferase was established by initially showing that they inhibited intracellular cholesterol esterification by subjecting them to the standard experimental test procedure of Ross et al., J. Biol. Chem. 259, 814 (1984). The results are reported in

the following table, where available, in terms of the percent inhibition at 25 μM and the IC_{50} (μM).

2. The ability of the compounds of this invention to inhibit the formation of cholesteryl esters and thereby interfere with and prevent assimilation of cholesterol into the lymphatic system and ultimately the blood stream was established by incubating the compounds at 37C. with a mixture of cholesterol and oleic acid in the presence of buffered cholesterol esterase [(EC 3.1.1.13) Sigma Company, St. Louis, Mo., U.S.A., No. C-1892, from bovine pancreas] and measuring the amount of ester formed, according to the procedure of Field. J. of Lipid Research, 25, 389 (1984). The concentration of test compound that inhibits one-half of the ester formation (IC_{50} μM) is given in the following table.

The *in vivo* cholesterol absorption studies were conducted in normal rats by oral administration of the compound being tested in propylene glycol and olive oil followed by oral administration of [4- ^{14}C] cholesterol in propylene glycol and olive oil, otherwise following the procedure of Cayen et al., J. Lipid Res. 20 162 (1979). The serum radioactivity was measured at six hours after dosing. The results of this study are reported in the following table as percent decrease compared to control at the dose stated.

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Table
In Vitro Results
 % inhibition at
 25 μ M/IC₅₀ (μ M)

In Vivo Results
 Effect on Absorption of
¹⁴C-cholesterol - 6 hr - normal

Examples

<u>Compound</u>	<u>ACAT</u>	<u>CEH</u>	<u>% Decrease (dose mg/kg)</u>
6	97%/1.78	0.42	59% (3)
7	76%/6.41	0.67	42% (20)
8	98%/2.34	0.54	65% (3)
9	95%/1.59	0.08	49% (10)
10	83%/5.0	0.62	22% (20)
11	24%	28.2	6% (20)
12	83%/1.72	0.31	76% (10)
13	47%	15.5	20% (20)
14	41%	> 100	2% (20)
16	NT	0.73	68% (10)
18	NT	0.51	50% (10)

5

Thus, the representative compounds of this invention reduce absorption of cholesterol into the blood and thus can be used in the treatment of atherosclerosis, familial hypercholesterolemia, hyperlipidemia and like diseases where a reduction in cholesterol absorption is desired. The dosage requirement for therapeutic use of the anti-hypercholesterolemic agents of this invention will vary according to the particular compound chosen as well as the age of the patient and severity and nature of the disease being treated. Therapy should be initiated at lower doses, the dosage thereafter being increased, if necessary, to produce the desired effect. In general, the compounds of this invention are most desirably administered at a concentration that will generally afford effective results without causing any harmful or deleterious side effects. Based upon the *in vivo* potency of the representative anticholesterolemic agents of this invention as reported in the table, the initial dosing will be from about 0.5 to 6 mg/kg with a projected maximum dose of about 100 mg/kg. The preferred dosage range will be from about 1 to 50 mg/kg.

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This invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

5

The compounds of formula (I) can be formulated into oral dosage forms such as tablets, capsules and the like. The compounds can be administered alone or by combining them with conventional carriers, such as magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, low melting wax, cocoa butter and the like. Diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, tablet-disintegrating agents and the like may be employed. The compounds may be encapsulated with or without other carriers. In all cases, the proportion of active ingredients in said compositions both solid and liquid will be sufficient at last to impart the desired activity thereto on oral administration. The compounds may also be injected parenterally in which case they are used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

10

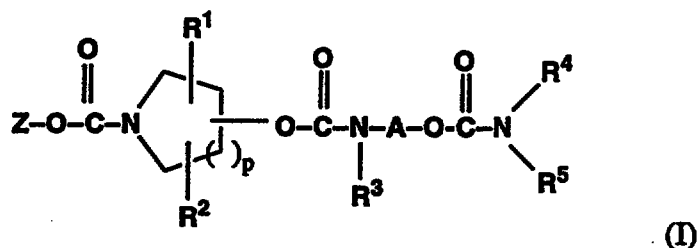
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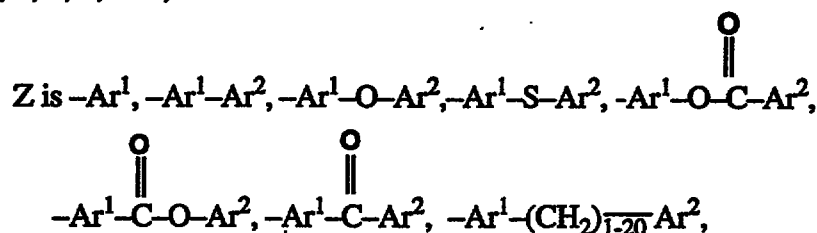
CLAIMS:

1. A compound having the formula:



wherein

p is 0, 1, 2, 3, or 4;



or $-\text{Ar}^1-(\text{CR}^6=\text{CR}^6)_{1-3}-\text{Ar}^2$ or $-\text{Ar}^1-\text{NR}^7-\text{Ar}^2$; where R^6 is hydrogen or C_1-C_8 alkyl and R^7 is hydrogen, C_1-C_8 alkyl, C_1-C_8 alkylcarbonyl or C_1-C_8 alkoxy carbonyl;

and Ar^1 and Ar^2 are, independently, selected from phenyl, naphthyl, furanyl, benzofuranyl, dibenzofuranyl, pyridinyl, pyrimidinyl, pyrazinyl, thienyl, benzothienyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, benzthiazolyl, isoxazolyl, benzisoxazolyl, indenyl, indolyl, quinolinyl, isoquinolinyl, benzotriazolyl, carbazolyl, benzimidazolyl, or fluorenyl,

and Ar^1 and Ar^2 , independently, are optionally substituted by fluorine, chlorine, bromine, iodine, cyano, nitro, $-\text{CO}_2\text{H}$, C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_8 cycloalkyl, C_1-C_{20} alkoxy, C_1-C_{20} alkyl-O-(C_1-C_{20} alkyl)-, C_1-C_{20} alkyl-O-(C_1-C_{20} alkyl)-O-, trifluoromethyl, C_1-C_{20} alkylcarbonyl, C_3-C_8 cycloalkyloxy, C_1-C_{20} alkylcarbonyloxy, C_1-C_{20} alkoxy carbonyl, mono or di

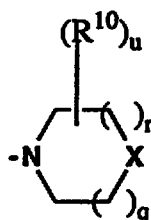


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C₁-C₂₀ alkylaminocarbonyl, tetrazolyl, -OH, -(CH₂)₁₋₆-OH, -SH, -NH₂ or -(CH₂)₁₋₆-NR⁸R⁹

where R⁸ is C₁-C₂₀ alkyl, C₁-C₂₀ alkylcarbonyl, C₁-C₂₀ alkoxy carbonyl and R⁹ is hydrogen or C₁-C₂₀ alkyl or R⁸ and R⁹ together with the interposed nitrogen atom form a heterocyclic ring of the formula:



where q is 0, 1 or 2, r is 1 or 2, u is 0, 1 or 2, R¹⁰ is C₁-C₈ alkyl and X is -O-, -S-, -NR¹¹- where R¹¹ is H, C₁-C₂₀ alkyl or benzyl or -CR¹²R¹³- where R¹² is H, OH, C₁-C₂₀ alkyl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylcarbonyloxy, Ar¹ or -(CH₂)₁₋₁₀-Ar¹, R¹³ is H, C₁-C₂₀ alkyl, or R¹² and R¹³ together with the interposed carbon forms a 3 to 8 membered carbocyclic ring;

A is a bridging group selected from:

a saturated or unsaturated, straight or branched hydrocarbon chain of 1 to 20 carbons and which may have 1 to 6 sites of olefinic and/or acetylenic unsaturation;

a group of the formula:



where m and n are each 1 to 19, m+n is 2 to 20 and W is a group selected from -O-, -S-, or -NR¹⁴- where R¹⁴ is hydrogen, C₁-C₂₀ alkyl, C₁-C₂₀ alkylcarbonyl, C₁-C₂₀ alkoxy carbonyl, or benzyl;

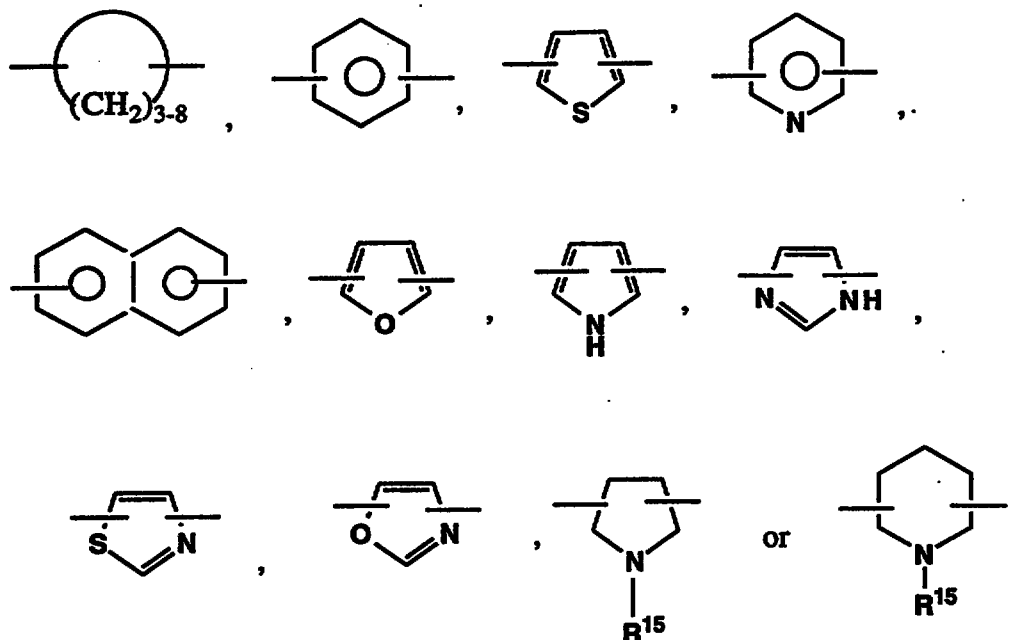
a group of the formula:



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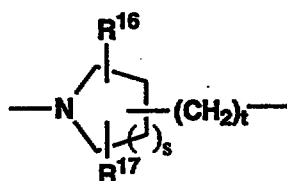


where b and c are each 0 to 20, b+c is 1 to 20 and Y is selected from the group consisting of:



where R^{15} is H, C_1 - C_8 alkyl, C_1 - C_{20} alkylcarbonyl, C_1 - C_{20} alkoxy carbonyl, or benzyl; or

A together with R^3 and the interposed nitrogen form a heterocyclic moiety of the formula:



where s is 0, 1, 2, 3 or 4, t is 0 to 15, and R^{16} and R^{17} are, independently, hydrogen, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, C_1 - C_8 alkylcarbonyl, hydroxy, cyano, C_1 - C_8 alkylcarbonyloxy, or $-(CH_2)_{0-6}-NR^{18}R^{19}$ where R^{18} is C_1 - C_8 alkyl, C_1 - C_8 alkoxy carbonyl, or C_1 - C_8 alkylcarbonyl and R^{19} is hydrogen or C_1 - C_8 alkyl;

R^1 and R^2 are independently hydrogen, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, C_1 - C_8 alkylcarbonyl, hydroxy, cyano, C_1 - C_8 alkylcarbonyloxy, or



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$-(CH_2)_{0-6}-NR^{18}R^{19}$ where R^{18} is C_1-C_8 alkyl, C_1-C_8 alkoxy carbonyl, or C_1-C_8 alkyl carbonyl and R^{19} is hydrogen or C_1-C_8 alkyl;

R^3 is H, C_1-C_8 alkyl or C_7-C_{15} arylalkyl where aryl is phenyl optionally substituted with a C_1-C_6 alkyl group or is combined with A to form a heterocyclic ring as described above;

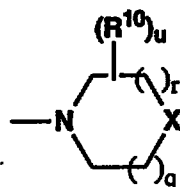
R^4 and R^5 are independently hydrogen, C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl,

$-(CH_2)_{1-20}(C_{3-10} \text{ cycloalkyl})$, $-(CH_2)_{1-20}Ar^1$, or $-(CH_2)_{1-20}NR^{20}R^{21}$

where R^{20} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_1-C_{20} alkyl carbonyl,

C_1-C_{20} alkoxy carbonyl or benzyl; and R^{21} is hydrogen or C_1-C_{20} alkyl, wherein Ar^1 is defined above, or

R^4 and R^5 together with the interposed nitrogen form a heterocyclic moiety of the formula:



where r , q , u , R^{10} and X are as defined above,

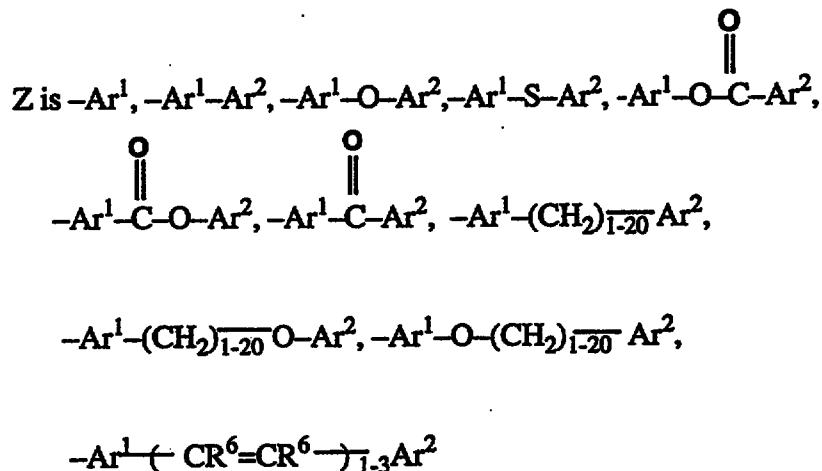
providing that when more than one of Ar^1 , R^6 , R^{10} , R^{18} , R^{19} , n , r , X or q is present they may be the same or different, or a pharmaceutically acceptable salt thereof.



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2. A compound according to Claim 1 wherein



where R^6 is H or $\text{C}_1\text{-C}_8$ alkyl, or $-\text{Ar}^1-\text{NR}^7-\text{Ar}^2$ where R^7 is hydrogen, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_1\text{-C}_8$ alkylcarbonyl or $\text{C}_1\text{-C}_8$ alkoxy carbonyl and Ar^1 and Ar^2 are selected from phenyl, naphthyl, furanyl, benzofuranyl, dibenzofuranyl, pyridinyl, thienyl, benzothienyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, benzthiazolyl, isoxazolyl, benzisoxazolyl, indenyl, indolyl, quinolinyl, isoquinolinyl, carbazolyl, benzimidazolyl or fluorenyl; and Ar^1 and Ar^2 may be optionally substituted by fluorine, chlorine, bromine, iodine, cyano, nitro, $-\text{CO}_2\text{H}$, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_1\text{-C}_8$ alkoxy, $\text{C}_2\text{-C}_8$ alkenyl, trifluoromethyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_3\text{-C}_8$ cycloalkyloxy, $\text{C}_1\text{-C}_8$ alkylcarbonyl, $\text{C}_1\text{-C}_8$ alkoxy carbonyl, $\text{C}_1\text{-C}_8$ alkylcarbonyloxy, $-\text{NH}_2$, $-(\text{CH}_2)_{1-6}-\text{NR}^8\text{R}^9$ where R^8 is $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_1\text{-C}_8$ alkylcarbonyl or $\text{C}_1\text{-C}_8$ alkoxy carbonyl, and R^9 is hydrogen or $\text{C}_1\text{-C}_8$ alkyl.

3. A compound according to Claim 1 or Claim 2 wherein

A is a bridging group selected from:

a saturated or unsaturated, straight or branched hydrocarbon chain of 1 to 20 carbon atoms which may have 1 to 6 sites of olefinic and/or acetylenic unsaturation;

a group of the formula:



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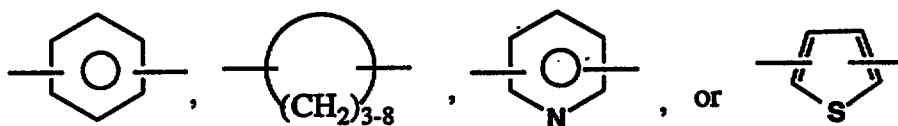


where m and n are 1 to 19, $m+n$ is 2 to 20 and W is a group selected from $-O-$, $-S-$, or $-NR^{14}$ where R^{14} is hydrogen, C_1 - C_8 alkyl, C_1 - C_8 alkylcarbonyl, C_1 - C_8 alkoxy carbonyl or benzyl;

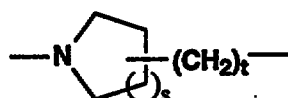
a group of the formula:



where b and c are 0 to 20, $b+c$ is 1 to 20, and Y is selected from the group consisting of:

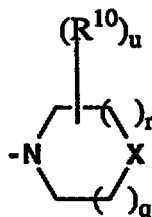


or A together with R^3 and the interposed nitrogen form a heterocyclic moiety of the formula:



where s is 0, 1, 2 or 3 and t is 0 to 15.

4. A compound according to any one of Claims 1 to 3 wherein R^4 and R^5 are, independently, hydrogen, C_1 - C_{12} alkyl, C_2 - C_8 alkenyl, C_3 - C_8 cycloalkyl, $-(CH_2)_{1-10}$ (C_3 - C_{10} cycloalkyl), $-(CH_2)_{1-10}Ar^1$, $-(CH_2)_{1-10}-NR^{20}R^{21}$ where R^{20} is C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_1 - C_8 alkylcarbonyl, C_1 - C_8 alkoxy carbonyl or benzyl, and R^{21} is hydrogen or C_1 - C_8 alkyl, or R^4 and R^5 together with the interposed nitrogen forms a heterocyclic moiety of the formula:



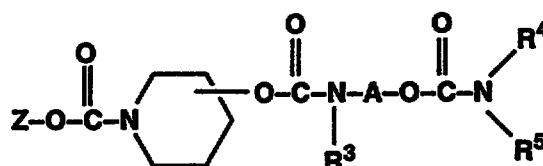
where q is 0, 1 or 2, r is 1 or 2, u is 0, 1 or 2, R^{10} is C_1 - C_8 alkyl and X is $-O-$, $-S-$, $-NR^{11}$ where R^{11} is hydrogen, C_1 - C_8 alkyl or benzyl or X is $CR^{12}R^{13}$ where R^{12} is hydrogen, hydroxy, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, and R^{13} is hydrogen or

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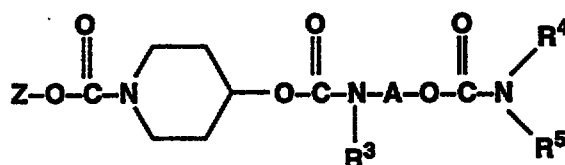
C_1 - C_8 alkyl, or R^{12} and R^{13} together with the interposed carbon forms a 3 to 8 membered carbocyclic ring.

5. A compound according to any one of Claims 1 to 4 having the formula:



in which Z, R^3 , R^4 and R^5 are defined in any one of Claims 1 to 4 or a pharmaceutically salt thereof.

6. A compound according to any one of Claims 1 to 4 having the formula:



in which Z, R^3 , R^4 and R^5 are defined in any one of Claims 1 to 4 or a pharmaceutically salt thereof.

7. A compound according to any one of Claims 1 to 6 wherein Ar^1 is phenyl or naphthyl.
8. A compound according to any one of Claims 1 to 7 wherein Z is 4-phenoxyphenyl.
9. A compound according to Claim 1 which is 4-[6-(hexylcarbamoyloxy)hexylcarbamoyl-oxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester, or a pharmaceutically acceptable salt thereof.
10. A compound according to Claim 1 which is 8-aza-spiro[4.5]decane-8-carboxylic acid 6-[[1-(4-phenoxy-phenoxy-carbonyl)-piperidine-4-oxycarbonyl]amino]hexyl ester, or a pharmaceutically acceptable salt thereof.
11. A compound according to Claim 1 which is one of the following:



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- 4-[6-(dihexyl-carbamoyloxy)-hexylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,
- 4-[6-(piperidine-1-carbonyloxy)-hexylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,
- 4-[6-dibenzyl-carbamoyloxy)-hexyl-carbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,
- 4-[12-(hexylcarbamoyloxy)-dodecylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,
- 4-{6-[4-(2,2-dimethyl-propyl)-benzyl]-heptyl-carbamoyloxy]-hexyl-carbamoyloxy}-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,
- (Z)-4-[6-(octadec-9-enylcarbamoyloxy)-hexylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,
- (Z)-4-[12-(octadec-9-enylcarbamoyloxy)-dodecylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,
- 4-[6-(hexylcarbamoyloxy)-propylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,
- 4-[9-(nonylcarbamoyloxy)-propylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,
- 8-aza-spiro[4.5]decane-8-carboxylic acid 6-{{1-(4-phenoxy-phenoxy-carbonyl)-piperidine-4-oxycarbonyl]-amino}-propyl ester,
- 8-aza-spiro[4.5]decane-8-carboxylic acid 6-{{1-(4-nitro-phenoxy-carbonyl)-piperidine-4-oxycarbonyl]-amino}hexyl ester,
- 8-aza-spiro[4.5]decane-8-carboxylic acid 6-{{1-(dibenzofuran-2-yloxy-carbonyl)piperidine-4-yl]-oxycarbonylamino}-hexyl ester,
- 8-aza-spiro[4.5]decane-8-carboxylic acid 6-{{1-(4-phenyl-phenoxy-carbonyl)-piperidine-4-oxycarbonyl]-amino}-hexyl ester,



8-aza-spiro[4.5]decane-8-carboxylic acid 6-[[1-(4-pentyl-phenoxy-carbonyl)-piperidine-4-oxycarbonyl]-amino]-hexyl ester,

4-[4-(hexylcarbamoyloxymethyl)-benzylcarbamoyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,

8-aza-spiro[4.5]decane-8-carboxylic acid 6-[[1-(3-phenoxy-phenoxy-carbonyl)-piperidine-4-oxycarbonyl]-amino]-hexyl ester,

8-aza-spiro[4.5]decane-8-carboxylic acid 6-[[1-(4-benzyl-phenoxy-carbonyl)-piperidine-4-yl-oxycarbonyl]-amino]-hexyl ester,

8-aza-spiro[4.5]decane-8-carboxylic acid 1-[1-(4-phenoxy-phenoxy-carbonyl)-piperidine-4-yl-oxycarbonyl]-piperidine-4-yl ester,

4-[4-(4-phenyl-butylcarbamoyloxy)-piperidine-1-carbonyloxy]-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,

4-(4-hexylcarbamoyl-cyclohexylcarbamoyloxy)-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,

4-[6-(hexylcarbamoyloxy)-hexylcarbamoyloxy]-piperidine-1-carboxylic acid 4-cyclohexyl-phenyl ester,

8-aza-spiro[4.5]decane-8-carboxylic acid 4-[[1-(4-phenoxy-phenoxy-carbonyl)-piperidine-4-carbonyl]amino]-cyclohexyl ester,

4-(4-hexylcarbamoyl-piperidine-1-carbonyloxy)-piperidine-1-carboxylic acid 4-phenoxyphenyl ester,

or

4-{4-[(hexylcarbamoyloxy)methyl]-(cyclohexylmethylcarbamoyl)oxy}piperidine-1-carboxylic acid 4-phenoxyphenyl ester.

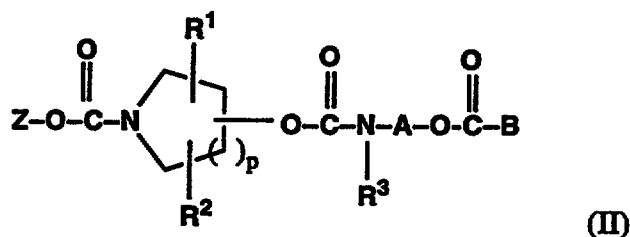
or a pharmaceutically acceptable salt thereof.

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12. A process for preparing a compound of formula (I) as claimed in Claim 1 which comprises one of the following:

a) reacting a compound of formula:



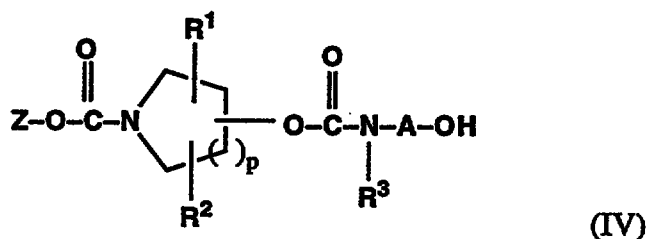
wherein p , R^1 , R^2 , R^3 , A and Z are as defined in Claim 1 and B is a leaving group such as chlorine, p -nitrophenyl or imidazolyl, with an amine of formula:



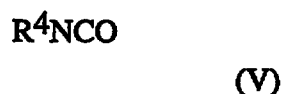
wherein R^4 and R^5 are as defined above, to give a compound of formula I as defined above,

or

b) reacting a compound of formula:



wherein p , R^1 , R^2 , R^3 , A and Z are as defined in Claim 1, with an isocyanate of formula:



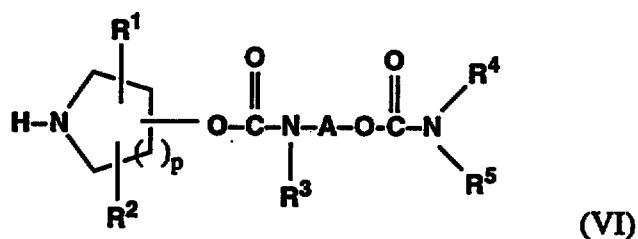
wherein R^4 is as defined above excepting hydrogen, to give a corresponding compound of formula I where R^4 is as defined in connection with formula V and R^5 is hydrogen,

or

c) reacting a compound of formula:

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wherein p, R¹⁻⁵ and A are as defined above with a compound of formula:



wherein Z is as defined above and B is a leaving group, e.g. p-nitrophenyl, chlorine or imidazolyl, and
if desired after any of the aforementioned processes isolating the compound of formula I as a pharmaceutically acceptable salt or as the free base.

13. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in Claim 1 and a pharmaceutically acceptable carrier.

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