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SPIROCYCLOALKYL-SUBSTITUTED AZETIDINONES USEFUL AS HYPOCHOLESTEROLEMIC AGENTS

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(56) Prior Art Documents
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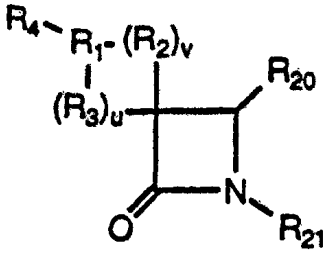
(57) The present invention relates to spirocycloalkyl-substituted azetidinones useful as hypocholesterolemic agents in the treatment and prevention of atherosclerosis, and to the combination of a spirocycloalkyl-substituted azetidinone of this invention and a cholesterol biosynthesis inhibitor for the treatment and prevention of atherosclerosis.

Claim

1. A compound represented by the formula



or a pharmaceutically acceptable salt thereof, wherein:

R_1 is

$-\overset{|}{C}H-$, $-\overset{|}{C}$(lower alkyl)-, $-\overset{|}{C}F-$, $-\overset{|}{C}(OH)-$, $-\overset{|}{C}(C_6H_5)-$, $-\overset{|}{C}(C_6H_4\text{-}R_{15})-$,

$-\overset{|}{N}-$ or $-\overset{|}{\overset{+}{N}}O^-$;

R_2 and R_3 are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)-, -C(di-lower alkyl)-, -CH=CH- and

.../2

-C(lower alkyl)=CH-; or R_1 together with an adjacent R_2, or R_1 together with an adjacent R_3, form a -C =CH- or a -C =C(lower alkyl)- group;

u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R_2 is -CH=CH- or -C(lower alkyl)=CH-, v is 1; provided that when R_3 is -CH=CH- or -C(lower alkyl)=CH-, u is 1; provided that when v is 2 or 3, the R_2's can be the same or different; and provided that when u is 2 or 3, the R_3's can be the same or different;

R_4 is B-$(CH_2)_m$C(O)-, wherein m is 0, 1, 2, 3, 4 or 5;

B-$(CH_2)_q$-, wherein q is 0, 1, 2, 3, 4, 5 or 6;

B-$(CH_2)_e$-Z-$(CH_2)_r$-, wherein Z is -O-, -C(O)-, phenylene, -N(R_8)- or -S(O)$_{0-2}$-, e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5, provided that the sum of e and r is 0, 1, 2, 3, 4, 5 or 6;

B-(C_2-C_6 alkenylene)-; B'-(C_4-C_6 alkadienylene)-;

B-$(CH_2)_t$-Z-(C_2-C_6 alkenylene)-, wherein Z is as defined above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

B-$(CH_2)_f$-V-$(CH_2)_g$-, wherein V is C_3-C_6 cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6;

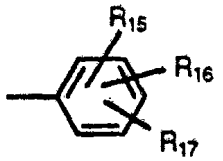
B-$(CH_2)_t$-V-(C_2-C_6 alkenylene)- or B'-(C_2-C_6 alkenylene)-V-$(CH_2)_f$-, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

B-$(CH_2)_a$-Z-$(CH_2)_b$-V-$(CH_2)_d$-, wherein Z and V are as defined above and a, b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6;

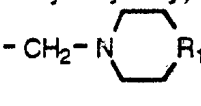
T-$(CH_2)_s$-, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

R_1 and R_4 together form the group B-CH=C- ;

B is indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, or



W is 1 to 3 substituents independently selected from the group

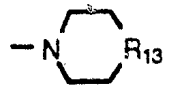
consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, R_7-benzyl, benzyloxy, R_7-benzyloxy, phenoxy, R_7-phenoxy, dioxolanyl, NO_2, $-N(R_8)(R_9)$, $N(R_8)(R_9)$-lower alkylene-, $N(R_8)(R_9)$-lower alkylenyloxy-, OH, halogeno, -CN, $-N_3$, $-NHC(O)OR_{10}$, $-NHC(O)R_{10}$, $R_{11}O_2SNH-$, $(R_{11}O_2S)_2N-$, $-S(O)_2NH_2$, $-S(O)_{0-2}R_8$, tert-butyldimethylsilyloxymethyl, $-C(O)R_{12}$, $-COOR_{19}$, $-CON(R_8)(R_9)$, $-CH=CHC(O)R_{12}$, -lower alkylene-$C(O)R_{12}$, $R_{10}C(O)$(lower alkylenyloxy)-, $N(R_8)(R_9)C(O)$(lower alkylenyloxy)- and  for substitution on ring carbon atoms, and the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, $-C(O)OR_{10}$, $-C(O)R_{10}$, OH, $N(R_8)(R_9)$-lower alkylene-, $N(R_8)(R_9)$-lower alkylenyloxy-, $-S(O)_2NH_2$ and 2-(trimethylsilyl)-ethoxymethyl;

" is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO_2, $-N(R_8)(R_9)$, OH or halogeno;

R_8 and R_9 are independently H or lower alkyl;

R_{10} is lower alkyl, phenyl, R_7-phenyl, benzyl or R_7-benzyl;

R_{11} is OH, lower alkyl, phenyl, benzyl, R_7-phenyl or R_7-benzyl;

R_{12} is H, OH, alkoxy, phenoxy, benzyloxy,  , $-N(R_8)(R_9)$, lower alkyl, phenyl or R_7-phenyl;

R_{13} is -O-, $-CH_2-$, -NH-, -N(lower alkyl)- or $-NC(O)R_{19}$;

R_{15}, R_{16} and R_{17} are independently selected from the group consisting of H and the groups defined for W; or R_{15} is hydrogen and R_{16} and R_{17}, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

R_{19} is H, lower alkyl, phenyl or phenyl lower alkyl; and

R_{20} and R_{21} are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

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(75) Inventors/Applicants *(for US only)*: DUGAR, Sundeep [IN/US]; 749 Wingate Drive, Bridgewater, NJ 08807 (US). CLADER, John, W. [US/US]; 428 North Union Avenue, Cranford, NJ 07016 (US). BURNETT, Duane, A. [US/US]; 59 Helen Street, Fanwood, NJ 07023 (US). BROWNE, Margaret, E. [US/US]; 84 Park Street, Montclair, NJ 07042 (US). DAVIS, Harry, R. [US/US]; 64 River Bend Road, Berkeley Heights, NJ 07922 (US).

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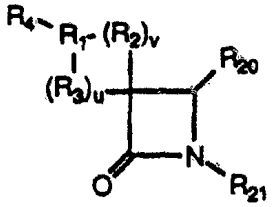


(1)

-CH-, -C(lower alkyl)-, -CF-, -C(OH)-, -C(C_6H_5)-, -C(C_6H_4-R_{15})-, -N- or -N→O (A)

B-CH=C- (A')

(57) Abstract

Novel compounds of formula (1) or a pharmaceutically acceptable salt thereof, wherein R_1 is (A); R_2 and R_3 are independently selected from the group consisting of -CH_2-, -CH(lower alkyl)-, -C(di-lower alkyl)-, -CH=CH- and -C(lower alkyl)=CH-; or R_1 together with an adjacent R_2, or R_1 together with an adjacent R_3, form a -CH=CH- or a -CH=C(lower alkyl)- group; u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R_2 is -CH=CH- or -C(lower alkyl)=CH-, v is 1; provided that when R_3 is -CH=CH- or -C(lower alkyl)=CH-, u is 1; provided that when v is 2 or 3, the R_2's can be the same or different; and provided that when u is 2 or 3, the R_3's can be the same or different; R_4 is B-$(CH_2)_m$C(O)-, wherein m is 0-5; B-$(CH_2)_q$-, wherein q is 0-6; B-$(CH_2)_e$-Z-$(CH_2)_r$-, wherein Z is -O-, -C(O)-, phenylene, -N(R_8)- or -S$(O)_{0-2}$-, e is 0-5 and r is 0-5, provided that the sum of e and r is 0-6; B-(C_2-C_6 alkenylene)-; B'-(C_4-C_6 alkadienylene)-; B-$(CH_2)_t$-Z-(C_2-C_6 alkenylene)-, wherein t is 0-3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2-6; B-$(CH_2)_f$-V-$(CH_2)_g$-, wherein V is C_3-C_6 cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6; B-$(CH_2)_t$-V-(C_2-C_6 alkenylene)- or B'-(C_2-C_6 alkenylene)-V-$(CH_2)_t$-, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6; B-$(CH_2)_a$-Z-$(CH_2)_b$-V-$(CH_2)_d$-, wherein a, b and d are independently 0-6, provided that the sum of a, b and d is 0-6; T-$(CH_2)_s$-, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0-6; or R_1 and R_4 together form the group (A'); B is optionally-substituted phenyl, indanyl, indenyl, naphthyl, tetrahydronaphthyl or optionally substituted-heteroaryl; and R_{20} and R_{21} are independently optionally-substituted phenyl, optionally-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, optionally-substituted heteroaryl, optionally-substituted benzofused heteroaryl or cyclopropyl are disclosed, as well as pharmaceutical compositions comprising said compounds, the use of said compounds as hypocholesterolemic agents, processes for preparing the compounds, and the use of said compounds in combination with cholesterol biosynthesis inhibitors to treat or prevent atherosclerosis.

SPIROCYCLOALKYL-SUBSTITUTED AZETIDINONES USEFUL AS HYPOCHOLESTEROLEMIC AGENTS

BACKGROUND OF THE INVENTION

The present invention relates to spirocycloalkyl-substituted azetidinones useful as hypocholesterolemic agents in the treatment and prevention of atherosclerosis, and to the combination of a spirocycloalkyl-substituted azetidinone of this invention and a cholesterol biosynthesis inhibitor for the treatment and prevention of atherosclerosis.

Atherosclerotic coronary heart disease represents the major cause for death and cardiovascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male sex, cigarette smoke and serum cholesterol. A total cholesterol level in excess of 225-250 mg/dl is associated with significant elevation of risk.

Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a key step in the intestinal absorption of dietary cholesterol. Thus, inhibition of cholesteryl ester formation and reduction of serum cholesterol is likely to inhibit the progression of atherosclerotic lesion formation, decrease the accumulation of cholesteryl esters in the arterial wall, and block the intestinal absorption of dietary cholesterol.

A few azetidinones have been reported as being useful in lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. 4,983,597 discloses N-sulfonyl-2-azetidinones as anticholesterolemic agents and Ram, et al., in Indian J Chem., Sect. B, 29B, 12 (1990), p. 1134-7, disclose ethyl 4-(2-oxoazetidin-4-yl)phenoxy-alkanoates as hypolipidemic agents.

European Patent Application 337,549 discloses elastase inhibitory substituted azetidinones comprising a spirocyclo substituent at the 3-position; elastase inhibitors are said to be useful in treating inflammatory conditions resulting in tissue destruction which are associated with various disease states, e.g. atherosclerosis.

PCT/US92/05972, filed July 21, 1992, and published as WO93/02048 on February 4, 1993 discloses β-lactam (i.e., azetidinone) cholesterol absorption inhibitors which lack a spirocycloalkyl group at the 3-position.

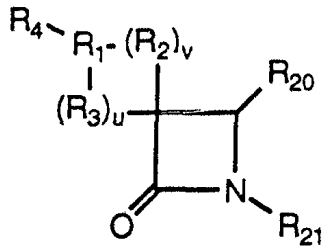
In addition to regulation of dietary cholesterol, the regulation of whole-body cholesterol homeostasis in humans and animals involves modulation of cholesterol biosynthesis, bile acid biosynthesis, and the catabolism of the cholesterol-containing plasma lipoproteins. The liver is the major organ responsible for cholesterol biosynthesis and catabolism and, for this reason, it is a prime determinant of plasma cholesterol levels. The liver is the site of synthesis and secretion of very low density lipoproteins (VLDL) which are subsequently metabolized to low density lipoproteins (LDL) in the circulation. LDL are the predominant cholesterol-carrying lipoproteins in the plasma and an increase in their concentration is correlated with increased atherosclerosis.

When cholesterol absorption in the intestines is reduced, by whatever means, less cholesterol is delivered to the liver. The consequence of this action is a decreased hepatic lipoprotein (VLDL) production and an increase in the hepatic clearance of plasma cholesterol, mostly as LDL. Thus, the net effect of an inhibition of intestinal cholesterol absorption is a decrease in plasma cholesterol levels.

The inhibition of cholesterol biosynthesis by 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase EC1.1.1.34) inhibitors has been shown to be an effective way to reduce plasma cholesterol (Witzum, *Circulation, 80*, 5 (1989), p. 1101-1114) and reduce atherosclerosis. Combination therapy of an HMG CoA reductase inhibitor and a bile acid sequestrant has been demonstrated to be more effective in human hyperlipidemic patients than either agent in monotherapy (Illingworth, *Drugs , 36* (Suppl. 3) (1988), p. 63-71).

SUMMARY OF THE INVENTION

Novel hypocholesterolemic compounds of the present invention are represented by the formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is

$-\overset{|}{C}H-$, $-\overset{|}{C}$(lower alkyl)-, $-\overset{|}{C}F-$, $-\overset{|}{C}(OH)-$, $-\overset{|}{C}(C_6H_5)-$, $-\overset{|}{C}(C_6H_4-R_{15})-$,

$-\overset{|}{N}-$ or $-\overset{|}{\overset{+}{N}}O^-$;

R_2 and R_3 are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)-, -C(di-lower alkyl)-, -CH=CH- and -C(lower alkyl)=CH-; or R_1 together with an adjacent R_2, or R_1 together with an adjacent R_3, form a -CH=CH- or a -CH=C(lower alkyl)- group;

u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R_2 is -CH=CH- or -C(lower alkyl)=CH-, v is 1; provided that when R_3 is -CH=CH- or -C(lower alkyl)=CH-, u is 1; provided that when v is 2 or 3, the R_2's can be the same or different; and provided that when u is 2 or 3, the R_3's can be the same or different;

R_4 is $B-(CH_2)_mC(O)-$, wherein m is 0, 1, 2, 3, 4 or 5;

$B-(CH_2)_q-$, wherein q is 0, 1, 2, 3, 4, 5 or 6;

$B-(CH_2)_e-Z-(CH_2)_r-$, wherein Z is -O-, -C(O)-, phenylene, $-N(R_8)-$ or $-S(O)_{0-2}-$, e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5, provided that the sum of e and r is 0, 1, 2, 3, 4, 5 or 6;

B-(C_2-C_6 alkenylene)-; B'-(C_4-C_6 alkadienylene)-;

$B-(CH_2)_t-Z-(C_2-C_6$ alkenylene)-, wherein Z is as defined above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

$B-(CH_2)_f-V-(CH_2)_g-$, wherein V is C_3-C_6 cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6;

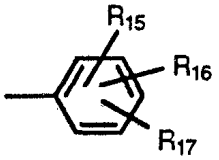
$B-(CH_2)_t-V-(C_2-C_6$ alkenylene)- or B'-(C_2-C_6 alkenylene)-V-$(CH_2)_t-$, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

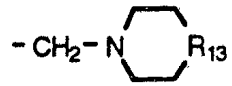
$B-(CH_2)_a-Z-(CH_2)_b-V-(CH_2)_d-$, wherein Z and V are as defined above and a, b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6;

T-$(CH_2)_s$-, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

R_1 and R_4 together form the group B-CH=C- ;

B is indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, or



W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, -CF_3, -OCF_3, benzyl, R_7-benzyl, benzyloxy, R_7-benzyloxy, phenoxy, R_7-phenoxy, dioxolanyl, NO_2, -N(R_8)(R_9), N(R_8)(R_9)-lower alkylene-, N(R_8)(R_9)-lower alkylenyloxy-, OH, halogeno, -CN, -N_3, -NHC(O)OR_{10}, -NHC(O)R_{10}, $R_{11}O_2SNH$-, $(R_{11}O_2S)_2N$-, -S(O)$_2NH_2$, -S(O)$_{0-2}R_8$, tert-butyldimethylsilyloxymethyl, -C(O)R_{12}, -COOR_{19}, -CON(R_8)(R_9), -CH=CHC(O)R_{12}, -lower alkylene-C(O)R_{12}, R_{10}C(O)(lower alkylenyloxy)-, N(R_8)(R_9)C(O)(lower alkylenyloxy)- and  for substitution on ring carbon atoms, and the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, -C(O)OR_{10}, -C(O)R_{10}, OH, N(R_8)(R_9)-lower alkylene-, N(R_8)(R_9)-lower alkylenyloxy-, -S(O)$_2NH_2$ and 2-(trimethylsilyl)-ethoxymethyl;

R_7 is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO_2, -N(R_8)(R_9), OH or halogeno;

R_8 and R_9 are independently H or lower alkyl;

R_{10} is lower alkyl, phenyl, R_7-phenyl, benzyl or R_7-benzyl;

R_{11} is OH, lower alkyl, phenyl, benzyl, R_7-phenyl or R_7-benzyl;

R_{12} is H, OH, alkoxy, phenoxy, benzyloxy,  ,

-N(R_8)(R_9), lower alkyl, phenyl or R_7-phenyl;

R_{13} is -O-, -CH_2-, -NH-, -N(lower alkyl)- or -NC(O)R_{19};

R_{15}, R_{16} and R_{17} are independently selected from the group consisting of H and the groups defined for W; or R_{15} is hydrogen and R_{16} and R_{17}, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

R_{19} is H, lower alkyl, phenyl or phenyl lower alkyl; and

R_{20} and R_{21} are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

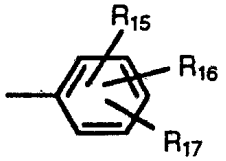
One group of preferred compounds of formula I is that wherein R_{21} is phenyl, W-substituted phenyl, indanyl, benzofuranyl, benzodioxolyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopropyl, wherein W is lower alkyl, lower alkoxy, OH, halogeno, -N(R_8)(R_9), -NHC(O)OR_{10}, -NHC(O)R_{10}, NO_2, -CN, -N_3, -SH, -S(O)$_{0-2}$-(lower alkyl), -COOR_{19}, -CON(R_8)(R_9), -COR_{12}, phenoxy, benzyloxy, -OCF_3, -CH=C(O)R_{12} or tert-butyldimethylsilyloxy, wherein R_8, R_9, R_{10}, R_{12} and R_{19} are as defined for formula I. When W is 2 or 3 substituents, the substituents can be the same or different.

Another group of preferred compounds of formula I is that wherein R_{20} is phenyl or W-substituted phenyl, wherein preferred meanings of W are as defined above for preferred definitions of R_{21}.

More preferred are compounds of formula I wherein R_{20} is phenyl or W-substituted phenyl and R_{21} is phenyl, W-substituted phenyl, indanyl, benzofuranyl, benzodioxolyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopropyl; W is lower alkyl, lower alkoxy, OH, halogeno, -N(R_8)(R_9), -NHC(O)OR_{10}, -NHC(O)R_{10}, NO_2, -CN, -N_3, -SH, -S(O)$_{0-2}$-(lower alkyl), -COOR_{19}, -CON(R_8)(R_9), -COR_{12}, phenoxy, benzyloxy, -CH=CHC(O)R_{12}, -OCF_3 or tert-butyl-dimethyl-silyloxy, wherein when W is 2 or 3 substituents, the substituents can be the same or different, and wherein R_8, R_9, R_{10}, R_{12} and R_{19} are as defined in formula I.

Also preferred are compounds of formula I wherein R_1 is $-\overset{|}{C}H-$ or $-\overset{|}{C}(OH)-$. Another group of preferred compounds of formula I is

that wherein R_2 and R_3 are each $-CH_2-$ and the sum of u and v is 2, 3 or 4, with u=v=2 being more preferred. R_4 is preferably $B-(CH_2)_q-$ or $B-(CH_2)_e-Z-(CH_2)_r-$, wherein B, Z, q, e and r are as defined above. B is preferably



, wherein R_{16} and R_{17} are each hydrogen and wherein R_{15} is preferably H, OH, lower alkoxy, especially methoxy, or halogeno, especially chloro. A preferred definition of Z is -O-, e is preferably 0, and r is preferably 0. A preferred definition of q is 0-2. R_{20} is preferably phenyl or W-substituted phenyl. Preferred W substituents for R_{20} are lower alkoxy, especially methoxy and ethoxy, OH, and $-C(O)R_{12}$, wherein R_{12} is preferably lower alkoxy. Preferred definitions for R_{21} are phenyl, lower alkoxy-substituted phenyl and F-phenyl.

Especially preferred are compounds of formula I wherein R_1 is $-\overset{|}{C}H-$, or $-\overset{|}{C}(OH)-$, R_2 and R_3 are each $-CH_2-$, u=v=2, R_4 is $B-(CH_2)_q-$, wherein B is phenyl or phenyl substituted by lower alkoxy or chloro, q is 0-2, R_{20} is phenyl, OH-phenyl, lower alkoxy-substituted phenyl or lower alkoxycarbonyl-substituted phenyl, and R_{21} is phenyl, lower alkoxy-substituted phenyl or F-phenyl.

This invention also relates to a method of lowering the serum cholesterol level in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I. That is, the use of a compound of the present invention as an hypocholesterolemic agent is also claimed.

In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

The present invention also relates to a method of reducing plasma cholesterol levels, and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a spirocycloalkyl-substituted azetidinone cholesterol absorption inhibitor of this invention and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a spirocycloalkyl-substituted azetidinone cholesterol absorption inhibitor for combined use with a cholesterol biosynthesis inhibitor (and, similarly, use of a cholesterol biosynthesis inhibitor for

combined use with a spirocycloalkyl-substituted azetidinone cholesterol absorption inhibitor) to treat or prevent atherscleroSis or to reduce plasma cholesterol levels

In yet another aspect, the invention relates to a pharmaceutical composition comprising an effective amount of a spirocycloalkyl-substituted azetidinone cholesterol absorption inhibitor, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the invention relates to a kit comprising in one container an effective amount of a spirocycloalkyl-substituted azetidinone cholesterol absorption inhibitor in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION:

As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms and "lower alkyoxy" similarly refers to alkoxy groups having 1 to 6 carbon atoms.

"Alkenyl" means straight or branched carbon chains having one or more double bonds in the chain, conjugated or unconjugated, and alkadienyl refers to chains having two double bonds in the chain.

Where an alkyl or alkenyl chain joins two other variables and is therefore bivalent, the terms alkylene and alkenylene are used.

"Cycloalkyl" means a saturated carbon ring of 3 to 6 carbon atoms, while "cycloalkylene" refers to a corresponding bivalent ring, wherein the points of attachment to other groups include all positional isomers.

"Halogeno" refers to fluorine, chlorine, bromine or iodine radicals.

"Heteroaryl" includes all positional isomers for a given heteroaryl group as defined above, for example 2-pyridyl, 3-pyridyl and 4-pyridyl. Benzofused heteroaryl refers to radicals formed by the bonding of a benzene radical to adjacent carbon atoms on a heteroaryl ring; examples are indolyl, quinolyl, quinazolinyl, quinoxalinyl, benzotriazolyl, indazolyl, benzoxazolyl, benzothienyl and benzofuranyl.

"Phenylene" means a bivalent phenyl group, including ortho, meta and para-substitution.

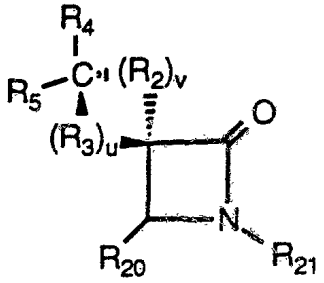
"(Lower alkoxyimino)lower alkyl" refers to the group (C_1-C_6 lower alkoxy)-N=CH-(C_1-C_5 lower alkyl). "Lower alkanedioyl" means

radicals of the formula -OC(O)$(CH_2)_{1-4}$C(O)OH, while "lower alkyl lower alkanedioyl" means radicals of the formula -OC(O)$(CH_2)_{1-4}$C(O)O-(lower alkyl).

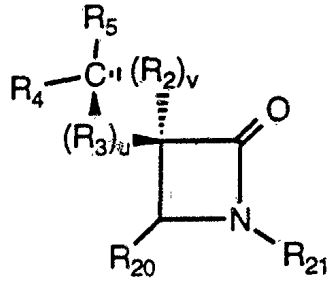
R_7-benzyl and R_7-benzyloxy refer to benzyl and benzyloxy radicals which are substituted on the phenyl ring.

Compounds of the invention have at least one asymmetrical carbon atom and therefore all isomers, including diastereomers and rotational isomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials or by separating isomers of a compound of formula I. Isomers may also include geometric isomers, e.g. when a double bond is present. All such geometric isomers are contemplated for this invention.

For compounds of the invention wherein R_1 is not N, at least two diastereomeric forms are possible. The following formulae IA and IB represent structures designated herein as "diastereomer A", wherein the lactam carbonyl group and the R_4 group are SYN, and "diastereomer B", wherein the lactam carbonyl group and the R_4 group are ANTI, respectively:



IA



IB

wherein R_5 is hydrogen, lower alkyl, fluoro, hydroxy, phenyl, or R_{15}-substituted phenyl, and R_2, R_3, R_4, R_{15}, R_{20}, R_{21}, u and v are as defined above.

Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological activity than another isomer.

Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids

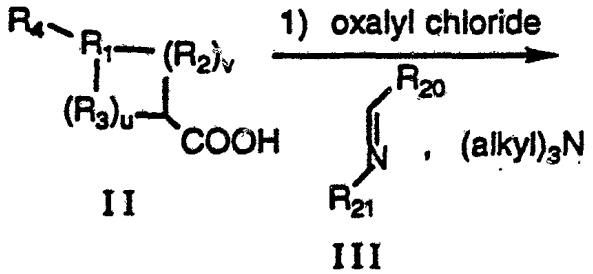
well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base forms for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin and atorvastatin also known as Cl-981; HMG CoA synthetase inhibitors, for example L-659,699 ((E,E-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalestatin 1; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride). Preferred HMG CoA reductase inhibitors are lovastatin, pravastatin and simvastatin.

Compounds of formula I, wherein R_1, R_2, R_3, R_4, R_{20}, R_{21}, u and v are as defined above, can be prepared by known methods as shown in the following processes A to F.

Process A:

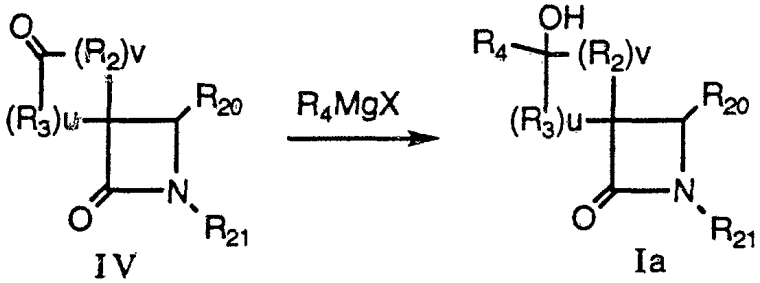


II III

A carboxylic acid of formula II can be converted to the corresponding acid chloride by refluxing with a reagent such as oxalyl

chloride in an inert solvent such as CH_2Cl_2. The acid chloride is then refluxed with an imine of formula III in an inert solvent such as CH_2Cl_2, heptane or toluene, in the presence of a trialkylamine (i.e., $(alkyl)_3N$) such as triethylamine, tributylamine or diisopropylethylamine. Generally, all possible diastereomers of formula I are produced by this process.

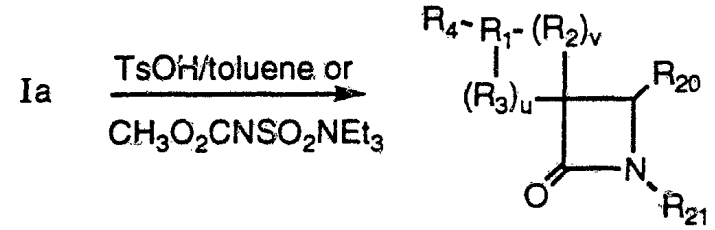
Process B:



IV Ia

A keto-azetidinone of formula IV can be converted to a carbinol of formula Ia, i.e., a compound of formula I wherein R_1 is $-\overset{|}{C}(OH)-$, by treatment with a Grignard reagent of formula R_4MgX, wherein R_4 is as defined above and X is a halogen such as bromine, chlorine or iodine.

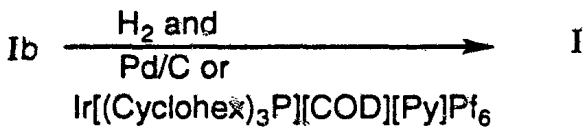
Process C:



Ib (wherein $R_1 + R_2 = -CH=CH-$)

A carbinol of formula Ia is converted to an olefin of formula Ib, wherein R_1 and an adjacent R_2 form a double bond (other R_2 groups can also be present) by dehydration with a mild acid such as p-toluenesulfonic acid (p-TsOH) under anhydrous conditions, e.g., using toluene as a solvent, or by treatment with a dehydrating agent such as (methoxycarbonylsulfamoyl)-triethylammonium hydroxide inner salt.

Process D:

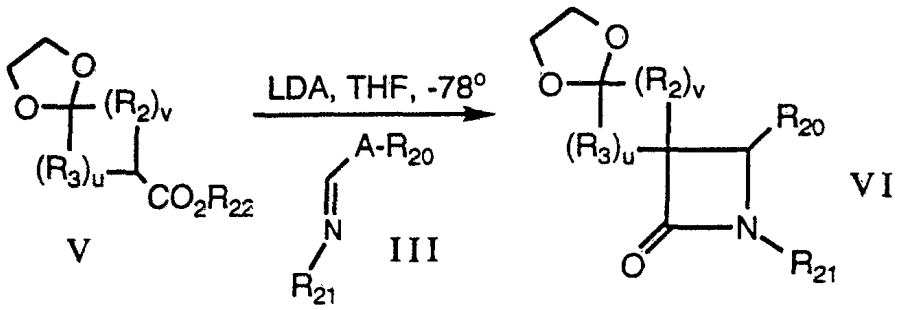


An olefin of formula Ib is reduced with hydrogen in the presence of a suitable catalyst such as palladium or an iridinium salt to

obtain the desired azetidinone of formula I. When the iridinium salt is used, the resulting products have primarily the ANTI stereochemistry, IB.

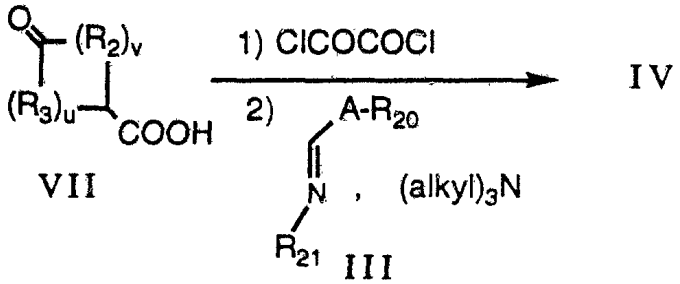
Keto-azetidinone starting materials of formula IV can be prepared, for example, by the following processes:

Process E:



A carboxylic acid ester of formula V, wherein R_{22} is lower alkyl, such as ethyl, or a chiral moiety such as menthyl or 10-(diisopropyl-sulfonamido)-isobornyl, is treated with a strong base such as lithium diisopropylamide (LDA) in a suitable solvent such as tetrahydrofuran (THF) at -78°C. An imine of formula III is added and the reaction mixture is stirred at -78°C for a suitable period, e.g., one hour, then allowed to warm to room temperature. The product of formula VI is isolated using conventional purification techniques. When the ester group R_{22} is chiral, the product is non-racemic. The ketal protecting group is removed by treatment with a mild acid such as p-TsOH to obtain the keto-azetidinone of formula IV.

Process F:

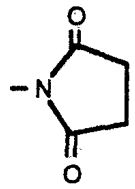


A ketoacid of formula VII can be treated with ClCOCOCl and reacted with an imine of formula III as described in Process A to obtain a keto-azetidinone of formula IV.

The carboxylic acids and imines of formulas II, III, V and VII used as starting materials in the above process are known in the art or can be prepared by one skilled in the art using well known procedures. Typical procedures for preparing a variety of carboxylic acids are described below in Preparations 1 to 6.

Reactive groups not involved in the above processes can be protected during the reactions with conventional protecting groups which can be removed by standard procedures after the reaction. The following Table 3 shows some typical protecting groups:

Table 3

Group to be Protected	Group to be Protected and Protecting Group
—COOH	—COOalkyl, —COObenzyl, —COOphenyl
>NH	>NCOalkyl, >NCObenzyl, >NCOphenyl, >NCH$_2$OCH$_2$CH$_2$Si(CH$_3$)$_3$, >NC(O)OC(CH$_3$)$_3$, N-benzyl, >NSi(CH$_3$)$_3$, >NSi-C(CH$_3$)$_3$ (CH$_3$, CH$_3$)
—NH$_2$	
—OH	—OCH$_3$, —OSi(CH$_3$)$_3$, —OSi-C(CH$_3$)$_3$ (CH$_3$, CH$_3$), —OC(O)alkyl

We have found that the compounds of this invention lower serum lipid levels, in particular serum cholesterol levels. Compounds of this invention have been found to inhibit the intestinal absorption of cholesterol and to significantly reduce the formation of liver cholesteryl esters in animal models. Thus, compounds of this invention are hypocholesterolemic agents by virtue of their ability to inhibit the esterification and/or intestinal absorption of cholesterol; they are, therefore, useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

The in vivo activity of the compounds of formula I can be determined by the following procedure:

In Vivo Assay of Hypolipidemic Agents Using the Hyperlipidemic Hamster

Hamsters are separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing 0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the face of test compounds. The animals are dosed with the test compound once daily beginning with the initiation of diet. Dosing is by oral gavage of 0.2mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by IM injection of ketamine and sacrificed by decapitation. Blood is collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Data is reported as percent reduction of lipid versus control.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. The compounds of formula I can be administered in any conventional dosage form, preferably an oral dosage form such as a capsule, tablet, powder, cachet, suspension or solution. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily hypocholesteremic dose of a compound of formula I is about 7 to about 30 mg/kg of body weight per day. For an average body weight of 70kg, the dosage level is therefore from about 500 to about 2000 mg of drug per day, given in a single dose or 2-4 divided doses . The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Following are examples of preparing carboxylic acid starting materials and novel compounds of formula I. The stereochemistry listed is relative stereochemistry unless otherwise noted.

Preparation 1

4-Phenyl-cyclohexanecarboxylic acid

STEP 1: Cool a mixture of 4-phenyl-cyclohexanone (30 g) and tosylmethyl isocyanide (36.9 g) in dimethoxyethane (800 mL) in an ice/acetone bath. Add a solution of potassium t-butoxide (38.7 g) in dimethoxyethane (300 mL) and t-butanol (300 mL). Stir the reaction mixture for 4h, pour into water and extract the product with ethyl acetate (EtOAc). Separate the organic layer, concentrate and use in STEP 2 without purification.

STEP 2: Dissolve the product from STEP 1 (32.8 g) in CH_3OH (240 mL) and add water (800 mL), $Ba(OH)_2$ (95 g) and NaOH (7.8 g). Heat the reaction mixture at reflux for 24h. Remove most of the CH_3OH under vacuum and extract the aqueous solution with ether (Et_2O). Separate the aqueous layer, acidify with conc. HCl and extract the product with Et_2O. Concentrate the ether solution to obtain the title compound (17.6 g).

4-Phenyl-4-methyl-cyclohexanecarboxylic acid is similarly prepared from 4-phenyl-4-methyl-cyclohexanone.

Preparation 2

4-(4-Chlorophenyl)-cyclohexanecarboxylic acid

STEP 1: Slowly add 4-chlorophenylmagnesium chloride (5.9 mL of 1M solution) to a solution of ethyl 4-oxo-cyclohexanecarboxylate (1.0 g) in Et_2O at 0°C. After 1h, pour the reaction mixture into 1N HCl and extract with Et_2O. Separate the organic layer, wash with water, brine and concentrate to give ethyl 4-(4-chlorophenyl)-4-hydroxy-cyclohexane-carboxylate (1.75 g) which is used without purification in the next step.

STEP 2: Dissolve the product (1.75 g) from STEP 1 in THF (100 mL), treat with 40% H_2SO_4 (25 mL) and heat the reaction mixture at reflux for 5.5h. Remove most of the solvent in vacuo, dilute the reaction mixture with water and extract with Et_2O. Separate the organic layer and concentrate to give 4-(4-chlorophenyl)-cyclohex-3-enecarboxylic acid (1.36 g).

STEP 3: Reduce a solution of the product of STEP 2 (1.36 g) in EtOAc (50 mL) over 10% Pd/C under H_2 (50 psi) for 14 h. Filter the catalyst and concentrate the solution to give the title compound (1.36 g).

4-(4-Methoxyphenyl)-cyclohexanecarboxylic acid is similarly prepared.

Preparation 3

4-Cyclohexyl-cyclohexanecarboxylic acid

Reduce a solution of 4-biphenylcarboxylic acid (10 g) in ethanol (EtOH) (175 mL) and EtOAc (30 mL) over 5% rhodium/alumina (7 g) under H_2 (60 psi) for 8 days. Filter the catalyst and concentrate the solution to obtain the title compound (9.92 g).

Preparation 4

4-Benzyl-cyclohexanecarboxylic acid

STEP 1: Reduce a solution of terphthalic acid mono-methyl ester (12.6 g) using a procedure similar to that of Preparation 3 to obtain 1,4-cyclo-hexanedicarboxylic acid mono-methy ester (12.64 g). The crude product is used without purification in the next step.

STEP 2: Add ClCOCOCl (4.1 g) to a solution of the product of STEP 1 (3.0 g) in CH_2Cl_2 (15 mL) and heat the mixture at reflux for 1.5h. Remove excess ClCOCOCl in vacuo and dissolve the product in benzene. Cool the reaction mixture in an ice/water bath and slowly add $AlCl_3$ (4.74 g). Stir the reaction mixture overnight as it warms to ambient temperature and pour into a conc. HCl/ice mixture. Extract the product with Et_2O, separate the organic layer, wash with water and brine, then concentrate to obtain methyl 4-(4-benzoyl)-cyclohexane-carboxylate (3.9 g).

STEP 3: Reduce a solution of the product of STEP 2 (2.5 g) in EtOAc (15 mL) and acetic acid (HOAc) (50 mL) over 10%Pd/C (0.3 g) under H_2 (60 psi) for 22h. Filter the catalyst, dilute the reaction mixture with water and extract the product with Et_2O. Separate the organic layer and concentrate to obtain a mixture of methyl 4-(α-hydroxybenzyl)-cyclohexanecarboxylate and methyl (4-benzylcyclohexane-carboxylate (2.46 g).

STEP 4: Dissolve the product from STEP 3 (2.46 g) in THF (100 mL), treat with 40% H_2SO_4 (25 mL) and heat the reaction mixture at reflux for 5 h. Pour the reaction mixture into excess water and extract with EtOAc. Separate the organic layer, concentrate, and reduce the crude mixture over 10%Pd/C (0.25 g) under H_2 (60 psi) overnight. Filter the catalyst and concentrate the solution to obtain the title compound (2.42 g).

Preparation 5

4-(2-Phenylethyl)-cyclohexanecarboxylic acid

STEP 1: Slowly add 2-phenylethyl bromide (2.6 g) to a slurry of Mg (0.37 g) in THF (50 mL) and heat at reflux for 4h. Cool the solution to ambient temperature and add to a solution of ethyl 4-oxo-cyclo-hexane-carboxylate (2.4 g) in THF (50 mL). After 2h, pour the reaction mixture into

a half-saturated solution of NH_4Cl and extract with EtOAc. Partially purify the product on a silica gel column, eluting with EtOAc. Dissolve the product in toluene (100 mL), treat with p-TsOH and heat at reflux overnight with azeotropic removal of water. Cool the reaction mixture, wash with saturated $NaHCO_3$ solution and concentrate. Purify the crude product on a silica gel column, eluting with CH_2Cl_2 to obtain ethyl 4-(2-phenylethyl)-cyclohex-3-enecarboxylate (0.45 g) and 1-(2-phenyl-ethyl)-2-oxabicyclo[2.2.2]octan-3-one (0.71 g). Dissolve 1-(2-phenyl-ethyl)-2-oxabicyclo[2.2.2]octan-3-one in EtOH, treat with conc.HCl (catalytic) and heat at reflux overnight. Dilute the reaction mixture with water and extract with EtOAc. Concentrate the organic layer to obtain additional ethyl 4-(2-phenylethyl)-cyclohex-3-enecarboxylate (0.88 g).

STEP 2: To a solution of the product of STEP 1 (1.33 g) in EtOAc (40 mL), add 10% Pd/C (0.2 g) and hydrogenate overnight at 58 psi. Filter the catalyst and concentrate the reaction mixture to give ethyl 4-(2-phenylethyl)-cyclohexanecarboxylate (1.26 g).

STEP 3: To a solution of the product of STEP 2 (1.26 g) in MeOH (20 mL), add water (5 mL) and LiOH (0.61 g) and stir overnight at ambient temperature. Dilute the reaction mixture with water and extract with Et_2O. Acidify the aqueous layer with conc.HCl and extract with EtOAc. Separate the organic layer, wash with water and brine, and concentrate to obtain the title compound (1.06 g).

Preparation 6

3-Benzyl-cyclobutanecarboxylic acid

STEP 1: Slowly add a solution of diethyl 2-benzylmalonate (20 g) in Et_2O (300 mL) to a slurry of $LiAlH_4$ (6 g) in Et_2O (300 mL), then heat the reaction mixture at reflux for 14h. Carefully add 4N NaOH to the reaction mixture until there is no precipitate, then extract with EtOAc. Concentrate the organic layer and purify the crude product on a silica gel column, eluting with EtOAc to obtain 2-benzyl-1,3-propanediol (8.45 g).

STEP 2: Slowly add $(C_6H_5)_3P$ (17.4 g) to a solution of the product of STEP 1 (5 g) in CH_2Cl_2 (200 mL) containing CBr_4 (21 g) at 0°C. Stir the reaction mixture overnight and allow to warm to ambient temperature. Evaporate the solvent in vacuo, triturate the crude product with pentane, filter, concentrate the filtrate and purify the residue on a silica gel column, eluting with hexane to give 2-benzyl-1,3-propanedibromide (5.47 g).

STEP 3: Add diethyl malonate (3 g) to a slurry of NaH (0.514 g) in dimethylformamide (DMF) (75 mL) at ambient temperature. After 1 h, heat

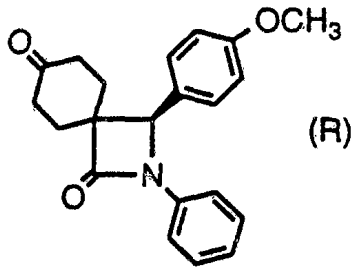
the reaction mixture to 100°C for 1h, cool to ambient temperature, add a solution of the product of STEP 2 (5 g) in DMF (25 mL) and stir at ambient temperature for 2.5h, followed by 2h at 150°C. Cool the mixture to ambient temperature, add NaH (0.514 g) and after 30 min., heat at 150°C overnight. Cool the reaction mixture, pour into excess water and extract with EtOAc. Separate the organic layer, wash with water and concentrate. Purify the crude product on a silica gel column, eluting with EtOAc:hexane (1:9) to obtain diethyl (3-benzyl)-cyclobutyl-1,1-dicarboxylate (3 g).

STEP 4: To a solution of the product of STEP 3 (3 g) in EtOH (20 mL), add water (5 mL) and KOH (2.9 g) and heat at reflux overnight. Dilute the reaction mixture with water and extract with Et_2O. Acidify the aqueous layer with conc.HCl and extract with CH_2Cl_2. Separate the organic layer and concentrat to give 3-benzyl-cyclobutyl-1,1-dicarboxylic acid (2.31 g).

STEP 5: Heat the product of STEP 4 (2.31 g) at 170-180°C under vacuum (60-70 mm) for 1.5h to obtain the title compound (1.85 g).

In a similar manner, 2-(2-phenylethyl)malonate is converted to 2-(2-phenylethyl)cyclobutanecarboxylic acid.

Preparation 7



(R) or (S)

STEP 1: Heat a mixture of 4-carbomethoxycyclohexanone (4.4 g, 0.028 moles), $HOCH_2CH_2OH$ (3.2 mL, 0.056 moles), and a catalytic amount of p-TsOH in toluene at reflux for 4 hr with continuous removal of water. Cool to room temperature, wash the organic layer with water, dry over $MgSO_4$, and evaporate to give the crude ketal. Dissolve ketal in MeOH (80 mL) containing KOH (5.6 g) and stir at room temperature overnight. Concentrate to dryness and dissolve in Et_2O (100 mL). Adjust to pH 2 with 1N HCl. Extract with Et_2O (3 x 100 mL), dry over $MgSO_4$ and evaporate to obtain 4.0 grams of the ethylene ketal of 4-cyclohexanonecarboxylic acid.

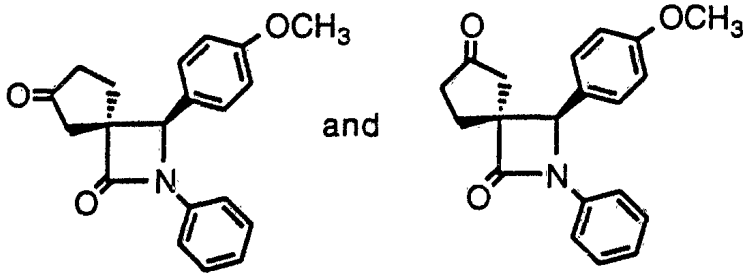
STEP 2: Add the product from Step 1 (0.344 g, 1.8 mmol) and 10-diisopropylsulfonamido)-isoborneol (0.570 g, 1.8 mmol) to a mixture of DCC (0.556 g, 2.7 mmol), dimethylaminopyridine (DMAP) (0.330 g, 2.7 mmol), and DMAP HCl (0.003 g) in CH_2Cl_2 (5 mL). Stir at room temp. overnight, dilute with Et_2O (150 mL) and filter. Concentrate the filtrate

under vacuum and purify the crude ester by chromatography on silica gel, eluting with 30% EtOAc/hexane to obtain 0.508 grams of the ester.

STEP 3: Prepare a solution of LDA (from $[(CH_3)_2CH]_2NH$ (0.23 mL) and 1.6M $CH_3(CH_2)_3Li$ (1.03 mL) in hexane) in THF (5 mL), cool to -78° C and add a solution of the product of Step 2 in THF (5 mL). Stir at -78° C for 1.5 hr, then add a solution of (N-(4-methoxy-benzylidine)aniline (0.278 g, 1.32 mmol) in THF (5 mL). Stir this mixture at -78° C for 1 hr and at room temperature for 1 hr. Quench the reaction with a solution of 10 % aqueous $KHSO_4$ (20 mL), extract with EtOAc (3x20 mL), dry the organic layers over $MgSO_4$ and evaporate. Purify the crude product by chromatography over silica gel, eluting with 40% EtOAc/hexane to obtain 0.266 g of product.

STEP 4: Stir the product of Step 3 overnight in 5:1 acetone: 3N HCl to obtain 0.21 grams of the title compound. If 10-diisolpropylsulfonamido)-isoborneol derived from (+)-10-camphorsulfonyl chloride is used in Step 1, the product has the (S)-configuration.

Preparation 8



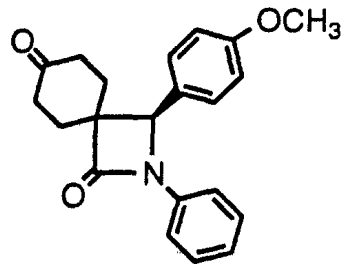
STEP 1: To a solution of ethyl 3-oxocyclopentanecarboxylate (2.63 g, 0.0169 moles) in benzene (50 mL), add $HOCH_2CH_2OH$ (2.10 g, 0.0338 moles) and pyridinium tosylate (0.85 g, 0.0034 moles). Heat at reflux with removal of water for 2.5 hr. Remove the solvent under vacuum and take up the residue in Et_2O (100 mL). Wash with saturated Na_2CO_3 and concentrate to a yellow oil. Purify by chromatography on silica gel, eluting with 10 % EtOAc/hexane to obtain 2.92 grams of the ketal ester.

STEP 2: React the product of Step 1 (0.30 g, 0.0015 moles) with LDA (1.2 equivalents) in THF followed by N-(4-methoxybenzylidine)aniline as described for Preparation 7, Step 3, to obtain 0.52 grams of the resulting azetidinone as a mixture of diastereomers. Separate these diastereomers by chromatography on silica gel, eluting with 20% EtOAc/hexane to obtain 0.16 grams of component A and 0.22 grams of component B.

STEP 3: Treat component A of Step 2 (1.38 g) with aqueous HCl as described for Preparation 7, Step 4, to obtain 1.15 grams of rel (3R,4R)-3-(4-methoxyphenyl)-2-phenyl-2-azaspiro[3.4]octane-1,6-dione. Similar

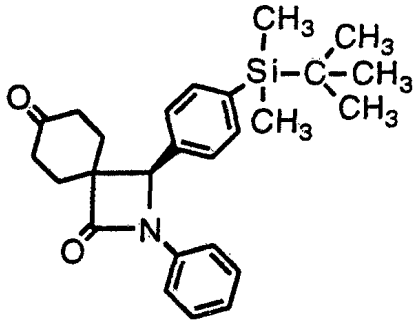
treatment of component B yields rel (3R,4S)-3-(4-methoxyphenyl)-2-phenyl-2-azaspiro[3.4]octane-1,6-dione.

Preparation 9



Treat a solution of 4-cyclohexanonecarboxylic acid (4.6 g, 0.0323 moles)in CH_2Cl_2 (50 mL) with ClCOCOCl (5.7 mL, 0.0648 moles) as described in Example 1, below. React the resulting acid chloride with N-(4-methoxybenzylidene)aniline using the procedure described in Example 1 to obtain the title compound (10.03 g).

In a similar manner, using N-(4-methoxybenzylidine)-4(t-butyl-dimethylsilyloxy)aniline, prepare:



Examples 1 and 1A

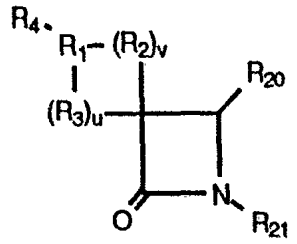
2,3-Bis-(4-methoxyphenyl)-7-(4-chlorophenyl)-2-azaspiro[3.5]nonan-1-one

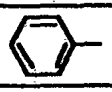
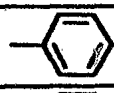
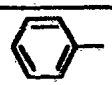
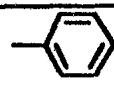
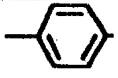
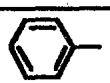
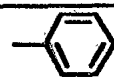
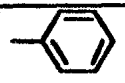
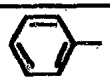
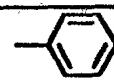
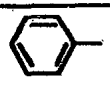
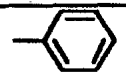
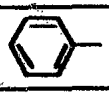
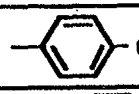
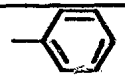
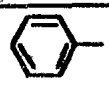
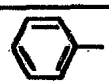
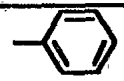
Add ClCOCOCl (1.43 g) to a solution of the product of Preparation 2 (1.34 g) in CH_2Cl_2 (15 mL) and heat at reflux for 2h. Remove the solvent and excess ClCOCOCl under vacuum. Dissolve the resultant acid chloride in CH_2Cl_2 (5 mL), add this solution to N-(4-methoxybenzylidene)anisidine (1.35 g) and triethylamine (Et_3N) (1.25 g) in CH_2Cl_2 (25 mL) and heat at reflux overnight. Pour the reaction mixture into 1N HCl and extract the product with CH_2Cl_2. Separate the organic layer, wash with saturated $NaHCO_3$ and concentrate. Purify the crude material on a silica gel column, eluting with CH_2Cl_2:hexane (95:5) to give:

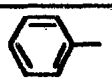
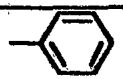
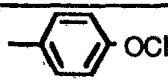
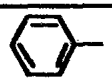
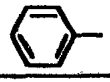
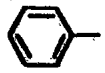
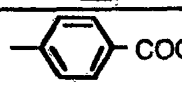
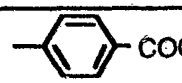
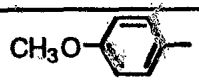
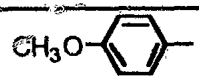
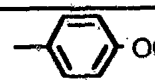
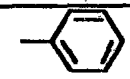
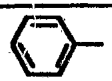
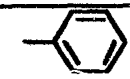
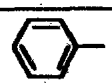
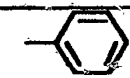
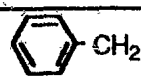
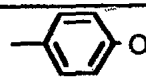
(1) Diastereomer A of the title compound: 0.52 g; m.p. 166-167;
Mass spectrum: Calculated 461 and observed 462;
Elemental analysis: Calculated: C=72.8, H=6.11, N=3.03
Found: C=72.72, H=6.11, N=3.15

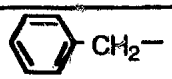
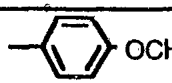
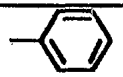
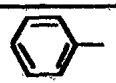
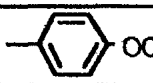
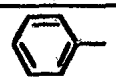
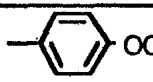
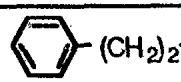
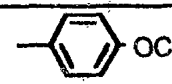
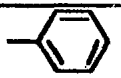
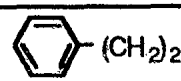
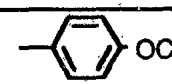
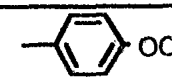
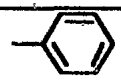
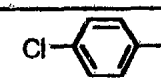
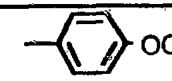
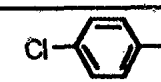
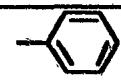
(1A) Diastereomer B of the title compound: 0.475 g; m.p. 87-89
Mass spectrum: Calculated 461 and observed 462;
Elemental analysis: Calculated: C=72.8, H=6.11, N=3.03
Found: C=72.79, H=6.17, N=3.12.

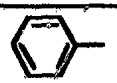
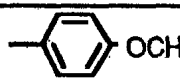
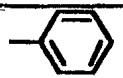
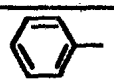
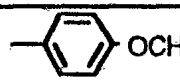
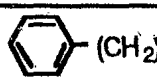
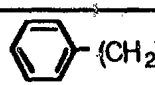
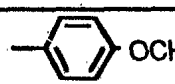
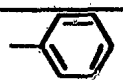
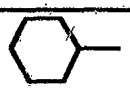
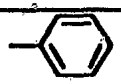
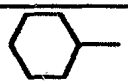
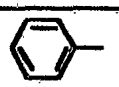
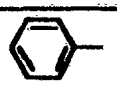
Other 2-azaspiro[3.5]nonan-1-ones and 2-azaspiro[3.3]-heptan-1-ones similarly prepared are shown in the following table:



Ex.	Diaster.	R_1	$-(R_2)_v-$	$-(R_3)_u-$	R_4	R_{20}	R_{21}	mp, C°	MS	Elem. Anal.
2	A	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				68-71	Calcd: 427 Obs: 427	
3	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				75-77	Calcd: 427 Obs: 427	Calcd: C: 78.66, H: 6.84, N: 3.28 Found: C: 78.26, H: 6.77, N: 3.36
4	A	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				–	Calcd: 397 Obs: 398	Calcd: C: 81.58, H: 6.85, N: 3.52 Found: C: 81.06, H: 6.76, N: 3.65
5	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				–	Calcd: 397 Obs: 398	Calcd: C: 81.58, H: 6.85, N: 3.52 Found: C: 80.87, H: 6.75, N: 3.68
6	A	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				–	Calcd: 411 Obs: 412	Calcd: C: 81.72, H: 7.10, N: 3.40 Found: C: 81.59, H: 7.05, N: 3.60
7	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				–	Calcd: 411 Obs: 411	
8	-	N	$-(CH_2)_2-$	$-(CH_2)_2-$				–	Calcd: 428 Obs: 429	Calcd: C: 75.68, H: 6.59, N: 6.54 Found: C: 75.40, H: 6.66, N: 6.52
9	A	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				191-193	Calcd: 396 Obs: 397	Calcd: C: 81.58, H: 6.85, N: 3.52 Found: C: 81.57, H: 6.84, N: 3.55

Ex.	Dia-ster.	R_1	$-(R_2)_v-$	$-(R_3)_u-$	R_4	R_{20}	R_{21}	mp, C°	MS	Elem. Anal.
10	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				178-180	Calcd: 396 Obs: 397	Calcd: C: 81.58, H: 6.85, N: 3.52 Found: C: 81.56, H: 6.82, N: 3.56
11	A	$C(CH_3)$	$-(CH_2)_2-$	$-(CH_2)_2-$				–	Calcd: 411 Obs: 412	
12	B	$C(CH_3)$	$-(CH_2)_2-$	$-(CH_2)_2-$				–	Calcd: 411 Obs: 412	
13	A	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				184-185	Calcd: 455 Obs: 455	Calcd: C: 76.46, H: 6.42, N: 3.07 Found: C: 76.20, H: 6.38, N: 3.07
14	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				125-127	Calcd: 455 Obs: 455	Calcd: C: 76.46, H: 6.42, N: 3.07 Found: C: 76.36, H: 6.72, N: 3.19
15	A	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				149-150	Calcd: 427 Obs: 428	Calcd: C: 78.66, H: 6.84, N: 3.28 Found C: 78.74, H: 6.89, N: 3.48
16	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				161-162	Calcd: 427 Obs: 428	Calcd: C: 78.66, H: 6.84, N: 3.28 Found: C: 78.53, H: 6.80, N: 3.47
17 A	A	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				–	Calcd: 413 Obs: 414	–
17 B	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				–	Calcd: 413 Obs: 413	–
18	A	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				65-69	Calcd: 411 Obs: 412	HRMS Calcd: 412.2277 Found: 412.2272

Ex.	Dia-ster.	R_1	$-(R_2)_v-$	$-(R_3)_u-$	R_4	R_{20}	R_{21}	mp, C°	MS	Elem. Anal.
19	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				126-130	Calcd: 411 Obs: 412	HRMS Calcd: 412.2277 Found: 412.2269
20	A	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				167-168	Calcd: 431 Obs: 432	Calcd: C: 75.08, H: 6.07, N: 3.24 Found: C: 75.07, H: 6.07, N: 3.31
21	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				76-78	Calcd: 431 Obs: 432	Calcd: C: 75.08, H: 6.07, N: 3.24 Found: C: 75.28, H: 6.04, N: 3.33
22*	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				76-77	Calcd: 427 Obs: 428	
23*	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				76-77	Calcd: 427 Obs: 428	Calcd: C: 78.85, H: 6.62, N: 3.28 Found: C: 78.84, H: 6.65, N: 3.30
24	A	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				57-59	Calcd: 425 Obs: 426	Calcd: C: 81.85, H: 7.34, N: 3.29 Found: C: 81.97, H: 7.34, N: 3.21
25	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				53-55	Calcd: 425 Obs: 426	Calcd: C: 81.85, H: 7.34, N: 3.29 Found: C: 81.77, H: 7.24, N: 3.29
26*	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				174-175	Calcd: 414 Obs: 415	Calcd: C: 78.16, H: 6.07, N: 3.38 Found - C: 78.20, H: 6.10, N: 3.39
27*	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				174-175	Calcd: 414 Obs: 415	Calcd: C: 78.16, H: 6.07, N: 3.38 Found: C: 78.17, H: 6.09, N: 3.38
28	-	$-\overset{\vert}{C}=CH-$		$-(CH_2)_2-$				163-164	Calcd: 429 Obs: 430	Calcd: C: 75.43, H: 5.63, N: 3.26 Found: C: 75.35, H: 5.67, N: 3.35

Ex.	Dia-ster.	R_1	$-(R_2)_v-$	$-(R_3)_u-$	R_4	R_{20}	R_{21}	mp, C°	MS	Elem. Anal.
29 A	A	CH	$-CH_2-$	$-CH_2-$				56-58	Calcd: 383 Obs: 384	Calcd: C: 81.43, H: 6.57, N: 3.65 Found: C: 81.54, H: 6.49, N: 3.56
29 B	B	CH	$-CH_2-$	$-CH_2-$				97-98	Calcd: 383 Obs: 384	Calcd: C: 81.43, H: 6.57, N: 3.65 Found: C: 81.09, H: 6.36, N: 3.42
30 A	A	CH	$-CH_2-$	$-CH_2-$				^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90-7.30(m, 14H), 4.71(s, 1H), 3.82(s, 3H), 2.66(ddd, 1H, J=3.00, 7.73, 11.60), 2.29(ddd, 1H, J=4.20, 7.94, 11.91), 1.94(dd, 1H, J=9.56, 11.60), 1.23(dd, 1H, J=8.54, 11.91), 2.46(m, 3H), 1.59(m, 2H)		
30 B	B	CH	$-CH_2-$	$-CH_2-$				^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90-7.32(m, 14H), 4.87(s, 1H), 3.82(s, 3H), 2.42-2.56(m, 3H), 2.95(dd, 1H, J=7.39, 11.9), 2.05(m 1H), 1.92(dd, 1H, J=7.63, 12.2), 1.64(ddd, J=8.24, 3.36, 11.9), 1.83(q, 2H, J=7.63)		
31	A	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				180-181	Calcd: 403 Obs: 404	Calcd: C: 80.36, H: 8.24, N: 3.47 Found: C: 80.41, H: 8.19, N: 3.57
32	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				141-143	Calcd: 403 Obs: 404	Calcd: C: 80.36, H: 8.24, N: 3.47 Found: C: 80.35, H: 8.15, N: 3.74
33	A	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				–	–	Calcd: C: 79.74, H: 7.53, N: 3.87 Found: C: 79.36, H: 7.57, N: 3.98
34	B	CH	$-(CH_2)_2-$	$-(CH_2)_2-$				–	Calcd: 361 Obs: 361	–

* = Single Enantiomers

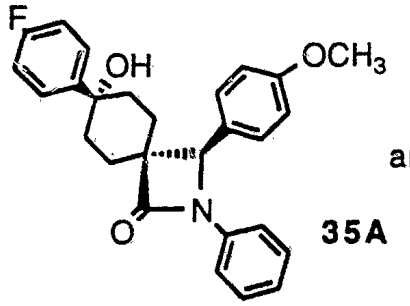
Enantiomeric compounds of Examples 22 and 23 were prepared by chromatographic resolution of the racemate in a CHIRACEL OD HPLC column eluting with 93:7 hexane:isopropanol at a flow rate of 5 mL/min.

Enantiomeric compounds of Examples 26 and 27 were prepared by chromatographic resolution of the racemate in a CHIRACEL OD HPLC column eluting with 95:5 hexane:isopropanol at a flow rate of 5 mL/min.

Example 26: $[\alpha]_D^{25} = +60.7^{\circ}$ (CH_3OH)

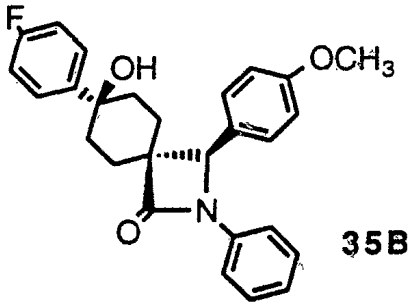
Example 27: $[\alpha]_D^{25} = -58.1^{\circ}$ (CH_3OH)

Examples 35A, 35B, 35C, 35D and 35E



35A

and

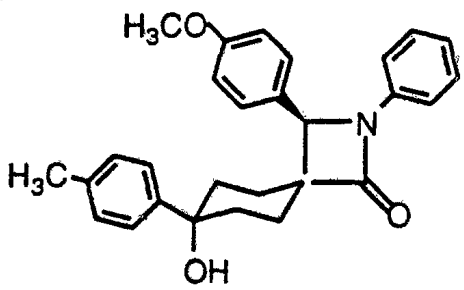


35B

To a solution of the product of Preparation 7 (1.1 g, 3.28 mmol) in Et_2O (20 mL) at 0°C, add a solution of 4-fluorophenylmagnesium bromide (4.9 mL, 4.92 mmol) in THF over 5 min. Stir at 0°C for 1.5 hr, then stir at room temperature for 3 hr. Quench the reaction with sat'd $NaHSO_4$ and extract with EtOAc (3 x 30 mL). Dry the organic layers over Na_2SO_4 and evaporate the solvent to obtain 1.57 grams of crude product. Purify by chromatography over silica gel, eluting with 95:5 Ch_2Cl_2:EtOAc to obtain 0.9 g of the ANTI isomer, mp=168-169° C, and 0.27 g of the SYN isomer.

In a similar manner, the following compounds are prepared:

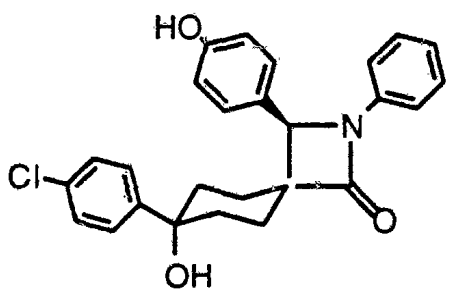
35C



mp=94-96°C

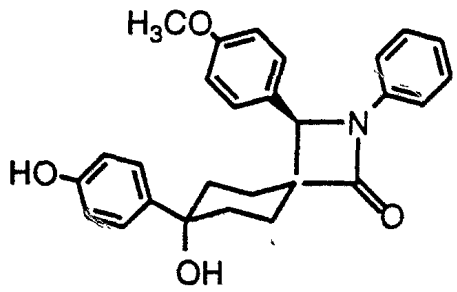
MS calcd: 427; obs: 427

35D



MS calcd: 433; obs: 416 ($M-H_2O$)

35E

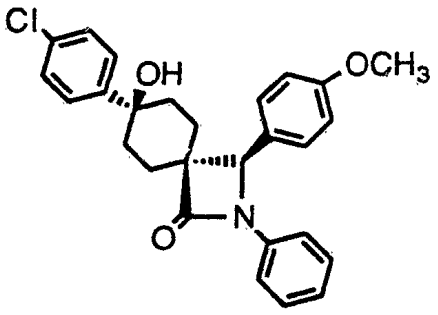


MS calcd: 429; obs: 412 ($M-H_2O$)

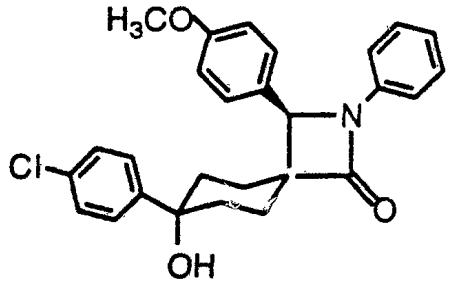
Examples 36, 36A, 36B, 37 and 38

Using appropriate starting materials in a procedure similar to that described in Example 35, the following compounds are prepared:

36



36A

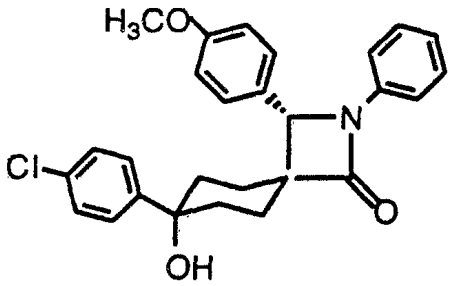


mp = 100.0-103.0°C

$[\alpha]_D^{20}$ = +55.9° (CH_3OH)

single enantiomer

36B

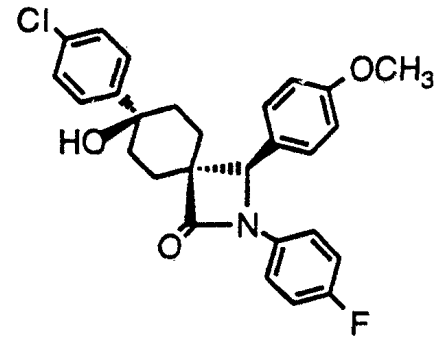


mp = 60.0-65.0°C

$[\alpha]_D^{24.2}$ = -52.0° (CH_3OH)

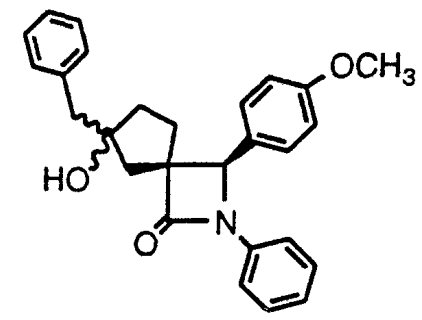
single enantiomer

37



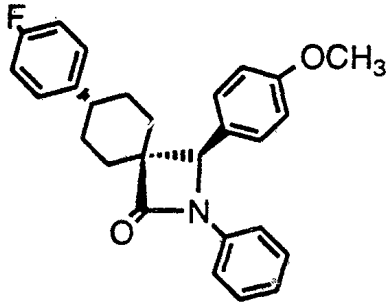
mp = 164.0-165.0°C

38



mp = 61.0-64.0°C

Examples 39, 40, 40A,

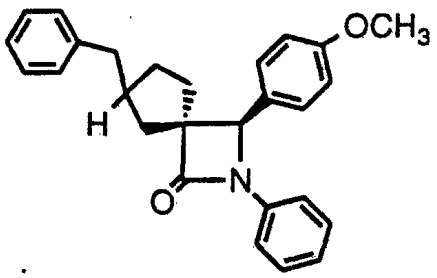


STEP 1: Add p-TsOH (0.08 g) to a solution of the product of Example 35 (0.5 g) and stir at 60° C over 4A sieves for 3.5 hr. Filter the mixture through celite, wash with sat'd $NaHCO_3$, dry over Na_2SO_4, and evaporate to obtain 7-(4-fluorophenyl)-7-hydroxy-3-(4-methoxyphenyl)-2-phenyl-2-azaspiro[3.5]non-6-en-1-one, which can be used in STEP 2 with or without purification by chromatography over silica gel.

STEP 2: To a solution of the product of STEP 1, (0.415 g,1 mmol) in CH_2Cl_2 (15 mL), add (tricyclohexylphosphine)-(1,5-cyclooactadiene)-(pyridine) Iridium(I) hexafluorophosphate (0.010 g, 0.05 mmol). Stir under one atm H_2 at room temperature for 52 hr. Filter the mixture through a bed of silica gel, eluting with CH_2Cl_2 to give 0.161 g of the title compound, mp=146-147° C. MS calcd: 415; obs: 415.

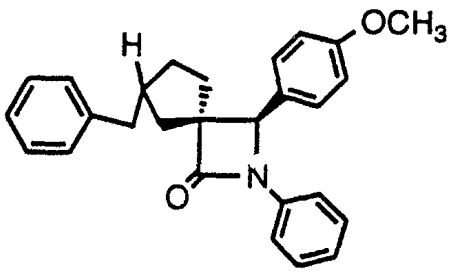
In a similar manner, except using 10% Pd/C as the hydrogenation catalyst, use the compound of Example 38 as the starting material to prepare the following compounds:

40



mp = 102-103°C

40A

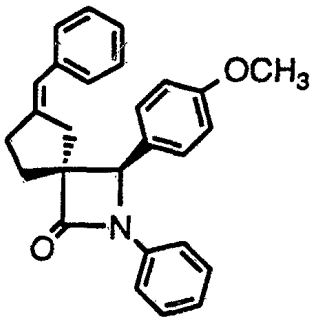


CI Mass Spectrum, M/z(intensity): 398 (100, M^+), 279 (13), 211 (18).

Examples 41, 42 and 42A

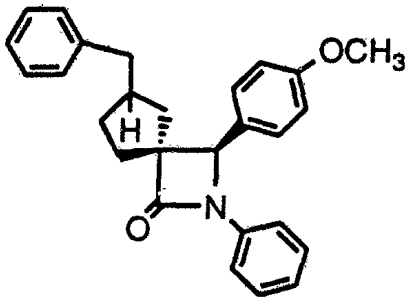
Use the product of Preparation 8 in the procedure of Example 35, followed by the procedure of Example 39, STEP 1, to obtain the compound of Example 41. Treat the compound of Example 41 using the procedure of Example 39, STEP 2, to obtain compounds of Examples 42 and 42A:

41



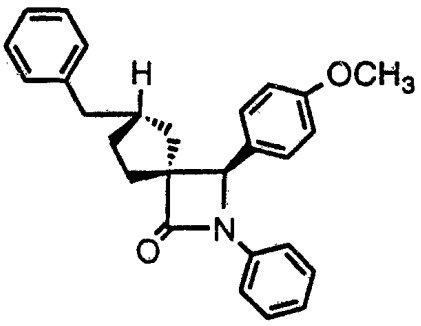
mp = 67.0-69.0°C

42



mp = 99-101°C

42A



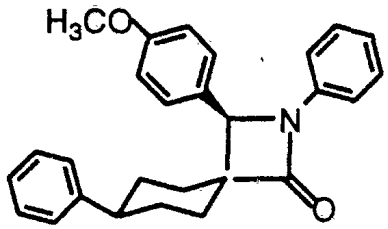
mp = 102.0-103.0°C

10

Examples 43A and 43B

Use the product of Preparation 7 in the procedure of Example 35, followed by the procedures of Example 39, STEP 1 and STEP 2, to obtain compounds of Examples 43A and 43B:

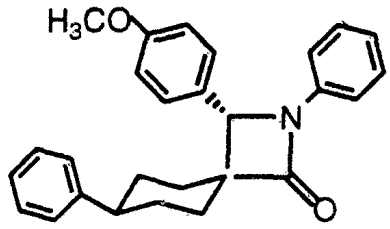
43A



$[\alpha]_D^{20}$ = +28.3° (MeOH)

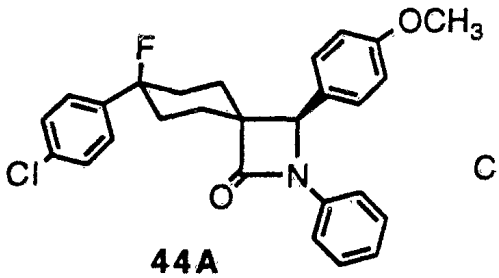
single enantiomer

43B

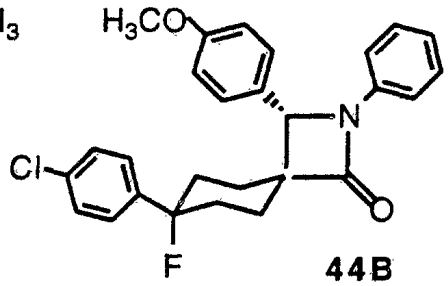


single enantiomer

Examples 44A and 44B



44A



44B

Dissolve the compound of Example 36 (0.31 g, 0.693 moles) in CH_2Cl_2 (7 mL) at -78°C and add dropwise, over 2-3 min., diethylamino-sulfur trifluoride (0.145 mL, 1.09 mmoles). Stir the mixture for 2 hr. at -78°C. Quench the mixture with ice-cold saturated $NaHCO_3$ and extract with CH_2Cl_2 (2x10 mL). Dry the combined organic layers over Na_2SO_4 and concentrate to an oil. Purify by flash chromatography on silica gel to obtain pure SYN diastereomer (0.146 mg) and impure ANTI diastereomer (0.72 mg). Purify the ANTI diastereomer by preparative TLC on a 20x20 cm silica gel plate, eluting with CH_2Cl_2 to obtain 0.026 g.

The following formulations exemplify some of the dosage forms of this invention. In each the term "active compound" designates a compound of formula I.

EXAMPLE A
Tablets

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	122	113
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4	Corn Starch, Food Grade	45	40
5	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B
Capsules

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	106	123
3	Corn Starch, Food Grade	40	70
4	Magnesium Stearate NF	4	7
	Total	250	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

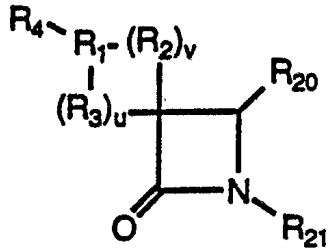
Using the test procedures described above, the following in vivo data were obtained for the exemplified compounds. Data is reported

as percent change (i.e., percent reduction in cholesterol esters) versus control, therefore, negative numbers indicate a positive lipid-lowering effect.

Ex. No.	% Change	Dose mpk	Ex. No.	% Change	Dose mpk	Ex. No.	% Change	Dose mpk
1	-25	50	18	0	50	35A	0	10
1A	-89	50	19	-43	50	35B	-93	10
2	-17	50	20	0	50	35C	-31	10
3	-87	50	21	-92	50	36	-92	10
4	0	50	22	--		36A	-85	3
5	-95	50	23	--			-62	1
6	-26	50	24	0	50	36B	-18	3
7	-64	50	25	-43	50	37	-91	10
8	-17	50	26	-97	25	38	-21	10
9	-46	50	27	-32	25	39	--	
10	0	50	28	-65	50	40	-90	50
11	-25	50	29A	-9	50		-89	10
12	-36	50	29B	0	50	40A	-65	10
13	-21	50	30A	-65	10	41	-35	10
14	-30	50	30B	-42	10	42	-84	50
15	31	50	31	-15	50	42A	0	10
16	0	50	32	-30	50	43A	-75	10
17A	--	--	33	0	50		-55.5	3
17B	--	--	34	0	50	43B	--	

We claim:

1. A compound represented by the formula



or a pharmaceutically acceptable salt thereof, wherein:

R_1 is

$-\overset{|}{C}H-$, $-\overset{|}{C}$(lower alkyl)-, $-\overset{|}{C}F-$, $-\overset{|}{C}(OH)-$, $-\overset{|}{C}(C_6H_5)-$, $-\overset{|}{C}(C_6H_4-R_{15})-$, $-\overset{|}{N}-$ or $-\overset{|}{\underset{|}{N}}O^-$;

R_2 and R_3 are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)-, -C(di-lower alkyl)-, -CH=CH- and -C(lower alkyl)=CH-; or R_1 together with an adjacent R_2, or R_1 together with an adjacent R_3, form a $-\overset{|}{C}=CH-$ or a $-\overset{|}{C}=C$(lower alkyl)- group;

u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R_2 is -CH=CH- or -C(lower alkyl)=CH-, v is 1; provided that when R_3 is -CH=CH- or -C(lower alkyl)=CH-, u is 1; provided that when v is 2 or 3, the R_2's can be the same or different; and provided that when u is 2 or 3, the R_3's can be the same or different;

R_4 is $B-(CH_2)_mC(O)-$, wherein m is 0, 1, 2, 3, 4 or 5;

$B-(CH_2)_q-$, wherein q is 0, 1, 2, 3, 4, 5 or 6;

$B-(CH_2)_e-Z-(CH_2)_r-$, wherein Z is -O-, -C(O)-, phenylene, $-N(R_8)-$ or $-S(O)_{0-2}-$, e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5, provided that the sum of e and r is 0, 1, 2, 3, 4, 5 or 6;

$B-(C_2-C_6$ alkenylene)-; $B'-(C_4-C_6$ alkadienylene)-;

$B-(CH_2)_t-Z-(C_2-C_6$ alkenylene)-, wherein Z is as defined above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

$B-(CH_2)_f-V-(CH_2)_g-$, wherein V is C_3-C_6 cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6;

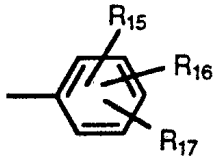
$B-(CH_2)_t-V-(C_2-C_6$ alkenylene)- or $B'-(C_2-C_6$ alkenylene)-V-$(CH_2)_r-$, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

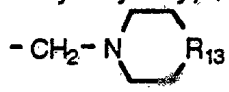
$B\text{-}(CH_2)_a\text{-}Z\text{-}(CH_2)_b\text{-}V\text{-}(CH_2)_d$-, wherein Z and V are as defined above and a, b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6;

$T\text{-}(CH_2)_s$-, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

R_1 and R_4 together form the group $B\text{-}CH{=}\overset{|}{C}$- ;

B is indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, or



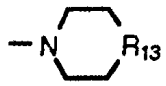
W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, R_7-benzyl, benzyloxy, R_7-benzyloxy, phenoxy, R_7-phenoxy, dioxolanyl, NO_2, $-N(R_8)(R_9)$, $N(R_8)(R_9)$-lower alkylene-, $N(R_8)(R_9)$-lower alkylenyloxy-, OH, halogeno, -CN, $-N_3$, $-NHC(O)OR_{10}$, $-NHC(O)R_{10}$, $R_{11}O_2SNH$-, $(R_{11}O_2S)_2N$-, $-S(O)_2NH_2$, $-S(O)_{0\text{-}2}R_8$, tert-butyldimethyl-silyloxymethyl, $-C(O)R_{12}$, $-COOR_{19}$, $-CON(R_8)(R_9)$, $-CH{=}CHC(O)R_{12}$, -lower alkylene-$C(O)R_{12}$, $R_{10}C(O)$(lower alkylenyloxy)-, $N(R_8)(R_9)C(O)$(lower alkylenyloxy)- and  for substitution on ring carbon atoms, and the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, $-C(O)OR_{10}$, $-C(O)R_{10}$, OH, $N(R_8)(R_9)$-lower alkylene-, $N(R_8)(R_9)$-lower alkylenyloxy-, $-S(O)_2NH_2$ and 2-(trimethylsilyl)-ethoxymethyl;

R_7 is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO_2, $-N(R_8)(R_9)$, OH or halogeno;

R_8 and R_9 are independently H or lower alkyl;

R_{10} is lower alkyl, phenyl, R_7-phenyl, benzyl or R_7-benzyl;

R_{11} is OH, lower alkyl, phenyl, benzyl, R_7-phenyl or R_7-benzyl;

R_{12} is H, OH, alkoxy, phenoxy, benzyloxy,  ,

$-N(R_8)(R_9)$, lower alkyl, phenyl or R_7-phenyl;

R_{13} is -O-, $-CH_2-$, -NH-, -N(lower alkyl)- or $-NC(O)R_{19}$;

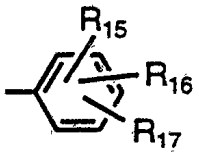
R_{15}, R_{16} and R_{17} are independently selected from the group consisting of H and the groups defined for W; or R_{15} is hydrogen and R_{16} and R_{17}, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

R_{19} is H, lower alkyl, phenyl or phenyl lower alkyl; and

R_{20} and R_{21} are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

2. A compound of claim 1 wherein R_1 is $-\overset{|}{C}H-$ or $-\overset{|}{C}(OH)-$.

3. A compound as claimed in claim 1 or claim 2 wherein R_2 and R_3 are each $-CH_2-$ and the sum of u and v is 2, 3 or 4.

4. A compound as claimed in any one of claims 1 to 3 wherein R_4 is $B-(CH_2)_q$ or $B-(CH_2)_e-Z-(CH_2)_r-$, wherein B is  , q is 0-2, Z is -O-, e is 0, r is 0, R_{16} is H, R_{17} is H and R_{15} is as defined in claim 1.

5. A compound as claimed in claim 4 wherein R_{15} is H, OH, lower alkoxy or chloro.

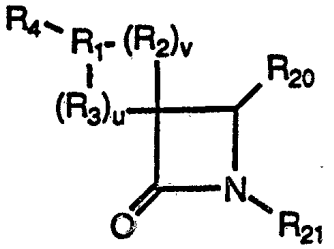
6. A compound as claimed in any one of claims 1 to 5 wherein R_{20} is phenyl or W-substituted phenyl, wherein W is as defined in claim 1.

7. A compound of claim 6 wherein R_{20} is W-substituted phenyl and W is lower alkoxy, OH or $-C(O)R_{12}$, wherein R_{12} is lower alkoxy.

8. A compound as claimed in any one of claims 1 to 7 wherein R_{21} is phenyl, W-substituted phenyl, indanyl, benzofuranyl, benzodioxolyl,

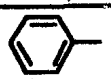
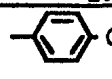
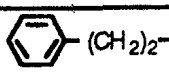
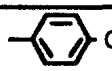
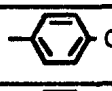
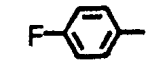
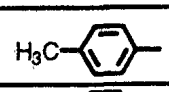
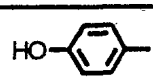
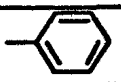
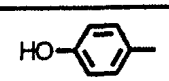
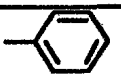
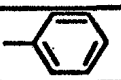
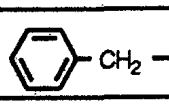
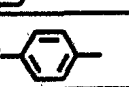
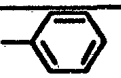
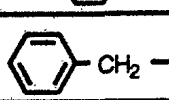
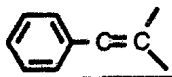
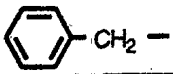
tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopropyl, wherein W is lower alkyl, lower alkoxy, OH, halogeno, -N(R_8)(R_9), -NHC(O)OR_{10}, -NHC(O)R_{10}, NO_2, -CN, -N_3, -SH, -S(O)$_{0-2}$-(lower alkyl), -$COOR_{19}$, -CON(R_8)(R_9), -COR_{12}, phenoxy, benzyloxy, -OCF_3, -CH=CHC(O)R_{12} or tert-butyldimethylsilyloxy, and when W is 2 or 3 substituents, the groups can be the same or different.

9. A compound of claim 1 represented by the formula



wherein R_1, R_2, R_3, R_4, R_{20}, R_{21}, u and v are as follows:

	R_1	-(R_2)$_v$-	-(R_3)$_u$-	R_4	R_{20}	R_{21}
i	CH	-$(CH_2)_2$-	-$(CH_2)_2$-	Cl-Ph	Ph-OCH_3	Ph-OCH_3
ii	CH	-$(CH_2)_2$-	-$(CH_2)_2$-	Ph	Ph-OCH_3	Ph-OCH_3
iii	CH	-$(CH_2)_2$-	-$(CH_2)_2$-	Ph	Ph-OCH_3	Ph
iv	CH	-$(CH_2)_2$-	-$(CH_2)_2$-	Ph	Ph-OCH_2CH_3	Ph
v	N	-$(CH_2)_2$-	-$(CH_2)_2$-	Ph	Ph-OCH_3	Ph-OCH_3
vi	CH	-$(CH_2)_2$-	-$(CH_2)_2$-	Ph	Ph	Ph-OCH_3
vii	C(CH_3)	-$(CH_2)_2$-	-$(CH_2)_2$-	Ph	Ph-OCH_3	Ph
viii	CH	-$(CH_2)_2$-	-$(CH_2)_2$-	Ph	Ph-$COOCH_3$	Ph-OCH_3
ix	CH	-$(CH_2)_2$-	-$(CH_2)_2$-	CH_3O-Ph	Ph-OCH_3	Ph
x	CH	-$(CH_2)_2$-	-$(CH_2)_2$-	Ph	Ph-SCH_3	Ph
xi	CH	-$(CH_2)_2$-	-$(CH_2)_2$-	Ph-CH_2-	Ph-OCH_3	Ph
xii	CH	-$(CH_2)_2$-	-$(CH_2)_2$-	Cl-Ph	Ph-OCH_3	Ph
xiii	CH	-$(CH_2)_2$-	-$(CH_2)_2$-	Ph-$(CH_2)_2$-	Ph-OCH_3	Ph
xiv	-C=CH-		-$(CH_2)_2$-	Cl-Ph	Ph-OCH_3	Ph

	R_1	$-(R_2)_v-$	$-(R_3)_u-$	R_4	R_{20}	R_{21}
xv	CH	$-CH_2-$	$-CH_2-$			
xvi	CH	$-CH_2-$	$-CH_2-$			
xvii	CH	$-(CH_2)_2-$	$-(CH_2)_2-$			
xviii	I $-C(OH)-$	$-(CH_2)_2-$	$-(CH_2)_2-$			
xix	I $-C(OH)-$	$-(CH_2)_2-$	$-(CH_2)_2-$			
xx	I $-C(OH)-$	$-(CH_2)_2-$	$-(CH_2)_2-$			
xxi	I $-C(OH)-$	$-(CH_2)_2-$	$-(CH_2)_2-$			
xxii	I $-C(OH)-$	$-(CH_2)_2-$	$-(CH_2)_2-$			
xxiii	I $-C(OH)-$	$-(CH_2)_2-$	$-(CH_2)_2-$			
xxiv	I $-C(OH)-$	$-(CH_2)_2-$	$-CH_2-$			
xxv	CH	$-(CH_2)_2-$	$-(CH_2)_2-$			
xxvi	CH	$-(CH_2)_2-$	$-CH_2-$			
xxvii	see R_4	$-CH_2-$	$-(CH_2)_2-$	R_1 and R_4 together are 		
xxviii	CH	$-CH_2-$	$-(CH_2)_2-$			
xxix	I $-C(F)-$	$-(CH_2)_2-$	$-(CH_2)_2-$			

10. A compound of claim 1 selected from the group consisting of: 7-(4-chlorophenyl)-3-(4-methoxyphenyl)-2-phenyl-2-azaspiro[3.5]nonan-1-one; 7-(4-chlorophenyl)-7-hydroxy-3-(4-methoxyphenyl)-2-phenyl-2-azaspiro[3.5]nonan-1-one; 7-(4-chlorophenyl)-2-(4-fluorophenyl)-7-hydroxy-3-(4-methoxyphenyl)-2-azaspiro[3.5]nonan-1-one; and 7-(4-chlorophenyl)-7-hydroxy-3-(4-hydroxyphenyl)-2-phenyl-2-azaspiro[3.5]nonan-1-one.

11. A pharmaceutical composition comprising an effective amount of a compound as claimed in any one of claims 1 to 10 in a pharmaceutically acceptable carrier.

12. A process for the preparation of a pharmaceutical composition comprising admixing a compound as defined in any one of claims 1 to 10 with a pharmaceutically acceptable carrier.

13. A method of lowering the serum cholesterol level, or treating or preventing atherosclerosis in a mammal in need of such treatment comprising administering to the mammal an effective amount of a compound as defined in any one of claims claim 1 to 10.

14. A pharmaceutical composition for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising a compound as defined in any one of claims 1 to 10, a cholesterol biosynthesis inhibitor and a pharmaceutically acceptable carrier.

15. A pharmaceutical composition according to claim 14, wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of HMG CoA reductase inhibitors.

16. A pharmaceutical composition as claimed in claim 14 or 15 wherein the cholesterol biosynthesis inhibitor is an HMG CoA reductase inhibitor selected from the group consisting of lovastatin, pravastatin, simvastatin, fluvastatin and atorvastatin.

17. A method for preparing a pharmaceutical composition comprising admixing a cholesterol biosynthesis inhibitor and a compound as defined in any one of claims 1 to 10 with a pharmaceutically acceptable carrier.

18. A method according to claim 17, wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of HMG CoA reductase inhibitors.

19. A method according to claim 17 or 18 wherein the cholesterol biosynthesis inhibitor is an HMG CoA reductase inhibitor selected from the group consisting of

lovastatin, pravastatin, simvastatin, fluvastatin and atorvastatin.

20. A kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat or prevent atherosclerosis or to reduce plasma cholesterol levels which comprises in one container an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier, and in a second container, an effective amount of a compound as defined in any one of claims 1 to 10 in a pharmaceutically acceptable carrier.

21. A kit according to claim 19, wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of HMG CoA reductase inhibitors.

22. A kit as claimed in claim 19 or 20, wherein the cholesterol biosynthesis inhibitor is an HMG CoA reductase inhibitor selected from the group consisting of lovastatin, pravastatin, simvastatin, fluvastatin and atorvastatin.

23. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising simultaneously or sequentially administering to a mammal in need of such treatment an effective amount of a cholesterol biosynthesis inhibitor and a compound as defined in any one of claims 1 to 10.

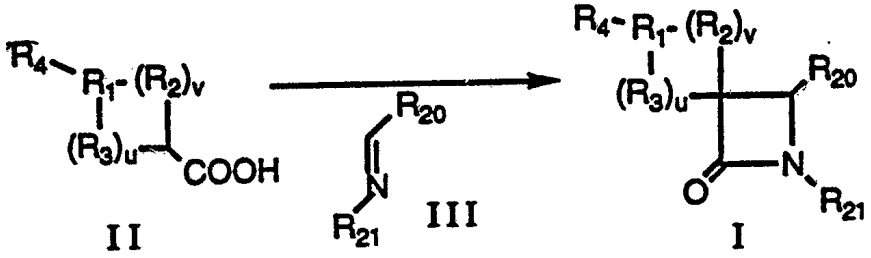
24. A method according to claim 23, wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of HMG CoA reductase inhibitors.

25. A method as claimed in claim 23 or 24, wherein the cholesterol biosynthesis inhibitor is an HMG CoA reductase inhibitor selected from the group consisting of lovastatin, pravastatin, simvastatin, flavastatin and atorvastatin.

26. A process for preparing a compound of claim 1 comprising:

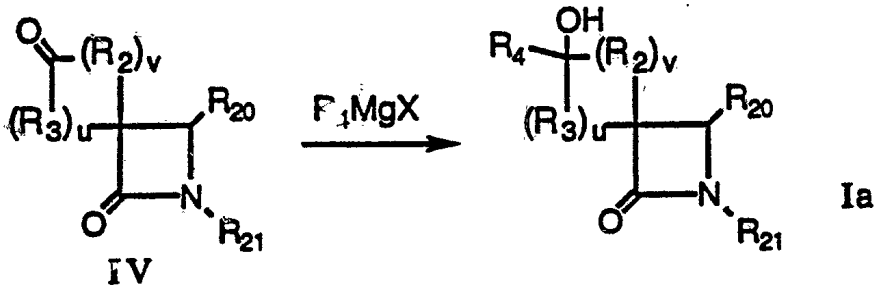
Process A: Converting a carboxylic acid of formula II to the corresponding acid chloride, followed by reacting with an imine of formula III in the presence of a

trialkylamine to obtain a compound of formula I



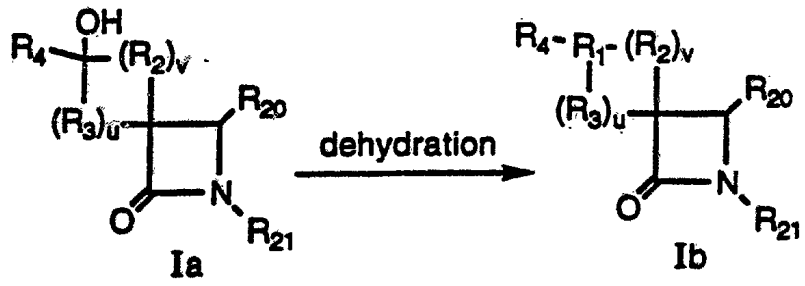
wherein R_1, R_2, R_3, R_4, R_{20}, R_{21}, u and v are as defined in claim 1;

Process B: Reacting a keto-azetidinone of formula IV with a Grignard reagent of the formula R_4MgX, wherein R_4 is as defined in claim 1 and X is halogen, to obtain a carbinol of formula Ia



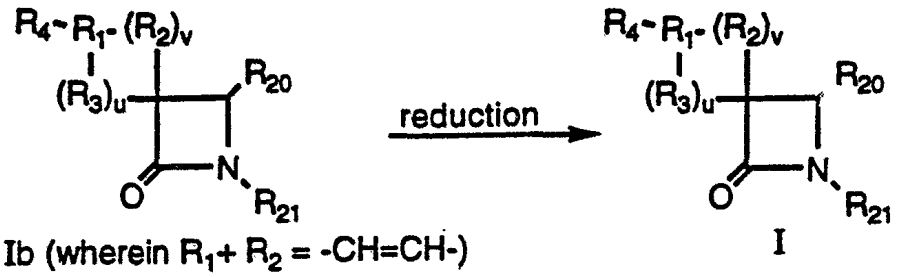
wherein R_2, R_3, R_4, R_{20}, R_{21}, u and v are as defined in claim 1 and R_1 is $-\overset{|}{C}(OH)-$;

Process C: Dehydrating a carbinol of formula Ia as defined in Process B to obtain an olefin of formula Ib



wherein $R_1 + R_2$ = -CH=CH- and R_2, R_3, R_4, R_{20}, R_{21}, u and v are as defined in claim 1; or

Process D: Reducing an olefin of formula Ib as defined in Process C to obtain a compound of formula I



Ib (wherein R_1+ R_2 = -CH=CH-) I

wherein R_1, R_2, R_3, R_4, R_{20}, R_{21}, u and v are as defined in claim 1.

27. A compound represented by a formula as defined in claim 1, substantially as hereinbefore described with reference to any one of Examples 1 to 44B.

28. A pharmaceutical composition comprising a compound represented by a formula as defined in claim 1 together with a pharmaceutically acceptable carrier, substantially as hereinbefore described with reference to any one of Examples 1 to 44B, Example A or Example B.

29. A method of lowering serum cholesterol level, or treating or preventing atherosclerosis in a mammal comprising the step of administering to the mammal an effective amount of a compound represented by a formula as defined in claim 1, substantially as hereinbefore described with reference to any one of Examples 1 to 44B.

Dated this 21st day of July 1997

SCHERING CORPORATION

By their Patent Attorneys

GRIFFITH HACK

INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/US 94/00421

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D205/12 C07D471/10 A61K31/395 //(C07D471/10,221:00, 205:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TETRAHEDRON LETTERS vol. 33, no. 15 , 1992 , OXFORD GB pages 1993 - 1996 S. LE BLANC ET AL. 'New access to spiranic beta-lactams' see the whole document ---	1,28
A	CHEMICAL ABSTRACTS, vol. 90, no. 11, 1979, Columbus, Ohio, US; abstract no. 87242k, O. IWAO 'Beta-lactams from schiff bases and ketene silylacetals' see abstract & JP,A,78 108 962 (SAGAMI CHEMICAL RESEARCH CENTER) 22 September 1978 ---	1,28
A	GB,A,1 356 145 (B.A.S.F. AG.) 12 June 1974 see page 3, line 106 - line 110; example 5 ---	1,11,28

-/-

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 1994	26. 04. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr ial Application No
PCT/US 94/00421

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 97, no. 9, 1982, Columbus, Ohio, US; abstract no. 72198w, KHRISTOSKOVA S. ET AL. 'Asymmetric synthesis of 3-anilinopropanols and 2-azetidinones' see abstract & DOKL. BOLG. AKAD. NAUK vol. 34, no. 11 , 1981 , SOFIA pages 1509 - 1512 ---	1,28
A	CHEMICAL ABSTRACTS, vol. 74, no. 21, 1971, Columbus, Ohio, US; abstract no. 111819w, SIMOVA E. ET AL. 'Reactions of schiff bases with carboxylic acid derivatives in the presence of alkaline catalysts. Synthesis of 3,3-disubstituted 1,4-diphenyl-2-azetidinones.' see abstract & IZV. OTD. KHIM. NAUKI, BULG. AKAD. NAUK. vol. 3, no. 3 , 1970 , SOFIA pages 497 - 508 ---	1,28
A	US,A,4 692 515 (V.S. GEORGIEV ET AL.) 8 September 1987 see the whole document ---	1,11,28
A	US,A,5 130 425 (M.S. MALAMAS) 14 July 1992 see the whole document ---	1,11,28
P,A	EP,A,0 524 595 (SCHERING CORPORATION) 27 January 1993 see claims & WO,A,93 02048 (SCHERING CORPORATION) 4 February 1993 cited in the application -----	1,11,28

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US94/00421

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claims 14, 26, 27 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition."

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

.formation on patent family members

Inter ıal Application No
PCT/US 94/00421

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
JP-A-78108962		NONE		
GB-A-1356145	12-06-74	DE-A-	2048080	25-05-72
		BE-A-	773173	28-03-72
		CH-A-	546759	15-03-74
		FR-A-	2108681	19-05-72
US-A-4692515	08-09-87	NONE		
US-A-5130425	14-07-92	NONE		
EP-A-0524595	27-01-93	AU-A-	2398092	23-02-93
		CN-A-	1069024	17-02-93
		WO-A-	9302048	04-02-93
WO-A-9302048	04-02-93	AU-A-	2398092	23-02-93
		CN-A-	1069024	17-02-93
		EP-A-	0524595	27-01-93