



No. 06-037990- -00003-0000

Fecha: 2007-12-27 15:25:29 Dep. 2020 NUECREACIONE
Ira. 11 PATENTICIVIL Eje: 378 FASENACIONAL
Act. 400 OPOSIOBSERVIER Folios: 97

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

SOLICITUD
PUBLICADA

Numero del expediente: 06-037990

Solicitante: ASTRAZENECA UK LIMITED

Apoderado: JUAN PABLO CADENA SARMIENTO

Título de la nueva creación o denominación del signo: "UNA COMPOSICION
FARMACEUTICA QUE COMPRENDE UNA COMBINACION DE CANDESARTAN Y ROSUVASTATINA".

Gaceta: 580

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A.	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78B -201	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: COLOMBIA	C.E. ☐	Otro ☐
	Lugar de Constitución: BARRANQUILLA	Cual _____	
	Teléfono: (571)3719900 Fax: (571)3730818	Numero 890.106.527-5	
	E-mail: _____		
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 13 No. 119-95 OF 104	C.C. ☐	NIT ☒
	Teléfono: (571)2131213 Fax: (571)6121979	C.E. ☐	Otro ☐
	E-mail: negocios@optimum-co.com	Cual _____	
		Número 51.975.664 TP 83823	

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: _____

C.C. 51.975.664

TP. 83823

REF ID: A66176039-2

SECRETARÍA DE ECONOMÍA



No. 06-037950--00003-0000

Dep: 2020 NUCLEACIONES
Lvs: 378 FASENACIONALI
Folios: 97

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
GYNOPHARM S.A.	CONSIGNACION	BANCO POPULAR	050-00110-6	71247173	18/12/2007	3,584,000.00

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LENAS COMERCIALES	256,000.00
		TOTAL :	\$ 256,000.00

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.



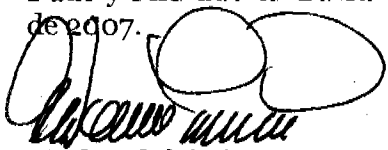
PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **06.037.990**, titulada "**UNA COMPOSICION FARMACEUTICA QUE COMPRENDE UNA COMBINACION DE CANDESARTAN Y ROSUVASTATINA**", cuyo titular es **ASTRAZENECA UK LIMITED**, publicada en la gaceta No. 580 del 28 de Septiembre de 2007.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 6 días del mes de Diciembre de 2007.


PROCAPS S.A.

WALTER TANAKA TATEKAWA
C.C. N° 16.251.923 de Palmira
Representante Legal

Acepto:


ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

DILIGENCIA DE PRESENTACION

El Notario Dieciocho (E) del Circulo de Bogota, D.C., hace constar que el presente documento fue presentado personalmente por: Elvira Isaura Valencia Gonzalez quien exhibio la C.C. ST 978 664 de B7 y Tarjeta Profesional No. 83823 C.S.J., y declaro que la firma y la huella que aparecen en el presente documento son suyas.

BOGOTA, D.C.,

Claudia M. Betancourt
FIRMA

HECTOR FABIO CORTES DIAZ
NOTARIO 18 (E)

HUELLA DEL
INDICE DERECHO

LA PRESENTE DILIGENCIA
SE PRACTICA A PETICION
DE PARTE INTERESADA

DILIGENCIA DE RECONOCIMIENTO ANTE EL
SUSCRITO NOTARIO SEXTO DE BARRANQUILLA
COMPARECIO Isaura Valencia Gonzalez

IDENTIFICADO CON act 1623 913 Isaura (vlla)
y declaro que es cierto el contenido del documento
anterior y suya la firma

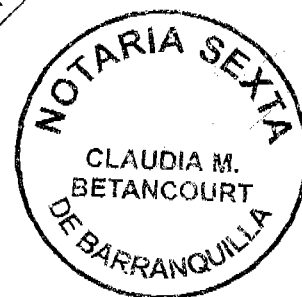
Barranquilla

10 DI 2007

Isaura Valencia Gonzalez



LA HUELLA DE ESTA
DILIGENCIA CORRESPONDE
AL COMPARECIENTE
NOTARIO SEXTO





***** Pag. 1
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

***** C O N T I N U A *****

UNIVERSAL C 4454 S.A. NIT. 890 321 151-0 FORMAS E-C-075

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE
DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996,
otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta
Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del
libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras
y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad
se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

***** C O N T I N U A *****



***** Pag. 2
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista,

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,224,500,000	*****1,224,500	*****1,000
Pagado		
\$*****1,224,500,000	*****1,224,500	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva.

La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente

***** C O N T I N U A *****



***** Pag. 3
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zilberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	*****
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	

***** C O N T I N U A *****



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C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

Minski Gontovnik Ruben
Suplente del Presidente

CC.*****7,463,982

Minski Minski Abraham
Vicepresidente

CC.*****802,575

Minski Gontovnik Meyer
Suplente del vicepresidente

CC.*****7,461,324

Minski Gontovnik Jose

CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Gerente General.

Uribe Ochoa Guillermo Luis

CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Suplente del Gerente.

Tanaka Tatekawa Walter

CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Revisor Fiscal Ppal.

Vargas Pertuz Ana Isabel

CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS

***** C O N T I N U A *****

FORMAS EFICIENTES 100-34505-C

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Lozada Villareal Milena	CC.*****32,748,111

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, otorgada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad: 1.-Se confiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial, amplio y suficiente, a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requiera por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, comparecer en juicios, pedir la practica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o

***** C O N T I N U A *****



***** Pag. 5
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.-----

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrito en esta Camara de Comercio el 8 de junio de 2000, bajo el No.1.786 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a KAREN FIGUEROA GARCIA, C.C.No.32.732.070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS S.A, en el giro normal de sus negocios y operaciones sociales.--

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No.2.290 del libro respectivo, el señor RUBEN MINSKI GONTOVNIK, C.C.No.7.463.982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPECIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.-----

C E R T I F I C A

Que segun documento privado del 10 de noviembre del 2004, inscrito en esta Camara de Comercio el 1 de diciembre del 2.004, bajo el No. 2.753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C.C. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a ANTONIO VARELA DIAZ, C.C.No.72.004.669 de Barranquilla, para que en nombre y representacion de la sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S.A., a suscribir en el giro normal de sus negocios y operaciones socia-

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

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les. Por lo anterior, el señor ANTONIO VARELA DIAZ, queda facultado para firmar las declaraciones comabiarías y demás documentos relacionados con las declaraciones, notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo acto necesario de tal forma que pueda cumplir con el mandato dado.-

C E R T I F I C A

Que segun documento privado del 22 de Febrero de 2005, inscrito en esta Camara de Comercio el 28 de Marzo de 2.005, bajo el No. 2.820 del libro respectivo, consta que WALTER TANAKA TATEKAWA C.C. 16.251-923 de Palmira, quien actua como representante legal de la sociedad PROCAPS S.A, otorga Poder Especial, Amplio y Suficiente al señor MARLON TATIS PAREDES C.C. No. 72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los tramites o registros de comercio exterior ante la direccion de impuestos y aduanas nacionales y/o cualquier entidad que haga sus veces, y para que responda todo tipo de requerimientos y/o solicitudes de informacion de las autoridades aduaneras en los ordenes distrital, departamental y nacional.-----

C E R T I F I C A

Que por Escritura Pública No. 2,011 del 10 de Octubre de 2006, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Dic/bre de 2006 bajo el No. 3,183 del libro respectivo,-----
Consta que RUBEN MINSKI GONTOVNIK CC.No.7.463.928, quien manifesto que en su condicion de Presidente y Representante Legal de la ----- sociedad PROCAPS S.A.,confiere poder especial amplio y suficiente a los siguientes señores que conforman el Grupo A y el Grupo B, para que conjuntamente suscriban contratos de suministro de mercancías y servicios con entidades oficiales, hasta por la suma de ochocientos mil dolares de los Estados Unidos de America (US\$800.000.00), ----
liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. Grupo A: IVAN VILLAREAL CAMACHO CC.No.91.201.749. FERNANDO RINCON RIVERA CC.No.79.484.187. CLAUDIA TANGARIFE CASTILLO CC.No.41.660.293.Grupo B. WALTER TANAKA TATEKAWA CC.No.16.251.923. CARMEN ALICIA FLOREZ DE LA ROTA -----
CC.No.22.434.044. RICARDO DORADO HURTADO CC.No.79.715.772.-----

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 20 de Marzo de 2007.

La información sobre embargos de establecimiento se suministra en

***** C O N T I N U A *****



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CAMARA DE COMERCIO
DE BARRANQUILLA
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

Certificados de Matrícula, la de contratos sujetos a registro, en
Certificados Especiales.

independiente

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Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 06-037990

Asunto : Oposición a la solicitud de patente de Invención titulada
"UNA COMPOSICIÓN FARMACÉUTICA QUE
COMPRENDE UNA COMBINACIÓN DE
CANDESARTAN Y ROSUVASTATINA"

Solicitante : ASTRAZENECA UK LIMITED.

Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 580 del 28 de septiembre de 2007

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad *PROCAPS S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "UNA COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE UNA COMBINACIÓN DE CANDESARTAN Y ROSUVASTATINA", cuyo titular es ASTRAZENECA UK

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LIMITED, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular candesartan y rosuvastatina. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 21 de abril de 2006, reivindicando prioridad bajo la solicitud GB20030022552 2003-09-26, y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 580 del 28 de septiembre de 2007, cuya publicación internacional corresponde a la WO2005030215 del 2005-04-07.

2.2. La solicitud colombiana 06-037990 objeto de la presente oposición, se refiere a una combinación que comprende candesartán o su sal de aceptación farmacéutica y rosuvastatina o su sal de aceptación farmacéutica para prevención o tratamiento de

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arteriosclerosis; donde en asociación con un diluyente o vehículo o de aceptación farmacéutica para uso en la prevención o tratamiento de arteriosclerosis; donde en asociación con un diluyente o vehículo de aceptación farmacéutica para uso en la prevención de acontecimientos cardiovasculares; donde la composición es para uso en la manufactura de un medicamento para la prevención o tratamiento de arteriosclerosis, para uso en la manufactura de un medicamento para la prevención de acontecimientos cardiovasculares, para uso como un medicamento para la prevención o tratamiento de arteriosclerosis, para uso como un medicamento para prevención o tratamiento de arteriosclerosis.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren al uso y a un método de tratamiento y no a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, la presente no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

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- D1: US20030069221 publicada el 10 de abril de 2003.
- D2: EP1314425 publicada el 28 de mayo de 2003.
- D3: US5663187 publicada el 2 de septiembre de 1997.

2.5. Ahora bien, el documento D1, particularmente en la descripción, revela una composición que incluye combinaciones terapéuticas entre al menos un inhibidor de absorción esteroide y al menos un agente cardiovascular diferente del inhibidor de absorción esteroide, que puede ser útil para tratar condiciones vasculares, obesidad, diabetes y bajar los niveles plasmáticos de esteroides. Según este documento anterior D1, se revelan combinaciones donde al menos un antagonista oral de los receptores de angiotensina II es seleccionado del grupo que consiste en candesartan (ver reivindicación 25 de D1) y donde el inhibidor de reductasa de HMG-CoA puede comprender rosuvastatina (reivindicación 37 de D1). Así, las cosas, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica, particularmente en el documento D1.

2.6. Por su parte, el documento D2 revela composiciones farmacéuticas que comprenden un inhibidor de reductasa de HMG-CoA y un antagonista oral de los receptores de angiotensina II. Particularmente, este documento D2 revela composiciones farmacéuticas para la prevención o el tratamiento de insuficiencia cardíaca, la prevención de enfermedad coronaria isquémica o la prevención de la repetición de enfermedad coronaria isquémica, donde dicha composición comprende un inhibidor de reductasa de HMG-CoA seleccionado del grupo que consiste en pravastatina, simvastatina, lovastatina, pitavastatina y ZD-4522 así como un antagonista oral de los receptores de angiotensina II. Por su parte, el documento D3 revela un método de tratamiento para la reducción de la aterosclerosis y/o colesterol que comprende el uso de un antagonista de angiotensina II en combinación con un inhibidor de reductasa de HMG-CoA. Así

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las cosas, con base en los que dictan estos documentos D2 y D3, cualquier persona versada en la materia, al combinar este conocimiento con aquel deducido del documento D1, puede llegar de manera obvia a la materia aquí pretendida. De hecho a partir de la combinación de estos documentos, cualquier persona versada en la materia puede llegar a deducir una composición farmacéutica para la prevención o el tratamiento de insuficiencia cardíaca, la prevención de enfermedad coronaria isquémica o la prevención de la repetición de enfermedad coronaria isquémica, donde dicha composición comprende un inhibidor de reductasa de HMG-CoA tal como rosuvastatina así como un antagonista de los receptores de angiotensina II tal como candesartan. Por lo tanto, a los ojos de estos documentos D2 y D3 en combinación con la materia revelada en D1, la presente solicitud carece de altura o nivel inventivo.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 06.037990 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8.1. **CARECE DE NOVEDAD**: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”* A la fecha de prioridad, 26 de septiembre de 2003 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, combinaciones entre candesartan y rosuvastatina, sobre el cual busca protección en el capítulo reivindicatorio.

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2.8.2. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 26 de septiembre de 2003, a partir de los documentos D2 y D3 en combinación con D1, es posible deducir combinaciones donde al menos un antagonista oral de los receptores de angiotensina II es seleccionado del grupo que consiste en candesartan y donde el inhibidor de reductasa de HMG-CoA puede comprender rosuvastatina sobre el cual busca protección en el capítulo reivindicatorio.

2.8.3. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la*

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tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”. La solicitud pretendida no cumple con los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada “UNA COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE UNA COMBINACIÓN DE CANDESARTAN Y ROSUVASTATINA”, cuyo titular es ASTRAZENECA UK LIMITED, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 580.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: US20030069221 publicada el 10 de abril de 2003.
- D2: EP1314425 publicada el 28 de mayo de 2003.
- D2: US5663187 publicada el 2 de septiembre de 1997.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del artículo 586 del Código de Comercio.

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4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

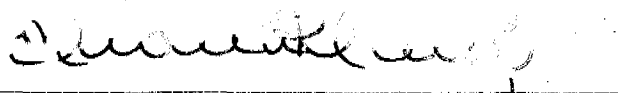
- D1: US20030069221 publicada el 10 de abril de 2003.
- D2: EP1314425 publicada el 28 de mayo de 2003.
- D2: US5663187 publicada el 2 de septiembre de 1997.

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6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.



US 20030069221A1

(19) **United States**

(12) **Patent Application Publication**
Kosoglou et al.

(10) **Pub. No.: US 2003/0069221 A1**
(43) **Pub. Date: Apr. 10, 2003**

(54) **COMBINATIONS OF STEROL ABSORPTION
INHIBITOR(S) WITH CARDIOVASCULAR
AGENT(S) FOR THE TREATMENT OF
VASCULAR CONDITIONS**

(75) **Inventors: Teddy Kosoglou, Jamison, PA (US);
Rudyard J. Ress, Flemington, NJ (US);
John T. Strony, Lebanon, NJ (US);
Enrico P. Veltri, Princeton, NJ (US);
William Hauer, Warren, NJ (US)**

**Correspondence Address:
SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530 (US)**

(73) **Assignee: Schering Corporation**

(21) **Appl. No.: 10/057,339**

(22) **Filed: Jan. 25, 2002**

Related U.S. Application Data

(60) **Provisional application No. 60/323,842, filed on Sep. 21, 2001. Provisional application No. 60/264,396, filed on Jan. 26, 2001. Provisional application No. 60/264,600, filed on Jan. 26, 2001. Provisional application No. 60/264,275, filed on Jan. 26, 2001.**

Publication Classification

(51) **Int. Cl.⁷ A61K 31/397**
(52) **U.S. Cl. 514/210.02**

(57) **ABSTRACT**

The present invention provides compositions, therapeutic combinations and methods including: (a) at least one sterol absorption inhibitor and (b) at least one cardiovascular agent different from the sterol absorption inhibitor, which can be useful for treating vascular conditions, obesity, diabetes and lowering plasma levels of sterols.

**COMBINATIONS OF STEROL ABSORPTION
INHIBITOR(S) WITH CARDIOVASCULAR
AGENT(S) FOR THE TREATMENT OF VASCULAR
CONDITIONS**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

[0001] This application claims the benefit of priority from U.S. Provisional Patent Application Serial No. 60/323,842 filed Sep. 21, 2001, U.S. Provisional Patent Application Serial No. 60/264,396 filed Jan. 26, 2001, U.S. Provisional Patent Application Serial No. 60/264,600 filed Jan. 26, 2001, and U.S. Provisional Patent Application Serial No. 60/264,275 filed Jan. 26, 2001, each incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to methods, compositions and therapeutic combinations comprising certain cardiovascular agents and sterol absorption inhibitors for treating atherosclerosis, coronary artery disease and other vascular conditions in mammals.

BACKGROUND OF THE INVENTION

[0003] Vascular disease is a term that broadly encompasses all disorders of blood vessels including small and large arteries and veins and blood flow. The most prevalent form of vascular disease is arteriosclerosis, a condition associated with the thickening and hardening of the arterial wall. Arteriosclerosis of the large vessels is referred to as atherosclerosis. Atherosclerosis is the predominant underlying factor in vascular disorders such as coronary artery disease, aortic aneurysm, arterial disease of the lower extremities and cerebrovascular disease.

[0004] One major risk factor for arteriosclerosis is high serum cholesterol. A total cholesterol level in excess of 225-250 mg/dl is associated with significant elevation of risk of vascular disease, particularly coronary heart disease.

[0005] 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 step in the intestinal absorption of dietary cholesterol. Thus, inhibition of cholesteryl ester formation and reduction of serum cholesterol can 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.

[0006] The regulation of whole-body cholesterol homeostasis in mammals and animals involves the regulation of dietary cholesterol and 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 intestinal cholesterol absorption is reduced, by what-

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

[0007] U.S. Pat. Nos. 5,767,115, 5,624,920, 5,668,990, 5,656,624 and 5,688,787, respectively, disclose hydroxy-substituted azetidinone compounds and substituted β -lactam compounds useful for lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. Pat. Nos. 5,846,966 and 5,661,145, respectively, disclose hydroxy-substituted azetidinone compounds or substituted β -lactam compounds in combination with HMG CoA reductase inhibitors for preventing or treating atherosclerosis and reducing plasma cholesterol levels.

[0008] PCT Patent Application No. WO 00/38725 discloses cardiovascular therapeutic combinations including an ileal bile acid transport inhibitor or cholesteryl ester transport protein inhibitor in combination with a fibric acid derivative, nicotinic acid derivative, microsomal triglyceride transfer protein inhibitor, cholesterol absorption antagonist, phytosterol, stanol, antihypertensive agent or bile acid sequestrant.

[0009] U.S. Pat. No. 5,698,527 discloses ergostanone derivatives substituted with disaccharides as cholesterol absorption inhibitors, employed alone or in combination with certain other cholesterol lowering agents, which are useful in the treatment of hypercholesterolemia and related disorders.

[0010] Other vascular conditions frequently coexist with cholesterol levels associated with atherosclerosis. These may include hypertension, angina and/or arrhythmia. The relevance of, for example, elevated blood pressure as a risk factor for atherosclerosis, cardiovascular and cerebrovascular disease in both men and women has been clarified in a large number of epidemiological studies.

[0011] Clinical trials of blood pressure lowering using cardiovascular agents including, for example, calcium channel blockers, have shown beneficial effects in the treatment of early atherosclerotic lesions (see, e.g., Lichtien, P. R. et al. :Lancet, 335: 1109-1113 (1990) and Waters, D. et al. Circulation 82: 1940-1953 (1990)). Scott (PCT patent Application No. WO 99/11260) describes combinations of an HMG CoA reductase inhibitor with an antihypertensive agent for the treatment of atherosclerosis and other symptoms of vascular disease risk. Additionally, Egon et al. (PCT Patent Application No. WO 96/40255) describe a combination therapy of antihypertensive agents including eplerenone and angiotensin II antagonist for treating cardiovascular disease.

[0012] Despite recent improvements in the treatment of vascular disease, there remains a need in the art for improved compositions and treatments for atherosclerosis, other vascular diseases and conditions associated with vascular diseases such as hypertension, atherosclerosis, and hyperlipidaemia.

SUMMARY OF THE INVENTION

[0013] In one embodiment the present invention provides a composition comprising (a) at least one sterol absorption

inhibitor or pharmaceutically acceptable salt or solvate thereof or prodrug of the at least one sterol absorption inhibitor or of the salt or solvate thereof; and (b) at least one cardiovascular agent for treating a vascular condition, diabetes, obesity and/or lowering a concentration of a sterol in plasma of a mammal which is different from the at least one sterol absorption inhibitor.

[0014] Therapeutic combinations also are provided comprising: (a) a first amount of at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate thereof or prodrug of the at least one sterol absorption inhibitor or of the salt or solvate thereof; and (b) a second amount of at least one cardiovascular agent for treating a vascular condition in a mammal which is different from the at least one sterol absorption inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity and/or lowering a concentration of a sterol in plasma of a mammal.

[0015] Pharmaceutical compositions for the treatment or prevention of vascular conditions, obesity, diabetes and/or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the above compositions or therapeutic combinations and a pharmaceutically acceptable carrier also are provided.

[0016] Methods of treating or preventing vascular conditions, obesity, diabetes or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the above compositions or therapeutic combinations also are provided.

[0017] Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about."

DETAILED DESCRIPTION

[0018] In one embodiment, the present invention is directed to compositions, pharmaceutical compositions, therapeutic combinations, kits and methods of treatment using the same comprising (a) at least one (one or more) sterol absorption inhibitor(s), such as but not limited to, substituted azetidinone sterol absorption inhibitors or substituted β -lactam sterol absorption inhibitors discussed in detail below, or pharmaceutically acceptable salts or solvates thereof or prodrugs of the at least one sterol absorption inhibitor or of the salts or solvates thereof; and (b) at least one (one or more) cardiovascular agent(s) different from the sterol absorption inhibitor(s) (component (a)).

[0019] The compositions and therapeutic combinations of the present invention can be administered to a mammal in need of such treatment in a therapeutically effective amount to treat vascular conditions such as atherosclerosis, hyperlipidaemia (including but not limited to hypercholesterolaemia, hypertriglyceridaemia, sitosterolemia), hypertension, vascular inflammation, angina, cardiac arrhythmias, stroke, as well as diabetes, obesity, and/or to reduce the level of sterol(s) in the plasma. The compositions and treatments can be administered by any suitable means which produce contact of these compounds with the site of action in the body, for example in the plasma, liver or small intestine of a mammal or human.

[0020] "Cardiovascular agents" which may be used to treat the vascular conditions of the present invention, obesity or diabetes and/or to reduce the level of sterol(s) in the plasma, as used herein, are members of different classes, including calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists, diuretics, adrenergic blockers including beta-adrenergic receptor blockers and alpha-adrenergic receptor blockers, adrenergic stimulants, coronary vasodilators, antihypertensive agents, diuretics, anti-anginal agents and combinations thereof. The phrase "cardiovascular agents" as used herein does not include HMGCoA reductase inhibitors. The cardiovascular agents as defined above are chemically or structurally different from the sterol absorption inhibitor(s) discussed below, for example, they contain one or more different atoms, have a different arrangement of atoms or a different number of one or more atoms than the sterol absorption inhibitor(s) discussed below.

[0021] Useful "adrenergic blockers" include those compounds which are β -receptor inhibitors and/or α -receptor inhibitors. Adrenergic blockers which are β receptor inhibitors include a class of drugs that antagonize the cardiovascular effects of catecholamines in hypertension, angina pectoris, and cardiac arrhythmias. β -adrenergic receptor blockers include, but are not limited to, bunolol hydrochloride (1(2H)-Naphthalenone, 5-[3-(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydro-, hydrochloride, CAS RN 31969-05-8 which can be obtained from Parke-Davis); acebutolol ($\pm$ N-[3-Acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]-butanamide, or ($\pm$)-3'-Acetyl-4'-[2-hydroxy-3-(isopropylamino)propoxy]butyranilide); acebutolol hydrochloride (such as N-[3-acetyl-4-[2-hydroxy-3-[(1-methyl-ethyl)amino]propoxy]phenyl]-, monohydrochloride, ($\pm$)-; 3'-Acetyl-4'-[2-hydroxy-3-(isopropylamino)propoxy]butyranilide monohydrochloride, for example, SECTRAL® Capsules available from Wyeth-Ayerst); alprenolol hydrochloride (2-Propanol, 1-[(1-methylethyl)amino]-3-[2-(2-propenyl)phenoxy]-, hydrochloride, CAS RN 13707-88-5 see Netherlands Patent Application No. 6,605,692); atenolol (such as benzeneacetamide 4-[2'-hydroxy-3'-[(1-methylethyl)amino]propoxy]-, for example, TENORMIN® I.V. Injection available from AstraZeneca); carteolol hydrochloride (such as 5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydro-2(1H)-quinolinone monohydrochloride, for example, Cartrol® Filmtab® Tablets available from Abbott); Celiprolol hydrochloride (3-[3-Acetyl-4-[3-(tert-butylamino)-2-hydroxypropoxy]phenyl]-1,1-diethylurea monohydrochloride, CAS RN 57470-78-7, also see in U.S. Pat. No. 4,034,009); cetamolol hydrochloride (Acetamide, 2-[2-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]phenoxy]-N-methyl-, monohydrochloride, CAS RN 77590-95-5, see also U.S. Pat. No. 4,059,622); labetalol hydrochloride (such as 5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]salicylamide monohydrochloride, for example, NORMODYNE® Tablets available from Schering; esmolol hydrochloride ($\pm$)-Methyl p-[2-hydroxy-3-(isopropylamino)propoxy]hydrocinnamate hydrochloride, for example, BREVIBLOC® Injection available from Baxter); levobetaxolol hydrochloride (such as (S)-1-[p-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)-2-propanol hydrochloride, for example, BETAXON™ Ophthalmic Suspension available from Alcon); levobunolol hydrochloride (such as (-)-5-[3-(tert-

Butylamino)-2-hydroxypropoxy]-3,4-dihydro-1 (2H)-naphthalenone hydrochloride, for example, BETAGAN® Liquid® with C CAP® Compliance Cap available from Allergan); nadolol (such as 1-(tert-butylamino)-3-[(5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol, for example, Nadolol Tablets available from Mylan); practolol (Acetamide, N-[4-[2-hydroxy-3-[1-methylethylamino]-propoxy]phenyl]-, CAS RN 6673-35-4, see also U.S. Pat. No. 3,408,387); propranolol hydrochloride (1-(Isopropylamino)-3-(1-naphthyl)oxy)-2-propanol hydrochloride CAS RN 318-98-9); sotalol hydrochloride (such as d,l-N-[4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-phenyl]methane-sulfonamide monohydrochloride, for example, BETAPACE AF™ Tablets available from Berlex); timolol (2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-, hemihydrate, (S)-, CAS RN 91524-16-2); timolol maleate (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (Z)-2-butenedioate (1:1) salt, CAS RN 26921-17-5); bisoprolol (2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethylamino)-, (±), CAS RN 66722-44-9); bisoprolol fumarate (such as (±)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethylamino)-2-propanol (E)-2-butenedioate (2:1) (salt), for example, ZEBETA™ Tablets available from Lederle Consumer); nebivolol (2H-1-Benzopyran-2-methanol, $\alpha\alpha'$ -[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-, CAS RN 99200-09-6 see also U.S. Pat. No. 4,654,362); cicloprolol hydrochloride, such as 2-Propanol, 1-[4-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-[1-methylethylamino]-, hydrochloride, A.A.S. RN 63686-79-3); and dexpropranolol hydrochloride (2-Propanol, 1-[1-methylethylamino]-3-(1-naphthalenyloxy)-hydrochloride (CAS RN 13071-11-9); diacetolol hydrochloride (Acetamide, N-[3-acetyl-4-[2-hydroxy-3-[(1-methyl-ethyl)amino]propoxy]phenyl]-, monohydrochloride CAS RN 69796-04-9); dilevalol hydrochloride (Benzamide, 2-hydroxy-5-[1-hydroxy-2-[1-methyl-3-phenylpropyl]amino]ethyl]-, monohydrochloride, CAS RN 75659-08-4); exaprolol hydrochloride (2-Propanol, 1-(2-cyclohexylphenoxy)-3-[(1-methylethylamino)-, hydrochloride CAS RN 59333-90-3); fleistol sulfate (Benzoic acid, 2-fluoro-3-[[2-[aminocarbonyl]amino]-dimethylethyl]amino)-2-hydroxypropyl ester, (±)- sulfate (1:1) (salt), CAS RN 88844-73-9; metolol hydrochloride (Methanesulfonamide, N-[4-[1-hydroxy-2-(methylanilino)propyl]phenyl]-, monohydrochloride CAS RN 7701-65-7); metoprolol 2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[1-methylethylamino]-; CAS RN 37350-58-6); metoprolol tartrate (such as 2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethylamino)-, for example, LOPRESSOR® available from Novartis); pamatolol sulfate (Carbamic acid, [2-[4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]-ethyl]-, methyl ester, (±) sulfate (salt) (2:1), CAS RN 59954-01-7); penbutolol sulfate (2-Propanol, 1-(2-cyclopentylphenoxy)-3-[1,1-dimethylethylamino]1, (S)-, sulfate (2:1) (salt), CAS RN 38363-32-5); practolol (Acetamide, N-[4-[2-hydroxy-3-[(1-methylethyl)amino]-propoxy]phenyl]-, CAS RN 6673-35-4); tiprenolol hydrochloride (Propanol, 1-[(1-methylethyl)amino]-3-[2-(methylthio)-phenoxy]-, hydrochloride, (±), CAS RN 39832-43-4); tolamolol (Benzamide, 4-[2-[[2-hydroxy-3-(2-methylphenoxy)-propyl]amino]ethoxy]-, CAS RN 38103-61-6).

[0022] Adrenergic receptors which are α -receptor inhibitors act to block vasoconstriction induced by endogenous catecholamines. The resulting fall in peripheral resistance leads to a fall in mean blood pressure. The magnitude of this effect is dependent upon the degree of sympathetic tone at the time the antagonist is administered.

[0023] Suitable adrenergic receptors which are α -receptor inhibitors include, but are not limited to, fenpropiride hydrochloride (which may be prepared as disclosed in U.S. Pat. No. 3,399,192 herein incorporated by reference); proroxan (CAS RN 33743-96-3); alfuzosin hydrochloride (CAS RN: 81403-68-1); and labetalol hydrochloride as described above or combinations thereof.

[0024] Adrenergic blockers with α and β receptor inhibitor activity which may be used with the present invention include, but are not limited to, bretylium tosylate (CAS RN: 61-75-6); dihydroergotamine mesylate (such as ergotaman-3', 6', 18-trione, 9, 10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-, (5'(α))-, monomethanesulfonate, for example, DHE 45® Injection available from Novartis); carvedilol (such as (±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol, for example, COREG® Tablets available from SmithKline Beecham); labetalol (such as 5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]salicylamide monohydrochloride, for example, NORMODYNE® Tablets available from Schering); bretylium tosylate (Benzenemethanaminium, 2-bromo-N-ethyl-N,N-dimethyl-, salt with 4-methylbenzenesulfonic acid (1:1) CAS RN 61-75-6); phentolamine mesylate (Phenol, 3-[[[(4,5-dihydro-1H-imidazol-2-yl)methyl](4-methylphenyl)amino]-, monomethanesulfonate (salt) CAS RN 65-28-1); solypertine tartrate (5H-1,3-Dioxolo[4,5-f]indole, 7-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) CAS RN 5591-43-5); zolertine hydrochloride (Piperazine, 1-phenyl-4-[2-(1H-tetrazol-5-yl)ethyl]-, monohydrochloride (8Cl, 9Cl) CAS RN 7241-94-3).

[0025] Vascular conditions may be caused or aggravated by hypertension. Hypertension is defined as persistently high blood pressure. Generally, adults are classified as being hypertensive when systolic blood pressure is persistently above 140 mmHg or when diastolic blood pressure is above 90 mmHg. Long-term risks for cardiovascular mortality increase in a direct relationship with persistent blood pressure. Suitable examples of antihypertensive agents which may be used in the present invention include althiazide (2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-3-[(2-propenylthio)methyl]-, 1,1-dioxide CAS RN 5588-16-9); benzthiazide (2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3-[[[phenylmethyl]thio]methyl]-, 1,1-dioxide CAS RN 91-33-8); captopril (L-Proline, 1-[(2S)-3-mercapto-2-methyl-1-oxopropyl]- CAS RN 62571-86-2); carvedilol (2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- CAS RN 72956-09-3); chlorothiazide (sodium 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- CAS RN 72956-09-3); clonidine hydrochloride (1H-Imidazol-2-amine, N-(2,6-dichlorophenyl)-4,5-dihydro-, monohydrochloride CAS RN 4205-91-8); cyclothiazide (2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-, 1,1-dioxide CAS RN 2259-96-3); delapril hydrochloride (2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,

4-dihydro-, 1,1-dioxide CAS RN 2259-96-3); dilevalol hydrochloride (2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-, 1,1-dioxide CAS RN 2259-96-3); delapril hydrochloride (Glycine, N-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-N-(2,3-dihydro-1H-inden-2-yl)-, monohydrochloride CAS RN 83435-67-0); doxazosin mesylate (Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate CAS RN 77883-43-3); fosinopril sodium (L-Proline, 4-cyclohexyl-1-[(R)-[(1S)-2-methyl-1-(1-oxopropoxy)propox]; moexipril hydrochloride (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, (3S)- CAS RN 82586-52-5); monatepil maleate (1-Piperazinebutanamide, N-(6,11-dihydrodibenzo(b,e)thiepin-11-yl)-4-(4-fluorophenyl)-, (±)-, (Z)-2-butenedioate (1:1) (±)-N-(6,11-Dihydrodibenzo(b,e)thiepin-11-yl)-4-(p-fluorophenyl)-1-piperazinebutyramide maleate (1:1) CAS RN 132046-06-1); Metoprolol succinate (Butanedioic acid, compd. with 1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-2-propanol (1:2) CAS RN 98418-47-4); guanfacine hydrochloride (Benzeneacetamide, N-(aminoiminomethyl)-2,6-dichloro-, monohydrochloride CAS RN 29110-48-3); methyl dopa (L-Tyrosine, 3-hydroxy- α -methyl- CAS RN 555-30-6); quinaprilat (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[(1S)-1-carboxy-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- CAS RN 82768-85-2); quinapril hydrochloride (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, (3S)- CAS RN 82586-55-8); Primidolol (2,4(1H,3H)-Pyrimidinedione, 1-[2-[[2-hydroxy-3-(2-methylphenoxy)propyl]amino]ethyl]-5-methyl- CAS RN 67227-55-8); prazosin hydrochloride (Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcabonyl)-, monohydrochloride CAS RN 19237-84-4); peflanserlin hydrochloride 2,4(1H,3H)-Quinazolin-3-one, 3-[3-(4-phenyl-1-piperazinyl)propyl]-, monohydrochloride CAS RN 42877-18-9); phenoxymethamine hydrochloride (Benzenemethanamine, N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)-, hydrochloride CAS RN 63-92-3); candesartan cilexetil (1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-, 1-[(cyclohexyloxy)carbonyl]oxy]ethyl ester CAS RN 145040-37-5); telmisartan (1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- CAS RN 144701-48-4); candesartan (1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-, 1-[(cyclohexyloxy)carbonyl]oxy]ethyl ester CAS RN 139481-59-7); losartan potassium (1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-, monopotassium Irbesartan 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]- CAS RN 138402-11-6).

[0026] An angiotensin system inhibitor is an agent that interferes with the function, synthesis or catabolism of angiotensin II. These agents which may be used in the present invention include but are not limited to angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, angiotensin II receptor antagonists, agents that activate the catabolism of angiotensin II and agents that prevent the synthesis of angiotensin I from which angiotensin II is ultimately derived. The renin-angiotensin system is involved in the regulation of hemodynamics and water and electrolyte balance. Factors that lower blood volume, renal perfusion, or the concentration of Na⁺ in plasma tend to activate the system, while factors that increase these parameters tend to suppress its function. Angiotensin I and angiotensin II are synthesized by the enzymatic renin-angiotensin pathway. The synthetic process is initiated when the enzyme renin acts on angiotensinogen, a pseudoglobulin in blood plasma, to produce the decapeptide angiotensin I. Angiotensin I is converted by angiotensin-converting enzyme (ACE) to angiotensin II. The latter is an active pressor substance which has been implicated as a causative agent in several forms of hypertension in various mammalian species.

[0027] "Angiotensin II receptor antagonists" are compounds which interfere with the activity of angiotensin II by binding to angiotensin II receptors and interfering with its activity. Well known angiotensin II receptor antagonists which may be used in the present invention include peptide compounds and non-peptide compounds. Non-limiting examples of angiotensin II receptor antagonists include: candesartan cilexetil (1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-, 1-[(cyclohexyloxy)carbonyl]oxy]ethyl ester) CAS RN 145040-37-5); telmisartan ([1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- CAS RN 144701-48-4); candesartan (1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-, 1-[(cyclohexyloxy)carbonyl]oxy]ethyl ester) CAS RN 139481-59-7); losartan potassium (1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-, monopotassium Irbesartan 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]- CAS RN 138402-11-6).

[0028] "Angiotensin-converting enzyme (ACE), is an enzyme which catalyzes the conversion of angiotensin I to angiotensin II. ACE inhibitors which may be used in the present invention include amino acids and derivatives thereof, peptides, including di and tri peptides and antibodies to ACE which intervene renin-angiotensin system by inhibiting the activity of ACE thereby reducing or eliminating the formation of pressor substance angiotensin II. ACE inhibitors have been used medically to treat hypertension, congestive heart failure, myocardial infarction and renal disease. Suitable ACE inhibitors include, but are not limited to, benazepril hydrochloride (such as 3-[[1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-(3S)-benzazepine-1-acetic acid monohydrochloride, for example, LOTREL® Capsules available from Novartis); captopril (such as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, for example, CAPTOPRIL Tablets available from Mylan); fosinopril (such as 1-proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy) propoxy](4-phenylbutyl) phosphinyl]acetyl]-, sodium salt, trans-, for example, MONOPRIL® Tablets available from Bristol-Myers Squibb); moexipril hydrochloride (such as [3S]-[2

[0026] An angiotensin system inhibitor is an agent that interferes with the function, synthesis or catabolism of angiotensin II. These agents which may be used in the present invention include but are not limited to angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, angiotensin II receptor antagonists, agents that activate the catabolism of angiotensin II and agents that prevent the synthesis of angiotensin I from which angiotensin II is ultimately derived. The renin-angiotensin system is involved in the regulation of hemodynamics and water and electrolyte balance. Factors that lower blood volume, renal perfusion, or the concentration of Na⁺ in plasma tend to activate the system, while factors that increase these parameters tend to suppress its function. Angiotensin I and angiotensin II are synthesized by the enzymatic renin-angiotensin pathway. The synthetic process is initiated when the enzyme renin acts on angiotensinogen, a pseudoglobulin in blood plasma, to produce the decapeptide angiotensin I. Angiotensin I is converted by angiotensin-converting enzyme (ACE) to angiotensin II. The latter is an active pressor substance which has been implicated as a causative agent in several forms of hypertension in various mammalian species.

[0027] "Angiotensin II receptor antagonists" are compounds which interfere with the activity of angiotensin II by binding to angiotensin II receptors and interfering with its activity. Well known angiotensin II receptor antagonists which may be used in the present invention include peptide compounds and non-peptide compounds. Non-limiting examples of angiotensin II receptor antagonists include: candesartan cilexetil (1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-, 1-[(cyclohexyloxy)carbonyl]oxy]ethyl ester) CAS RN 145040-37-5); telmisartan ([1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- CAS RN 144701-48-4); candesartan (1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-, 1-[(cyclohexyloxy)carbonyl]oxy]ethyl ester) CAS RN 139481-59-7); losartan potassium (1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-, monopotassium Irbesartan 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]- CAS RN 138402-11-6).

[0028] "Angiotensin-converting enzyme (ACE), is an enzyme which catalyzes the conversion of angiotensin I to angiotensin II. ACE inhibitors which may be used in the present invention include amino acids and derivatives thereof, peptides, including di and tri peptides and antibodies to ACE which intervene renin-angiotensin system by inhibiting the activity of ACE thereby reducing or eliminating the formation of pressor substance angiotensin II. ACE inhibitors have been used medically to treat hypertension, congestive heart failure, myocardial infarction and renal disease. Suitable ACE inhibitors include, but are not limited to, benazepril hydrochloride (such as 3-[[1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-(3S)-benzazepine-1-acetic acid monohydrochloride, for example, LOTREL® Capsules available from Novartis); captopril (such as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, for example, CAPTOPRIL Tablets available from Mylan); fosinopril (such as 1-proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy) propoxy](4-phenylbutyl) phosphinyl]acetyl]-, sodium salt, trans-, for example, MONOPRIL® Tablets available from Bristol-Myers Squibb); moexipril hydrochloride (such as [3S]-[2

[R*(R*),3R*]-2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, monohydrochloride, for example, UNIRETIC® Tablets available from Schwarz); perindopril erbumine (such as 2S,3aS,7aS)-1-[(S)-N-[(S)-1-Carboxybutyl]alanyl]hexahydro-2-indolinecarboxylic acid, 1-ethyl ester, compound with tert-butylamine (1:1), for example, ACEON® Tablets available from Solvay; quinapril (such as [3S-[2[R*(R*),3R*]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride, for example, ACCURETIC® Tablets available from Parke-Davis); ramipril (such as 2-aza-bicyclo [3.3.0]octane-3-carboxylic acid derivative, for example, ALTACE® Capsules available from Monarch); enalapril maleate (such as (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1), for example, VASOTEC® Tablets available from Merck); lisinopril (such as (S)-1-[N-2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate, for example, PRINZIDE® Tablets available from Merck); delapril (which may be prepared as disclosed in U.S. Pat. No. 4,385,051); and spirapril (which may be prepared as disclosed in U.S. Pat. No. 4,470,972); benazeprilat (1H-1-Benzazepine-1-acetic acid, 3-[[[(1S)-1-carboxy-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, (3S)- CAS RN 86541-78-8); delapril hydrochloride (Glycine, N-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-N-(2,3-dihydro-1H-inden-2-yl)-, monohydrochloride CAS RN 83435-67-0); fosinopril sodium (L-Proline, 4-cyclohexyl-1-[(R)-[(1S)-2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]actyl]-, sodium salt, (4S)- CAS RN 88889-14-9); libenzapril (1H-1-Benzazepine-1-acetic acid, 3-[[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-, (3S)- CAS RN 109214-55-3); pentopril (1H-Indole-1-pentanoic acid, 2-carboxy-2,3-dihydro-, α -, γ -dimethyl-, δ -, α -, α -ethyl ester, (α , γ , δ , 2S)- CAS RN 82924-03-6); perindopril 1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[[(1S)-1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-, (2S,3aS,7aS)- CAS RN 82834-16-0); quinapril hydrochloride (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, (3S)- CAS RN 82586-55-); quinaprilat (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[[(1S)-1-carboxy-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- CAS RN 82768-85-2); spirapril hydrochloride (1,4-Dithia-7-azaspiro[4.4]nonane-8-carboxylic acid, 7-[(2S)-2-[[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-, monohydrochloride, (8S)- CAS RN 94841-17-5); spiraprilat 1 (4,4-Dithia-7-azaspiro[4.4]nonane-8-carboxylic acid, 7-[(2S)-2-[[[(1S)-1-carboxy-3-phenylpropyl]amino]-1-oxopropyl]-, (8S)- CAS RN 83602-05-5); teprotide (Bradykinin potentiator BPP9a CAS RN 35115-60-7); lisinopril (L-Proline, N₂-[(1S)-1-carboxy-3-phenylpropyl]-L-lysyl- CAS RN 76547-98-3); zofenopril (L-Proline, 1-[(2S)-3-(benzoylthio)-2-methyl-1-oxopropyl]4-(phenylthio)-, calcium salt (2:1), (4S)- CAS RN 81938-43-4).

[0029] "Calcium channel blockers" are a chemically diverse class of compounds having important therapeutic value in the control of a variety of diseases including several cardiovascular disorders such as hypertension, angina, and cardiac arrhythmias (Fleckenstein, *Cir. Res.* V. 52 (suppl. 1), p. 13-16 (1983); Fleckenstein, *Experimental Facts and*

Therapeutic Prospects, John Wiley, New York (1983); McCall, D., *Curr. Pract. Cardiol.*, v. 10, p.1-11 (1985), each of which are incorporated herein by reference). Calcium channel blockers are a heterogeneous group of drugs that prevent or slow the entry of calcium into cells by regulating cellular calcium channels (Remington, *The Science and Practice of Pharmacy*, Nineteenth Edition, Mack Publishing Company, Eaton, Pa., p. 963 (1995) incorporated herein by reference). Calcium channel blockers useful in the present invention include but are not limited to, the besylate salt of amlodipine (such as 3-ethyl-5-methyl-2-(2-aminooctoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate, for example, NORVASC® available from Pfizer); clemizem maleate (1,5-Benzothiazepin-4(5H)-one, 3-(acetyloxy)-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-(2S-cis)-, (Z)-2-butenedioate (1:1), see also U.S. Pat. No. 4,567,195); isradipine (3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester, ($\pm$)-4(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, see also U.S. Pat. No. 4,466,972); nimodipine (such as isopropyl (2-methoxyethyl) 1, 4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine - dicarboxylate, for example, NIMOTOP® available from Bayer); felodipine (such as ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, for example, PLENDIL® Extended-Release Tablets available from AstraZeneca I.P); nilvadipine (3,5-Pyridinedicarboxylic acid, 2-cyano-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-,3-methyl 5-(1-methylethyl) ester, also see U.S. Pat. No. 3,799,934); nifedipine (such as 3,5-pyridinedicarboxylic acid,1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, for example, PROCARDIA XL® Extended Release Tablets available from Pfizer); diltiazem hydrochloride (such as 1,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,3-dihydro-2(4-methoxyphenyl)-, monohydrochloride, (+)-cis-, for example, TIAZAC® Capsules available from Forest); verapamil hydrochloride (such as benzeneacetonitrile, (α)-[[3-[2-(3,4-dimethoxyphenyl) ethyl]methylamino]propyl]-3,4-dimethoxy-(α)-(1-methylethyl) hydrochloride, for example, ISOPTIN® SR Tablets available from Knoll Labs); teludipine hydrochloride (3,5-Pyridinedicarboxylic acid, 2-[(dimethylamino)methyl]4-[2-[(1E)-3-(1,1-dimethylethoxy)-3-oxo-1-propenyl]phenyl]-1,4-dihydro-6-methyl-, diethyl ester, monohydrochloride) CAS RN 108700-03-4); belfosdil (Phosphonic acid, [2-(2-phenoxyethyl)-1,3-propanediyl]bis-, tetrabutyl ester CAS RN 103486-79-9); fosedil (Phosphonic acid, [[4-(2-benzothiazolyl)phenyl] methyl]-, diethyl ester CAS RN 75889-62-2).

[0030] Cardiovascular agents of the present invention which also act as "anti-angina agents" are useful in the present invention. Angina includes those symptoms that occur when myocardial oxygen availability is insufficient to meet myocardial oxygen demand. Non-limiting examples of these agents include: ranolazine (hydrochloride 1-Piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, dihydrochloride CAS RN 95635-56-6); betaxolol hydrochloride (2-Propanol, 1-[4-[2(cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]-, hydrochloride CAS RN 63659-19-8); butoprozine hydrochloride (Methanone, [4-[3(dibutylamino)propoxy]phenyl](2-ethyl-3-indolizyl)-, monohydrochloride CAS RN 62134-34-3); cinpezat maleate 1-Piperazineacetic

acid, 4-[1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-, ethyl ester, (2Z)-2-butenedioate (1:1) CAS RN 50679-07-7); tosisfen (Benzenesulfonamide, 4-methyl-N-[[[(1S)-1-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184); verapamilhydrochloride (Benzeneacetone nitrile, .alpha.-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-.alpha.-(1-methylethyl)-, monohydrochloride CAS RN 152-114); molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0); ranolazine hydrochloride (1-Piperazineacetamide, N-(2,6-dimethylphenyl)-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, dihydrochloride CAS RN 95635-56-6); tosisfen (Benzenesulfonamide, 4-methyl-N-[[[(1S)-1-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184).

[0031] "Coronary vasodilators" may act to reduce angina systems by increasing the oxygen supply to the heart. Coronary vasodilators useful in the present invention include, but are not limited to, diltiazem hydrochloride (such as 1,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,3-dihydro-2(4-methoxyphenyl)-, monohydrochloride, (+)-cis, for example, TIAZAC® Capsules available from Forest); isosorbide dinitrate (such as 1,4:3,6-dianhydro-D-glucitol 2,5-dinitrate, for example, ISORDIL® TITRADOSE® Tablets available from Wyeth-Ayerst); isosorbide mononitrate (such as 1,4:3,6-dianhydro-D-glucitol,5-nitrate, an organic nitrate, for example, Ismo® Tablets available from Wyeth-Ayerst); nitroglycerin (such as 2,3 propanetriol trinitrate, for example, NITROSTAT® Tablets available from Parke-Davis); verapamil hydrochloride (such as benzeneacetone nitrile, (±)-(alpha)[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-(alpha)- (1-methylethyl) hydrochloride, for example, COVERA HS® Extended-Release Tablets available from Searle); chromonar (which may be prepared as disclosed in U.S. Pat. No. 3,282,938); clonitate (Annalen 1870 155); droprenilamine (which may be prepared as disclosed in German Patent No. 2,521,113); lidoflazine (which may be prepared as disclosed in U.S. Pat. No. 3,267,104); prenylamine (which may be prepared as disclosed in U.S. Pat. No. 3,152,173); propatyl nitrate (which may be prepared as disclosed in French Patent No. 1,103,113); mioflazine hydrochloride (1-Piperazineacetamide, 3-(aminocarbonyl)-[4,4-bis(4-fluorophenyl)butyl]-N-(2,6-dichlorophenyl)-, dihydrochloride CAS RN 83898-67-3); mixidinc (Benzenethanamine, 3,4-dimethoxy-N-(1-methyl-2-pyrrolidinylidene)- Pyrrolidine, 2-[(3,4-dimethoxyphenethyl)imino]-1-methyl-1-Methyl-2-[(3,4-dimethoxyphenethyl)imino]pyrrolidine CAS RN 27737-38-8); molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0); isosorbide mononitrate (D-Glucitol, 1,4:3,6-dianhydro-, 5-nitrate CAS RN 16051-77-7); erythrityl tetranitrate (1,2,3,4-Butanetetrol, tetranitrate, (2R,3S)-rel-CAS RN 7297-25-8); clonitrate(1,2-Propanediol, 3-chloro-, dinitrate (7CI, 8CI, 9CI) CAS RN 2612-33-1); dipyrindamole Ethanol, 2,2', 2",2"-[(4,8-di-1-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetraakis- CAS RN 58-32-2); nicorandil (CAS RN 65141-46-0 3-); pyridinecarboxamide (N-[2-(nitrooxy)ethyl]-Nisoldipine3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester CAS RN 63675-72-9); nifedipine3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester CAS RN 21829-25-4);

perhexiline maleate (Piperidine, 2-(2,2-dicyclohexylethyl)-, (2Z)-2-butenedioate (1:1) CAS RN 6724-53-4); oxprenolol hydrochloride2-Propanol, 1-[(1-methylethyl)amino]-3-[2-(2-propenyloxy)phenoxy]-, hydrochloride CAS RN 6452-73-9); pentrinitrol (1,3-Propanediol, 2,2-bis[(nitrooxy)methyl]-, mononitrate (ester) CAS RN 1607-17-6); verapamil (Benzeneacetone nitrile, .alpha.-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-.alpha.-(1-methylethyl)- CAS RN 52-53-9).

[0032] The term "diuretic" includes compounds that increase the excretion of solutes (mainly NaCl) and water. In general, the primary goal of diuretic therapy is to reduce extracellular fluid volume in order to lower blood pressure or rid the body of excess interstitial fluid (edema). Non-limiting examples of diuretics which may be used within the scope of this invention include althiazide (which may be prepared as disclosed in British Patent No. 902,658); benzthiazide (which may be prepared as disclosed in U.S. Pat. No. 3,108,097); buthiazide (which may be prepared as disclosed in British Patent Nos. 861,367); chlorothiazide (which may be prepared as disclosed in U.S. 2,809,194); spironolactone (CAS Number 52-01-7); and triamterene (CAS Number 396-01-0).

[0033] "Adrenergic stimulants" useful as cardiovascular agents in the present invention include, but are not limited to, guanfacine hydrochloride (such as N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride, for example, TENEX® Tablets available from Robins); methyl dopa-hydrochlorothiazide (such as levo-3-(3,4-dihydroxyphenyl)-2-methylalanine) combined with Hydrochlorothiazide (such as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, for example, the combination as, for example, ALDORIL® Tablets available from Merck); methyl dopa-chlorothiazide (such as 6-chloro-2H-1, 2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and methyl dopa as described above, for example, ALDOCLOR® Tablets available from Merck); clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride and chlorthalidone (such as 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolyl) benzenesulfonamide), for example, COM-BIPRES® Tablets available from Boehringer Ingelheim); clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride, for example, CATAP-RES® Tablets available from Boehringer Ingelheim); clonidine (1H-Imidazol-2-amine, N-(2,6-dichlorophenyl)4,5-dihydro- CAS RN 4205-90-7).

[0034] Generally, a total dosage of the above-described agents or medications can range from 1 to 3,000 mg/day, preferably from about 1 to 1,000 mg/day and more preferably from about 1 to 200 mg/day in single or 24 divided doses.

[0035] The cardiovascular agents useful for treating vascular conditions are administered in a therapeutically effective amount to treat the specified condition, for example, in a daily dose preferably ranging from about 1 to about 3000 mg per day, and more preferably about 5 to about 200 mg per day, given in a single dose or 24 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on such factors as the potency of the compound

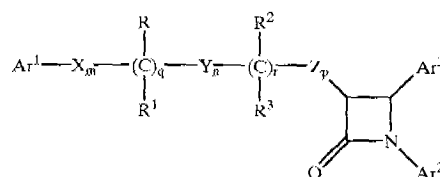
administered, the age, weight, condition and response of the patient.

[0036] The term "therapeutically effective amount" means that amount of a therapeutic agent of the composition, such as the cardiovascular agents, sterol absorption inhibitor(s) and other pharmacological or therapeutic agents described below, that will elicit a biological or medical response of a tissue, system, animal or mammal that is being sought by the administrator (such as a researcher, doctor or veterinarian) which includes alleviation of the symptoms of the condition or disease being treated and the prevention, slowing or halting of progression of the condition (for example a vascular condition as discussed above).

[0037] As used herein, "combination therapy" or "therapeutic combination" means the administration of two or more different therapeutic agents, such as cardiovascular agent(s) and sterol absorption inhibitor(s), to prevent or treat a vascular condition, such as hyperlipidaemia (for example atherosclerosis, hypercholesterolemia or sitosterolemia), stroke, diabetes, obesity and/or reduce the level of sterol(s) in the plasma. As used herein, "vascular" comprises cardiovascular, cerebrovascular and combinations thereof. Such administration includes coadministration of these therapeutic agents in a substantially simultaneous manner, such as in a single tablet or capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each therapeutic agent. Also, such administration includes use of each type of therapeutic agent in a sequential manner. In either case, the treatment using the combination therapy will provide beneficial effects in treating the vascular condition and other conditions as discussed above. A potential advantage of the combination therapy disclosed herein may be a reduction in the required amount of an individual therapeutic compound or the overall total amount of therapeutic compounds that are effective in treating the vascular condition. By using a combination of therapeutic agents, the side effects of the individual compounds can be reduced as compared to a monotherapy, which can improve patient compliance. Also, therapeutic agents can be selected to provide a broader range of complimentary effects or complimentary modes of action.

[0038] As discussed above, the compositions, pharmaceutical compositions and therapeutic combinations of the present invention comprise one or more sterol absorption inhibitors, such as the substituted azetidinone sterol absorption inhibitors or substituted β -lactam sterol absorption inhibitors discussed in detail below. As used herein, "sterol absorption inhibitor" means a compound capable of inhibiting the absorption of one or more sterols, including but not limited to cholesterol, phytosterols (such as sitosterol, campesterol, stigmasterol and avenasterol), 5α -stanols (such as cholestanol, 5α -campestanol, 5α -sitostanol), and mixtures thereof, when administered in a therapeutically effective (sterol absorption inhibiting) amount to a mammal or human.

[0039] In a preferred embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (I) below:



(I)

[0040] or isomers of the compounds of Formula (I), or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers of the compounds of Formula (I), or prodrugs of the compounds of Formula (I) or of the isomers, salts or solvates of the compounds of Formula (I), wherein, in Formula (I) above:

[0041] Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4 -substituted aryl;

[0042] Ar^3 is aryl or R^5 -substituted aryl;

[0043] X, Y and Z are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{lower alkyl})-$ and $-\text{C}(\text{dilower alkyl})-$;

[0044] R^1 and R^2 are independently selected from the group consisting of $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$ and $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$;

[0045] R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

[0046] q is 0 or 1; r is 0 or 1; m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

[0047] R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^6$, $-\text{NR}^6(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{SO}_2\text{R}^6$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{0-2}\text{R}^6$, $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^6$, $-\text{CH}=\text{CH}-\text{COOR}^6$, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$ and halogen;

[0048] R^5 is 1-5 substituents independently selected from the group consisting of $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^6$, $-\text{NR}^6(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{SO}_2\text{R}^6$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{0-2}\text{R}^6$, $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^6$ and $-\text{CH}=\text{CH}-\text{COOR}^6$;

[0049] R^6 , R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

[0050] R^2 is lower alkyl, aryl or aryl-substituted lower alkyl.

[0051] Preferably, R^4 is 1-3 independently selected substituents, and R^5 is preferably 1-3 independently selected substituents.

[0052] As used herein, the term "alkyl" or "lower alkyl" means straight or branched alkyl chains having from 1 to 6 carbon atoms and "alkoxy" means alkoxy groups having 1 to 6 carbon atoms. Non-limiting examples of lower alkyl groups include, for example, methyl, ethyl, propyl, and butyl groups.

[0053] "Alkenyl" means straight or branched carbon chains having one or more double bonds in the chain, conjugated or unconjugated. Similarly, "alkynyl" means straight or branched carbon chains having one or more triple bonds in the chain. Where an alkyl, alkenyl or alkynyl chain joins two other variables and is therefore bivalent, the terms alkenylene, alkenylene and alkynylene are used.

[0054] "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.

[0055] "Halogeno" refers to fluorine, chlorine, bromine or iodine radicals.

[0056] "Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl or indanyl.

[0057] "Phenylene" means a bivalent phenyl group, including ortho, meta and para-substitution.

[0058] The statements wherein, for example, R , R^1 , R^2 and R^3 are said to be independently selected from a group of substituents, mean that R , R^1 , R^2 and R^3 are independently selected, but also that where an R , R^1 , R^2 and R^3 variable occurs more than once in a molecule, each occurrence is independently selected (e.g., if R is $-\text{OR}^6$, wherein R^6 is hydrogen, R^2 can be $-\text{OR}^6$ wherein R^6 is lower alkyl). Those skilled in the art will recognize that the size and nature of the substituent(s) will affect the number of substituents that can be present.

[0059] Compounds of the invention have at least one asymmetrical carbon atom and therefore all isomers, including enantiomers, stereoisomers, rotamers, tautomers and racemates of the compounds of Formulae (I-XI) (where they exist) 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 optically pure or optically enriched starting materials or by separating isomers of a compound of the Formulae I-XI. Isomers may also include geometric isomers, e.g., when a double bond is present.

[0060] Those skilled in the art will appreciate that for some of the compounds of the Formulas I-XI, one isomer will show greater pharmacological activity than other isomers.

[0061] 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.

[0062] 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, hydroxy-alkylamines, N-methylglucamine and the like.

[0063] As used herein, "solvate" means a molecular or ionic complex of molecules or ions of solvent with those of solute (for example, one or more compounds of Formulae I-XI, isomers of the compounds of Formulae I-XI, or prodrugs of the compounds of Formulae I-XI). Non-limiting examples of useful solvents include polar, protic solvents such as water and/or alcohols (for example methanol).

[0064] As used herein, "prodrug" means compounds that are drug precursors which, following administration to a patient, release the drug in vivo via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form).

[0065] Preferred compounds of Formula (I) are those in which Ar^1 is phenyl or R^4 -substituted phenyl, more preferably (4- R^4)-substituted phenyl. Ar^3 is preferably phenyl or R^4 -substituted phenyl, more preferably (4- R^4)-substituted phenyl. Ar^5 is preferably R^5 -substituted phenyl, more preferably (4- R^5)-substituted phenyl. When Ar^1 is (4- R^4)-substituted phenyl, R^4 is preferably a halogen. When Ar^2 and Ar^3 are R^4 - and R^5 -substituted phenyl, respectively, R^4 is preferably halogen or $-\text{OR}^6$ and R^5 is preferably $-\text{OR}^6$, wherein R^6 is lower alkyl or hydrogen. Especially preferred are compounds wherein each of Ar^1 and Ar^2 is 4-fluorophenyl and Ar^3 is 4-hydroxyphenyl or 4-methoxyphenyl.

[0066] X , Y and Z are each preferably $-\text{CH}_2-$. R^1 and R^3 are each preferably hydrogen. R^1 and R^2 are preferably $-\text{OR}^6$ wherein R^6 is hydrogen, or a group readily metabolizable to a hydroxyl (such as $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$ and $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, defined above).

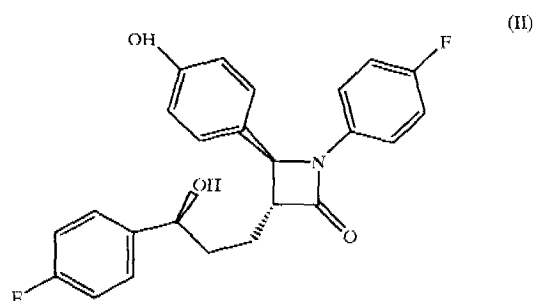
[0067] The sum of m , n , p , q and r is preferably 2, 3 or 4, more preferably 3. Preferred are compounds wherein m , n and r are each zero, q is 1 and p is 2.

[0068] Also preferred are compounds of Formula (I) in which p , q and n are each zero, r is 1 and m is 2 or 3. More preferred are compounds wherein m , n and r are each zero, q is 1, p is 2, Z is $-\text{CH}_2-$ and R is $-\text{OR}^6$, especially when R^6 is hydrogen.

[0069] Also more preferred are compounds of Formula (I) wherein p , q and n are each zero, r is 1, m is 2, X is $-\text{CH}_2-$ and R^2 is $-\text{OR}^6$, especially when R^6 is hydrogen.

[0070] Another group of preferred compounds of Formula (I) is that in which Ar^1 is phenyl or R^4 -substituted phenyl, Ar^2 is phenyl or R^4 -substituted phenyl and Ar^3 is R^5 -substituted phenyl. Also preferred are compounds in which Ar^1 is phenyl or R^5 -substituted phenyl, Ar^2 is phenyl or R^4 -substituted phenyl, Ar^3 is R^5 -substituted phenyl, and the sum of m , n , p , q and r is 2, 3 or 4, more preferably 3. More preferred are compounds wherein Ar^3 is phenyl or R^5 -substituted phenyl, Ar^2 is phenyl or R^4 -substituted phenyl, Ar^1 is R^5 -substituted phenyl, and wherein m , n and r are each zero, q is 1 and p is 2, or wherein p , q and n are each zero, r is 1 and m is 2 or 3.

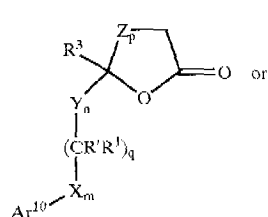
[0071] In a preferred embodiment, a sterol inhibitor of Formula (I) useful in the compositions, therapeutic combinations and methods of the present invention is represented by Formula (II) (ezetimibe) below:



[0072] or pharmaceutically acceptable salts or solvates of the compounds of Formula (II), or prodrugs of the compound of Formula (II) or of the salts or solvates of the compound of Formula (II).

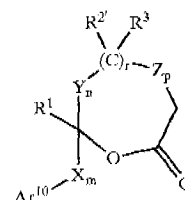
[0073] Compounds of Formula I can be prepared by a variety of methods well known to those skilled in the art, for example such as are disclosed in U.S. Pat. Nos. 5,631,365, 5,767,115, 5,846,966, 6,207,822, U.S. Provisional Patent Application No. 60/279,288 filed Mar. 28, 2001 and PCT Patent Application WO 93/02048, each of which is incorporated herein by reference, and in the Example below. For example, suitable compounds of Formula I can be prepared by a method comprising the steps of:

[0074] (a) treating with a strong base a lactone of the Formula A or B:



A

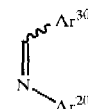
-continued



B

[0075] wherein R^1 and R^2 are R and R^2 , respectively, or are suitably protected hydroxy groups; Ar^{10} is Ar^1 , a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and the remaining variables are as defined above for Formula I, provided that in lactone of formula B, when n and r are each zero, p is 1-4;

[0076] (b) reacting the product of step (a) with an imine of the formula



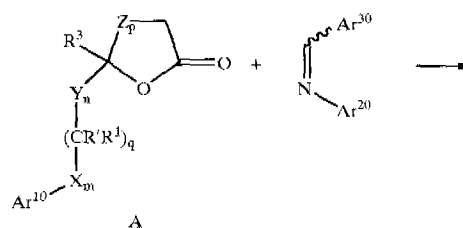
[0077] wherein Ar^{20} is Ar^2 , a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and Ar^{30} is Ar^3 , a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl;

[0078] c) quenching the reaction with an acid;

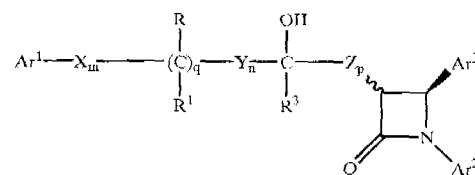
[0079] d) optionally removing the protecting groups from R^1 , R^2 , Ar^{10} , Ar^{20} and Ar^{30} , when present; and

[0080] e) optionally functionalizing hydroxy or amino substituents at R , R^2 , Ar^1 , Ar^2 and Ar^3 .

[0081] Using the lactones shown above, compounds of Formula IA and IB are obtained as follows:

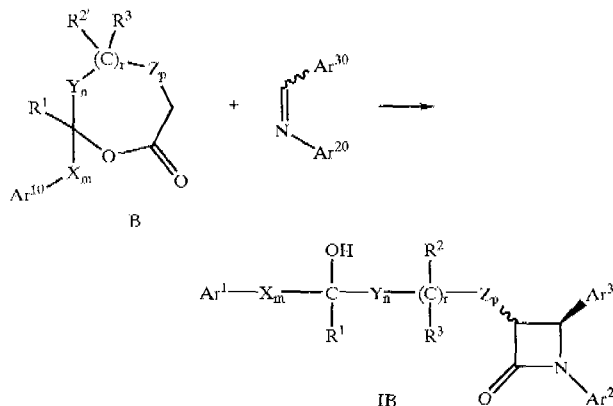


A



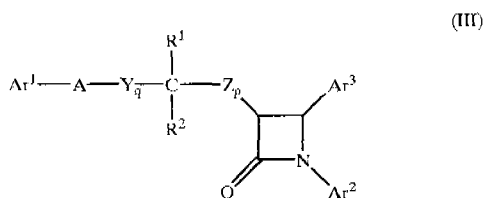
IA

[0082] wherein the variables are as defined above; and



[0083] wherein the variables are as defined above.

[0084] Alternative sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (III) below:



[0085] or isomers of the compounds of Formula (III), or pharmaceutically acceptable salts or solvates of the compounds of Formula (III) or of the isomers of the compounds of Formula (III), or prodrugs of the compounds of Formula (III) or of the isomers, salts or solvates of the compounds of Formula (III), wherein, in Formula (III) above:

- [0086] Ar¹ is R³-substituted aryl;
[0087] Ar² is R⁴-substituted aryl;
[0088] Ar³ is R⁵-substituted aryl;
[0089] Y and Z are independently selected from the group consisting of —CH₂—, —CH(lower alkyl)— and —C(dilower alkyl)—;
[0090] Λ is selected from —O—, —S—, —S(O)— or —S(O)_n—;
[0091] R⁴ is selected from the group consisting of —OR⁶, —O(CO)R⁶, —O(CO)OR⁹ and —O(CO)NR⁶R⁷; R² is selected from the group consisting of hydrogen, lower alkyl and aryl; or R¹ and R² together are =O;
[0092] q is 1, 2 or 3;
[0093] p is 0, 1, 2, 3 or 4;
[0094] R⁵ is 1-3 substituents independently selected from the group consisting of —OR⁶, —O(CO)R⁶,

- $-\text{O}(\text{CO})\text{OR}^9$, $-\text{O}(\text{CH}_{2.1-5}\text{OR}^9$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$,
 $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^9$,
 $-\text{NR}^6(\text{CO})\text{NR}^7\text{R}^8$, $-\text{NR}^6\text{SO}_2\text{-lower alkyl}$,
 $-\text{NR}^6\text{SO}_2\text{-aryl}$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$,
 $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{0.2}\text{-alkyl}$, $\text{S}(\text{O})_{0.2}\text{-aryl}$,
 $-\text{O}(\text{CH}_2)_{1-10}\text{-COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$,
 o-halogeno , m-halogeno , o-lower alkyl , m-lower
 alkyl , $\text{-(lower alkylene)-COOR}^6$, and
 $-\text{CH}=\text{CH}-\text{COOR}^6$;

[0095] R^3 and R^4 are independently 1-3 substituents independently selected from the group consisting of R^5 , hydrogen, p-lower alkyl, aryl, $-\text{NO}_2$, $-\text{Cl}$, and p-halogeno;

[0096] R^6 , R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

[0097] Preferred compounds of Formula I include those in which Ar¹ is R³-substituted phenyl, especially (4-R³)-substituted phenyl. Ar² is preferably R⁴-substituted phenyl, especially (4-R⁴)-substituted phenyl. Ar³ is preferably R⁵-substituted phenyl, especially (4-R⁵)-substituted phenyl. Mono-substitution of each of Ar¹, Ar² and Ar³ is preferred.

[0098] Y and Z are each preferably $-\text{CH}_2-$. R^2 is preferably hydrogen. R^1 is preferably $-\text{OR}^6$ wherein R^6 is hydrogen, or a group readily metabolizable to a hydroxyl (such as $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^9$ and $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, defined above). Also preferred are compounds wherein R^1 and R^2 together are $=\text{O}$.

[0099] The sum of q and p is preferably 1 or 2, more preferably 1. Preferred are compounds wherein p is zero and q is 1. More preferred are compounds wherein p is zero, q is 1, Y is $-\text{CH}_2-$ and R^1 is $-\text{OR}^6$, especially when R^6 is hydrogen.

[0100] Another group of preferred compounds is that in which Ar¹ is R³-substituted phenyl, Ar² is R⁴-substituted phenyl and Ar³ is R⁵-substituted phenyl.

[0101] Also preferred are compounds wherein Ar¹ is R⁵-substituted phenyl, Ar² is R⁴-substituted phenyl, Ar³ is R⁵-substituted phenyl, and the sum of p and q is 1 or 2, especially 1. More preferred are compounds wherein Ar¹ is R⁵-substituted phenyl, Ar² is R⁴-substituted phenyl, Ar³ is R⁵-substituted phenyl, p is zero and q is 1.

[0102] A is preferably —O—.

[0103] R^3 is preferably $-\text{COOR}^6$, $-\text{CONR}^6R^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6R^7$, $\text{S}(\text{O})_{0.2}\text{-alkyl}$, $\text{S}(\text{O})_{0.2}\text{-aryl}$, NO_2 , or halogeno. A more preferred definition for R^3 is halogeno, especially fluoro or chloro.

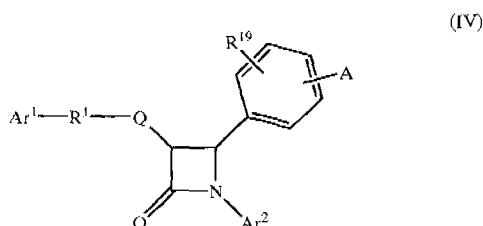
[0104] R⁴ is preferably hydrogen, lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CO)NR⁶R⁷, —NR⁶R⁷, COR⁸ or halogeno, wherein R⁶ and R⁷ are preferably independently hydrogen or lower alkyl, and R⁹ is preferably lower alkyl. A more preferred definition for R⁴ is hydrogen or halogeno, especially fluoro or chloro.

[0105] R⁵ is preferably —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —(lower alkyl)-COOR⁶ or —CH=CH—COOR⁶, wherein R⁶ and R⁷ are preferably independently hydrogen or lower alkyl, and R⁶ is preferably lower alkyl. A more preferred definition for

R^5 is $-\text{OR}^6$, $-(\text{lower alkylene})-\text{COOR}^6$ or $-\text{CH}=\text{CH}-\text{COOR}^6$, wherein R^6 is preferably hydrogen or lower alkyl.

[0106] Methods for making compounds of Formula III are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Pat. No. 5,688,990, which is incorporated herein by reference.

[0107] In another embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (IV):



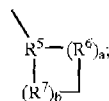
[0108] or isomers of the compounds of Formula (IV), or pharmaceutically acceptable salts or solvates of the compounds of Formula (IV) or of the isomers of the compounds of Formula (IV), or prodrugs of the compounds of Formula (IV) or of the isomers, salts or solvates of the compounds of Formula (IV), wherein, in Formula (IV) above:

[0109] A is selected from the group consisting of R^2 -substituted heterocycloalkyl, R^2 -substituted heteroaryl, R^2 -substituted benzofused heterocycloalkyl, and R^2 -substituted benzofused heteroaryl;

[0110] Ar^1 is aryl or R^3 -substituted aryl;

[0111] Ar^2 is aryl or R^4 -substituted aryl;

[0112] Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group



[0113] and

[0114] R^1 is selected from the group consisting of:

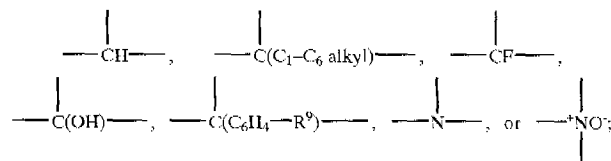
[0115] $-(\text{CH}_2)_q-$, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

[0116] $-(\text{CH}_2)_e-\text{G}-(\text{CH}_2)_r-$, wherein G is $-\text{O}-$, $-\text{C}(\text{O})-$, phenylene, $-\text{NR}^8-$ or $-\text{S}(\text{O})_{0-2}-$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

[0117] $-(\text{C}_2-\text{C}_6 \text{ alkenylene})-$; and

[0118] $-(\text{CH}_2)_f-\text{V}-(\text{CH}_2)_g-$, 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;

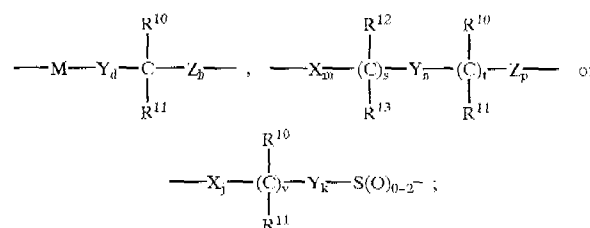
[0119] R^5 is selected from:



[0120] R^6 and R^7 are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{C}_1-\text{C}_6 \text{ alkyl})-$, $-\text{C}(\text{di}-(\text{C}_1-\text{C}_6 \text{ alkyl}))-$, $-\text{CH}=\text{CH}-$ and $-\text{C}(\text{C}_1-\text{C}_6 \text{ alkyl})=\text{CH}-$; or R^5 together with an adjacent R^6 , or R^5 together with an adjacent R^7 , form a $-\text{CH}=\text{CH}-$ or a $-\text{CH}=\text{C}(\text{C}_1-\text{C}_6 \text{ alkyl})-$ group;

[0121] a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^6 is $-\text{CH}=\text{CH}-$ or $-\text{C}(\text{C}_1-\text{C}_6 \text{ alkyl})=\text{CH}-$, a is 1; provided that when R^7 is $-\text{CH}=\text{CH}-$ or $-\text{C}(\text{C}_1-\text{C}_6 \text{ alkyl})=\text{CH}-$, b is 1; provided that when a is 2 or 3, the R^6 's can be the same or different; and provided that when b is 2 or 3, the R^7 's can be the same or different;

[0122] and when Q is a bond, R^1 also can be selected from:



[0123] where M is $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$ or $-\text{S}(\text{O})_2-$;

[0124] X, Y and Z are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{C}_1-\text{C}_6 \text{ alkyl})-$ and $-\text{C}(\text{di}-(\text{C}_1-\text{C}_6 \text{ alkyl}))-$;

[0125] R^{10} and R^{12} are independently selected from the group consisting of $-\text{OR}^{14}$, $-\text{O}(\text{CO})\text{R}^{14}$, $-\text{O}(\text{CO})\text{OR}^{16}$ and $-\text{O}(\text{CO})\text{NR}^{14}\text{R}^{15}$;

[0126] R^{11} and R^{13} are independently selected from the group consisting of hydrogen, $(\text{C}_1-\text{C}_6 \text{ alkyl})$ and aryl; or R^{10} and R^{11} together are $=\text{O}$, or R^{12} and R^{13} together are $=\text{O}$;

[0127] d is 1, 2 or 3;

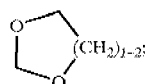
[0128] h is 0, 1, 2, 3 or 4;

[0129] s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4; provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

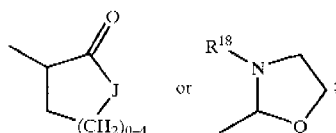
[0130] v is 0 or 1;

[0131] j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

[0132] R² is 1-3 substituents on the ring carbon atoms selected from the group consisting of hydrogen, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, R¹⁷-substituted aryl, R¹⁷-substituted benzyl, R¹⁷-substituted benzyloxy, R¹⁷-substituted aryloxy, halogeno, —NR¹⁷, —NR⁶R⁷(C₁-C₆ alkylene)-, —NR¹⁵C(O)(C₁-C₆ alkylene)-, —NHC(O)R¹⁶, OH, C₁-C₆ alkoxy, —OC(O)R¹⁶, —COR¹⁴, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, NO₂, —S(O)₀₋₂R¹⁶, —SO₂NR¹⁴R¹⁵ and —(C₁-C₆ alkylene)COOR¹⁴; when R² is a substituent on a heterocycloalkyl ring, R² is as defined, or is =O or



[0133] and, where R² is a substituent on a substitutable ring nitrogen, it is hydrogen, (C₁-C₆)alkyl, aryl, (C₁-C₆)alkoxy, aryloxy, (C₁-C₆)alkylcarbonyl, arylcarbonyl, hydroxy, —(CH₂)₁₋₆CONR¹⁸R¹⁸,



[0134] wherein J is —O—, —NH—, —NR¹⁸— or —CH₂—;

[0135] R³ and R⁴ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C₁-C₆)alkyl, —OR¹⁴, —O(CO)R¹⁴, —O(CO)OR¹⁶, —O(CH₂)₁₋₅OR¹⁴, —O(CO)NR¹⁴R¹⁵, —NR¹⁴R¹⁵, —NR¹⁴(CO)R¹⁵, —NR⁶(CO)OR¹⁶, —NR¹⁴(CO)NR¹⁵R¹⁹, —NR¹⁴SO₂R¹⁶, —COOR¹⁴, —CONR¹⁴R¹⁵, —COR¹⁴, —SO₂NR¹⁴R¹⁵, S(O)₀₋₂R¹⁶, —O(CH₂)₁₋₁₀—COOR¹⁴, —O(CH₂)₁₋₁₀CONR¹⁴R¹⁵, —(C₁-C₆ alkylene) —COOR¹⁴, —CH=CH—COOR¹⁴, —CF₃, —CN, —NO₂ and halogen;

[0136] R⁸ is hydrogen, (C₁-C₆)alkyl, aryl (C₁-C₆)alkyl, —C(O)R¹⁴ or —COOR¹⁴;

[0137] R⁹ and R¹⁷ are independently 1-3 groups independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, —COOH, NO₂, —NR¹⁴R¹⁵, OH and halogeno;

[0138] R¹⁴ and R¹⁵ are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, aryl and aryl-substituted (C₁-C₆)alkyl;

[0139] R¹⁶ is (C₁-C₆)alkyl, aryl or R¹⁷-substituted aryl;

[0140] R¹⁸ is hydrogen or (C₁-C₆)alkyl; and

[0141] R¹⁹ is hydrogen, hydroxy or (C₁-C₆)alkoxy.

[0142] As used in formula (IV) above, "Λ" is preferably an R²-substituted, 6-membered heterocycloalkyl ring containing 1 or 2 nitrogen atoms. Preferred heterocycloalkyl rings are piperidinyl, piperazinyl and morpholinyl groups. The ring "Λ" is preferably joined to the phenyl ring through a ring nitrogen. Preferred R² substituents are hydrogen and lower alkyl. R¹⁹ is preferably hydrogen.

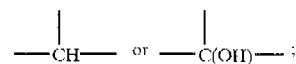
[0143] Ar² is preferably phenyl or R⁴-phenyl, especially (4-R⁴)-substituted phenyl. Preferred definitions of R⁴ are lower alkoxy, especially methoxy, and halogeno, especially fluoro.

[0144] Ar¹ is preferably phenyl or R³-substituted phenyl, especially (4-R³)-substituted phenyl.

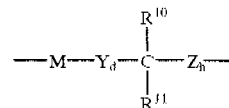
[0145] There are several preferred definitions for the —R¹—Q— combination of variables:

[0146] Q is a bond and R¹ is lower alkylene, preferably propylene;

[0147] Q is a spiro group as defined above, wherein preferably R⁶ and R⁶ are each ethylene and R⁵ is

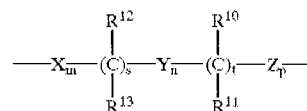


[0148] Q is a bond and R¹ is



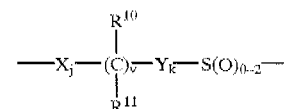
[0149] wherein the variables are chosen such that R¹ is —O—CH₂—CH(OH)—;

[0150] Q is a bond and R¹ is



[0151] wherein the variables are chosen such that R¹ is —CH(OH)—(CH₂)₂—; and

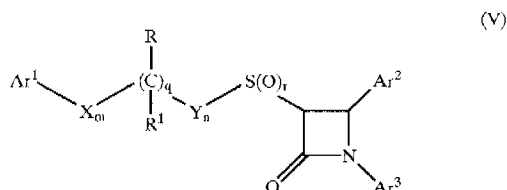
[0152] Q is a bond and R¹ is



[0153] wherein the variables are chosen such that R^1 is $-\text{CH}(\text{OH})-\text{CH}_2-\text{S}(\text{O})_{0-2}-$.

[0154] Methods for making compounds of Formula IV are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Pat. No. 5,656,624, which is incorporated herein by reference.

[0155] In another embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (V):



[0156] or isomers of the compounds of Formula (V), or pharmaceutically acceptable salts or solvates of the compounds of Formula (V) or of the isomers of the compounds of Formula (V), or prodrugs of the compounds of Formula (V) or of the isomers, salts or solvates of the compounds of Formula (V), wherein, in Formula (V) above:

[0157] Ar^1 is aryl, R^{10} -substituted aryl or heteroaryl;

[0158] Ar^2 is aryl or R^4 -substituted aryl;

[0159] Ar^3 is aryl or R^5 -substituted aryl;

[0160] X and Y are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{lower alkyl})-$ and $-\text{C}(\text{dilower alkyl})-$;

[0161] R is $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$ or $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$; R^1 is hydrogen, lower alkyl or aryl; or R and R^1 together are $=\text{O}$;

[0162] q is 0 or 1;

[0163] r is 0, 1 or 2;

[0164] m and n are independently 0, 1, 2, 3, 4 or 5; provided that the sum of m, n and q is 1, 2, 3, 4 or 5;

[0165] R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^6$, $-\text{NR}^6(\text{CO})\text{NR}^6\text{R}^8$, $-\text{NR}^6\text{SO}_2\text{R}^9$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{0-2}\text{R}^9$, $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^6$ and $-\text{CH}=\text{CH}-\text{COOR}^6$;

[0166] R^5 is 1-5 substituents independently selected from the group consisting of $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^6$, $-\text{NR}^6(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{SO}_2\text{R}^9$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{0-2}\text{R}^9$, $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-\text{Cl}$, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$, halogen,

[0167] $-(\text{lower alkylene})\text{COOR}^6$ and $-\text{CH}=\text{CH}-\text{COOR}^6$;

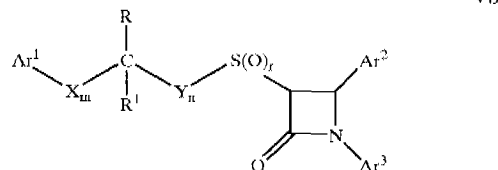
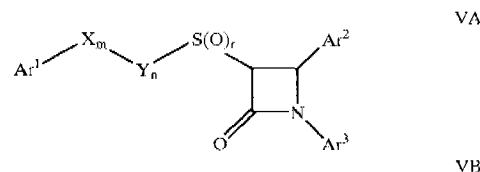
[0168] R^6 , R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

[0169] R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and

[0170] R^{10} is 1-5 substituents independently selected from the group consisting of lower alkyl, $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^6$, $-\text{NR}^6(\text{CO})\text{NR}^6\text{R}^8$, $-\text{NR}^6\text{SO}_2\text{R}^9$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $-\text{S}(\text{O})_{0-2}\text{R}^9$, $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$,

[0171] $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$ and halogen.

[0172] Within the scope of Formula V, there are included two preferred structures. In Formula VA, q is zero and the remaining variables are as defined above, and in Formula VB, q is 1 and the remaining variables are as defined above:



[0173] R^4 , R^5 and R^{10} are each preferably 1-3 independently selected substituents as set forth above. Preferred are compounds of Formula (V) wherein Ar^1 is phenyl, R^{10} -substituted phenyl or thienyl, especially (4- R^{10})-substituted phenyl or thienyl. Ar^2 is preferably R^4 -substituted phenyl, especially (4- R^4)-substituted phenyl. Ar^3 is preferably phenyl or R^5 -substituted phenyl, especially (4- R^5)-substituted phenyl. When Ar^1 is R^{10} -substituted phenyl, R^{10} is preferably halogeno, especially fluoro. When Ar^2 is R^4 -substituted phenyl, R^4 is preferably $-\text{OR}^6$ especially wherein R^6 is hydrogen or lower alkyl. When Ar^3 is R^5 -substituted phenyl, R^5 is preferably halogeno, especially fluoro. Especially preferred are compounds of Formula (V) wherein Ar^1 is phenyl, 4-fluorophenyl or thienyl, Ar^2 is 4-(alkoxy or hydroxy)phenyl, and Ar^3 is phenyl or 4-fluorophenyl.

[0174] X and Y are each preferably $-\text{CH}_2-$. The sum of m, n and q is preferably 2, 3 or 4, more preferably 2. When q is 1, n is preferably 1 to 5.

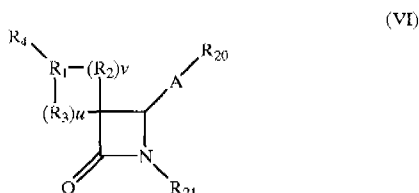
[0175] Preferences for X, Y, Ar^1 , Ar^2 and Ar^3 are the same in each of Formulae (VA) and (VB).

[0176] In compounds of Formula (VA), the sum of m and n is preferably 2, 3 or 4, more preferably 2. Also preferred are compounds wherein the sum of m and n is 2, and r is 0 or 1.

[0177] In compounds of Formula (VB), the sum of m and n is preferably 1, 2 or 3, more preferably 1. Especially preferred are compounds wherein m is zero and n is 1. R¹ is preferably hydrogen and R is preferably —OR⁶ wherein R⁶ is hydrogen, or a group readily metabolizable to a hydroxyl (such as —O(CO)R⁶, —O(CO)OR⁶ and —O(CO)NR⁶R⁷, defined above), or R and R¹ together form a =O group.

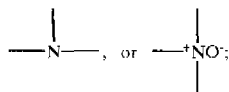
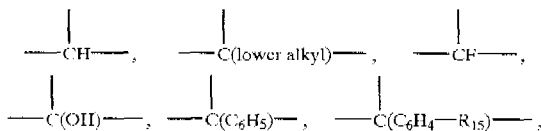
[0178] Methods for making compounds of Formula V are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Pat. No. 5,624,920, which is incorporated herein by reference.

[0179] In another embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (VI):



[0180] or isomers of the compounds of Formula (VI), or pharmaceutically acceptable salts or solvates of the compounds of Formula (VI) or of the isomers of the compounds of Formula (VI), or prodrugs of the compounds of Formula (VI) or of the isomers, salts or solvates of the compounds of Formula (VI), wherein:

[0181] R₁ is



[0182] R₂ and R₃ are independently selected from the group consisting of:

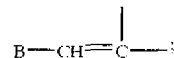
[0183] —CH₂—, —CH(lower alkyl)—, —C(di-lower alkyl)—, —CH=CH— and —C(lower alkyl)=CH—; or R₁ together with an adjacent R₂, or R₁ together with an adjacent R₃, form a —CH=CH— or a —CH=C(lower alkyl)— group;

[0184] u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R₂ is

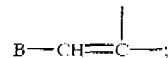
—CH=CH— or —C(lower alkyl)=CH—, v is 1; provided that when R₃ is —CH=CH— or —C(lower alkyl)=CH—, u is 1; provided that when v is 2 or 3, the R₂'s can be the same or different; and provided that when u is 2 or 3, the R₃'s can be the same or different;

[0185] R₄ is selected from B—(CH₂)_mC(O)—, wherein m is 0, 1, 2, 3, 4 or 5; B—(CH₂)_q—, wherein q is 0, 1, 2, 3, 4, 5 or 6; B—(CH₂)_e—Z—(CH₂)_f—, wherein Z is —O—, —C(O)—, phenylene, —N(R₈)— 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—(C₂-C₆ alkenylene)-; B—(C₂-C₆ alkenylene)-; B—(CH₂)_t—Z—(C₂-C₆ 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—(CH₂)_f—V—(CH₂)_g—, wherein V is C₃-C₆ 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—(CH₂)_t—V—(C₂-C₆ alkenylene)- or B—(C₂-C₆ alkenylene)-V—(CH₂)_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—(CH₂)_a—Z—(CH₂)_b—V—(CH₂)_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; or T—(CH₂)_s—, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

[0186] R₁ and R₄ together form the group

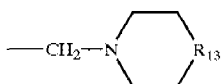


[0187] B is selected from indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, or



[0188] W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxy carbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, —CF₃, —OCF₃, benzyl, R₇-benzyl, benzyloxy, R₇-benzyloxy, phenoxy, R₇-phenoxy, dioxolanyl, NO₂, —N(R₈)(R₉), N(R₈)(R₉)-lower alkylene-, N(R₈)(R₉)-lower alkenylene-, OH, halogeno, —CN, —N₃, —NHC(O)OR₁₀, —NH-C(O)R₁₀, R₁₁O₂SNH—, (R₁₁O₂S)₂N—, —S(O)₂NH₂, —S(O)₀₋₂R⁸, tert-butylidimethyl-silyloxymethyl, —C(O)R₁₂, —COOR₁₀, —CON(R₈)(R₉), —CH=CHC(O)R₁₂, —lower alkenylene-C(O)R₁₂,

$R_{10}C(O)(\text{lower alkylenyloxy})-$, $N(R_8)(R_9)C(O)(\text{lower alkylenyloxy})-$ and



[0189] 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;

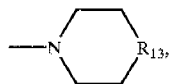
[0190] R^7 is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, $-COOH$, NO_2 , $-N(R_8)(R_9)$, OH, and halogeno;

[0191] R_8 and R_9 are independently selected from H or lower alkyl;

[0192] R_{10} is selected from lower alkyl, phenyl, R_7 -phenyl, benzyl or R_7 -benzyl;

[0193] R_{11} is selected from OH, lower alkyl, phenyl, benzyl, R_7 -phenyl or R_7 -benzyl;

[0194] R_{12} is selected from H, OH, alkoxy, phenoxy, benzyloxy,



[0195] $-N(R_8)(R_9)$, lower alkyl, phenyl or R_7 -phenyl;

[0196] R_{13} is selected from $-O-$, $-CH_2-$, $-NH-$, $-N(\text{lower alkyl})-$ or $-NC(O)R_{19}$;

[0197] 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;

[0198] R_{19} is H, lower alkyl, phenyl or phenyl lower alkyl; and

[0199] 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.

[0200] One group of preferred compounds of Formula VI is that in which R_{21} is selected from phenyl, W-substituted phenyl, indanyl, benzofuranyl, benzodioxolyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopropyl,

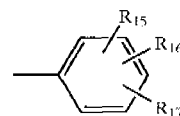
[0201] wherein W is lower alkyl, lower alkoxy, OH, halogeno, $-N(R_8)(R_9)$, $-NH(C(O)OR_{10})$, $-NH(C(O)R_{10})$, NO_2 , $-CN$, $-N_3$, $-SH$, $-S(O)_{0-2}$

(lower alkyl), $-COOR_{19}$, $-CON(R_8)(R_9)$, $-COR_{12}$, phenoxy, benzyloxy, $-OCF_3$, $-CH=C(O)R_{13}$ or tert-butyldimethylsilyloxy, wherein R_8 , R_9 , R_{10} , R_{12} and R_{19} are as defined for Formula IV. When W is 2 or 3 substituents, the substituents can be the same or different.

[0202] Another group of preferred compounds of Formula VI is that in which R_{20} is phenyl or W-substituted phenyl, wherein preferred meanings of W are as defined above for preferred definitions of R_{21} .

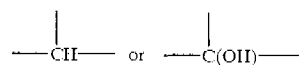
[0203] More preferred are compounds of Formula VI wherein R_{20} is phenyl or W-substituted phenyl and R_{21} is phenyl, W-substituted phenyl, indanyl, benzofuranyl, benzodioxolyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopropyl; W is lower alkyl, lower alkoxy, OH, halogeno, $-N(R_8)(R_9)$, $-NH(C(O)OR_{10})$, $-NH(C(O)R_{10})$, 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 VI.

[0204] Also preferred are compounds of Formula VI wherein R_1 is



[0205] Another group of preferred compounds of Formula VI is in which 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.

[0206] R_4 is preferably $B-(CH_2)_d$ or $B-(CH_2)_e-Z$ (CH_2)_r, wherein B, Z, q, e and r are as defined above. B is preferably



[0207] 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.

[0208] Preferably Z is $-O-$, c is 0, and r is 0.

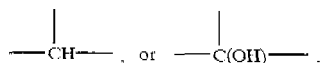
[0209] Preferably q is 0-2.

[0210] R_{20} is preferably phenyl or W-substituted phenyl.

[0211] 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.

[0212] Preferably R_{21} is selected from phenyl, lower alkoxy-substituted phenyl and F-phenyl.

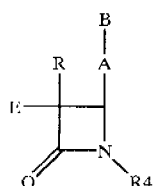
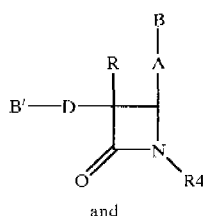
[0213] Especially preferred are compounds of Formula VI wherein R_1 is



[0214] R_2 and R_3 are each $\text{---CH}_2\text{---}$, $u=v=2$, R_4 is $\text{B---(CH}_2)_q\text{---}$, 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.

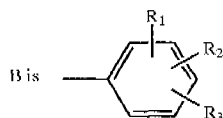
[0215] Methods for making compounds of Formula VI are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Pat. No. 5,698,548, which is incorporated herein by reference.

[0216] In another embodiment, sterol inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formulae is (VIIA) and (VIIB):

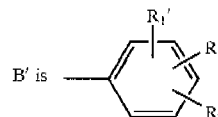


[0217] or isomers of the compounds of Formulae (VIIA) or (VIIB), or pharmaceutically acceptable salts or solvates of the compounds of Formulae (VIIA) or (VIIB) or of the isomers of the compounds of Formulae (VIIA) or (VIIB), or prodrugs of the compounds of Formulae (VIIA) or (VIIB) or of the isomers, salts or solvates of the compounds of Formulae (VIIA) or (VIIB), wherein in Formulae (VIIA) and (VIIB) above:

[0218] Λ is ---CH=CH--- , ---C=C--- or $\text{---(CH}_2)_p\text{---}$ wherein p is 0, 1 or 2;



-continued



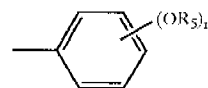
[0219] D is $\text{---(CH}_2)_m\text{C(O)---}$ or $\text{---(CH}_2)_q\text{---}$ wherein m is 1, 2, 3 or 4 and q is 2, 3 or 4;

[0220] E is C_{10} to C_{20} alkyl or $\text{---C(O)---(C}_9\text{ to C}_{19}\text{)---}$ alkyl, wherein the alkyl is straight or branched, saturated or containing one or more double bonds;

[0221] R is hydrogen, $\text{C}_{11}\text{---C}_{15}$ alkyl, straight or branched, saturated or containing one or more double bonds, or $\text{B---(CH}_2)_r\text{---}$, wherein r is 0, 1, 2, or 3;

[0222] $R_1, R_2, R_3, R_1', R_2',$ and R_3' are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, carboxy, NO_2 , NH_2 , OH, halogeno, lower alkylamino, dilower alkylamino, ---NHC(O)OR_5 , $\text{R}_6\text{O}_2\text{SNH---}$ and $\text{---S(O)}_2\text{NH}_2$;

[0223] R_4 is



[0224] wherein n is 0, 1, 2 or 3;

[0225] R_5 is lower alkyl; and

[0226] R_6 is OH, lower alkyl, phenyl, benzyl or substituted phenyl wherein the substituents are 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, carboxy, NO_2 , NH_2 , OH, halogeno, lower alkylamino and dilower alkylamino.

[0227] Preferred are compounds of Formula (VIIA) wherein R is hydrogen, saturated or mono-unsaturated $\text{C}_1\text{---C}_{10}$ alkyl or phenyl. Another group of preferred compounds of Formula (VIIA) is that in which D is propyl (i.e., $\text{---(CH}_2)_3\text{---}$ and q is 3). A third group of preferred compounds of Formula (VIIA) is that wherein R_4 is p-methoxyphenyl or 2,4,6-trimethoxyphenyl. Still another group of preferred compounds of Formula (VIIA) is that wherein Λ is ethylene or a bond (i.e., $\text{---(CH}_2)_p\text{---}$ wherein p is zero). $R_1', R_2',$ and R_3' are preferably each hydrogen, and preferably R_1 is hydrogen, hydroxy, nitro, lower alkoxy, amino or t-butoxycarbonyl-amino and R_2 and R_3 are each hydrogen.

[0228] More preferred are compounds of Formula (VIIA) wherein $R_1', R_2',$ and R_3' are each hydrogen; R_1 is hydrogen, hydroxy, nitro, lower alkoxy, amino or t-butoxycarbonyl-amino and R_2 and R_3 are each hydrogen; R is hydrogen, ethyl or phenyl; D is propyl; R_4 is p-methoxyphenyl or 2,4,6-trimethoxyphenyl; and Λ is ethylene or a bond.

[0229] Preferred compounds of Formula (VIIA), wherein B' is phenyl, are shown in the following table:

D	R	A	B	R ₄
—(CH ₂) ₃ —	H	—	p-MeO-phenyl	p-MeO-phenyl
—CH ₂ C(O)—	phenyl	—	phenyl	p-MeO-phenyl
—(CH ₂) ₃ —	H	—	phenyl	p-MeO-phenyl
—(CH ₂) ₃ —	H	—	p-OH-phenyl	p-MeO-phenyl
—(CH ₂) ₃ —	H	ethylenic	p-MeO-phenyl	p-MeO-phenyl
—(CH ₂) ₃ —	H	—	3-MeO-phenyl	p-MeO-phenyl
—(CH ₂) ₃ —	ethyl	—	phenyl	p-MeO-phenyl
—(CH ₂) ₃ —	phenyl	—	phenyl	p-MeO-phenyl
—(CH ₂) ₃ —	ethyl	—	phenyl	2,4,6-tri-MeO-phenyl
—(CH ₂) ₃ —	methyl	—	phenyl	p-MeO-phenyl
—(CH ₂) ₃ —	H	—	p-NH ₂ -phenyl	p-MeO-phenyl

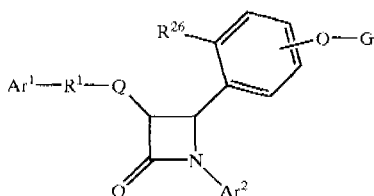
[0230] The first-listed compound in the above table having the (3R,4S) absolute stereochemistry is more preferred.

[0231] Preferred compounds of Formula (VIIB) are those wherein R is hydrogen, methyl, ethyl, phenyl or phenylpropyl. Another group of preferred compounds of Formula (VIIB) is that wherein R₄ is p-methoxyphenyl or 2,4,6-trimethoxyphenyl. Still another group of preferred compounds of Formula (VIIB) is that wherein A is ethylene or a bond. Yet another group of preferred compounds of Formula (VIIB) is that wherein E is decyl, oleoyl or 7-Z-hexadecenyl. Preferably R₁, R₂ and R₃ are each hydrogen.

[0232] More preferred compounds of Formula (VIIB) are those wherein R is hydrogen, methyl, ethyl, phenyl or phenylpropyl; R⁴ is p-methoxyphenyl or 2,4,6-trimethoxyphenyl; A is ethylene or a bond; E is decyl, oleoyl or 7-Z-hexadecenyl; and

[0233] R¹, R² and R³ are each hydrogen. A preferred compound of Formula (VIIB) is that wherein E is decyl, R is hydrogen, B—A is phenyl and R₄ is p-methoxyphenyl.

[0234] In another embodiment, sterol inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (VIII):



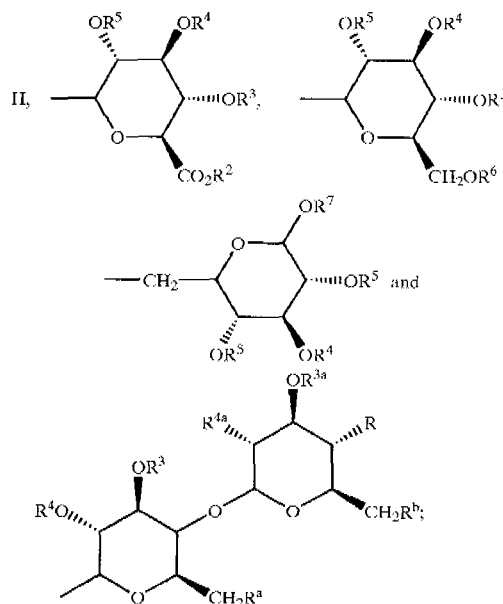
(VIII)

[0235] or isomers of the compounds of Formula (VIII), or pharmaceutically acceptable salts or solvates of the compounds of Formula (VII) or of the isomers of the compounds of Formula (VII), or prodrugs of the compounds of Formula

(VII) or of the isomers, salts or solvates of the compounds of Formula (VII), wherein, in Formula (VII) above,

[0236] R²⁶ is H or OG¹;

[0237] G and G¹ are independently selected from the group consisting of



provided that when R²⁶ is H or OH, G is not H;

[0238] provided that when R²⁶ is H or OH, G is not H;

[0239] R, R^a and R^b are independently selected from the group consisting of H, —OH, halogeno, —NH₂, azido, (C₁-C₆)alkoxy(C₁-C₆)alkoxy or —W—R³⁰;

[0240] W is independently selected from the group consisting of —NH—C(O)—, —O—C(O)—, —O—C(S)—, N(R³¹)—, —NH—C(O)—N(R³¹)— and —O—C(S)—N(R³¹)—;

[0241] R² and R⁶ are independently selected from the group consisting of H, (C₁-C₆)alkyl, aryl and aryl(C₁-C₆)alkyl;

[0242] R³, R⁴, R⁵, R⁷, R^{3a} and R^{4a} are independently selected from the group consisting of H, (C₁-C₆)alkyl, aryl(C₁-C₆)alkyl, —C(O)(C₁-C₆)alkyl and —C(O)aryl;

[0243] R³⁰ is selected from the group consisting of R³²-substituted T, R³²-substituted-T-(C₁-C₆)alkyl, R³²-substituted-(C₂-C₄)alkenyl, R³²-substituted-(C₁-C₆)alkyl, R³²-substituted-(C₃-C₇)cycloalkyl and R³²-substituted-(C₃-C₇)cycloalkyl(C₁-C₆)alkyl;

[0244] R³¹ is selected from the group consisting of H and (C₁-C₄)alkyl;

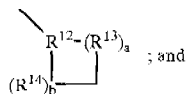
[0245] T is selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

[0246] R^{32} is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C_1-C_4) alkyl, $-OH$, phenoxy, $-CF_3$, $-NO_2$, (C_1-C_4) alkoxy, methylenedioxy, oxo, (C_1-C_4) alkylsulfanyl, (C_1-C_4) alkylsulfinyl, (C_1-C_4) alkylsulfonyl, $-N(CH_3)_2$, $-C(O)-NH(C_1-C_4)alkyl$, $-C(O)-N((C_1-C_4)alkyl)_2$, $-C(O)-(C_1-C_4)alkyl$, $-C(O)-(C_1-C_4)alkoxy$ and pyrrolidinylcarbonyl; or R^{32} is a covalent bond and R^{31} , the nitrogen to which it is attached and R^{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a (C_1-C_4) alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

[0247] Ar^1 is aryl or R^{10} -substituted aryl;

[0248] Ar^2 is aryl or R^{11} -substituted aryl;

[0249] Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group



[0250] and

[0251] R^1 is selected from the group consisting of

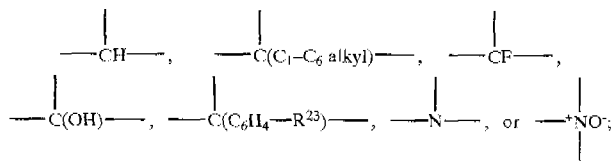
[0252] $-(CH_2)_q-$, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

[0253] $-(CH_2)_e-E-(CH_2)_r$, wherein E is $-O-$, $-C(O)-$, phenylene, $-NR^{22}-$ or $-S(O)_{0-2}-$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

[0254] $-(C_2-C_6)alkenylene-$; and

[0255] $-(CH_2)_f-V-(CH_2)_g-$, 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;

[0256] R^{12} is



[0257] R^{13} and R^{14} are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6)alkyl-$, $-C(di-(C_1-C_6)alkyl)-$, $-CH=CH-$ and $-C(C_1-C_6)alkyl=CH-$; or R^{12} together with an adjacent R^{13} , or R^{12} together with an adjacent R^{14} , form a $-CH=CH-$ or a $-CH=C(C_1-C_6)alkyl-$ group;

[0258] a and b are independently 0, 1, 2 or 3, provided both are not zero;

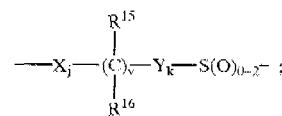
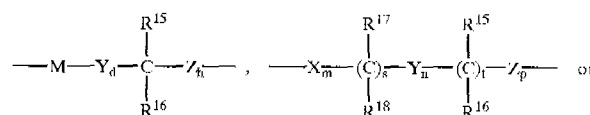
[0259] provided that when R^{13} is $-CH=CH-$ or $-C(C_1-C_6)alkyl=CH-$, a is 1;

[0260] provided that when R^{14} is $-CH=CH-$ or $-C(C_1-C_6)alkyl=CH-$, b is 1;

[0261] provided that when a is 2 or 3, the R^{13} 's can be the same or different; and

[0262] provided that when b is 2 or 3, the R^{14} 's can be the same or different;

[0263] and when Q is a bond, R^1 also can be:



[0264] M is $-O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$;

[0265] X , Y and Z are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6)alkyl-$ and $-C(di-(C_1-C_6)alkyl)-$;

[0266] R^{10} and R^{11} are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of $(C_1-C_6)alkyl$, $-OR^{19}$, $-O(CO)R^{19}$, $-O(CO)OR^{21}$, $-O(CH_2)_{1-5}OR^{19}$, $-O(CO)NR^{19}R^{20}$, $-NR^{19}R^{20}$, $-NR^{19}(CO)R^{20}$, $-NR^{19}(CO)OR^{21}$, $-NR^{19}(CO)NR^{20}R^{25}$, $-NR^{19}SO_2R^{21}$, $-COOR^{19}$, $-CONR^{19}R^{20}$, $-COR^{19}$, $-SO_2NR^{19}R^{20}$, $S(O)_{0-2}R^{21}$, $-O(CH_2)_{1-10}-COOR^{19}$, $-O(CH_2)_{1-10}CONR^{19}R^{20}$, $-(C_1-C_6)alkylene-COOR^{19}$, $-CH=CH-COOR^{19}$, $-CF_3$, $-CN$, $-NO_2$ and halogen;

[0267] R^{15} and R^{17} are independently selected from the group consisting of $-OR^{19}$, $-O(CO)R^{19}$, $-O(CO)OR^{21}$ and $-O(CO)NR^{19}R^{20}$;

[0268] R^{16} and R^{18} are independently selected from the group consisting of H , $(C_1-C_6)alkyl$ and aryl; or R^{15} and R^{16} together are $=O$, or R^{17} and R^{18} together are $=O$;

[0269] d is 1, 2 or 3;

[0270] h is 0, 1, 2, 3 or 4;

[0271] s is 0 or 1; t is 0 or 1; m , n and p are independently 0-4;

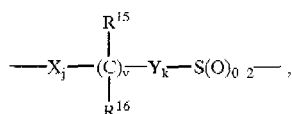
[0272] provided that at least one of s and t is 1, and the sum of m , n , p , s and t is 1-6;

[0273] provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

[0274] v is 0 or 1;

[0275] j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

[0276] and when Q is a bond and R¹ is



[0277] Ar¹ can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

[0278] R¹⁹ and R²⁰ are independently selected from the group consisting of H, (C₁-C₆)alkyl, aryl and aryl-substituted (C₁-C₆)alkyl;

[0279] R²¹ is (C₁-C₆)alkyl, aryl or R²⁴-substituted aryl;

[0280] R²² is H, (C₁-C₆)alkyl, aryl (C₁-C₆)alkyl, ---C(O)R¹⁹ or ---COOR¹⁹;

[0281] R²³ and R²⁴ are independently 1-3 groups independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, ---COOH, NO₂, ---NR¹⁹R²⁰, ---OH and halogeno; and

[0282] R²⁵ is H, ---OH or (C₁-C₆)alkoxy.

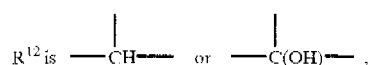
[0283] Ar² is preferably phenyl or R¹¹-phenyl, especially (4-R¹¹)-substituted phenyl. Preferred definitions of R¹¹ are lower alkoxy, especially methoxy, and halogeno, especially fluoro.

[0284] Ar¹ is preferably phenyl or R¹⁰-substituted phenyl, especially (4-R¹⁰)-substituted phenyl. Preferably R¹⁰ is halogeno, and more preferably fluoro.

[0285] There are several preferred definitions for the ---R¹---Q--- combination of variables:

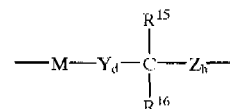
[0286] Q is a bond and R¹ is lower alkylene, preferably propylene;

[0287] Q is a spiro group as defined above, wherein preferably R¹³ and R¹⁴ are each ethylene and



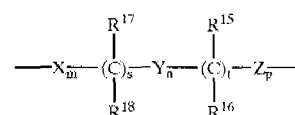
[0288] and R¹ is ---CH₂--- wherein q is 0-6;

[0289] Q is a bond and R¹ is



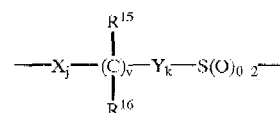
[0290] wherein the variables are chosen such that R¹ is ---O---CH₂---CH(OH)---;

[0291] Q is a bond and R¹ is



[0292] wherein the variables are chosen such that R¹ is ---CH(OH)---(CH₂)₂---; and

[0293] Q is a bond and R¹ is



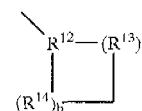
[0294] wherein the variables are chosen such that R¹ is ---CH(OH)---CH₂---S(O)₀₋₂---.

[0295] A preferred compound of Formula (VIII) therefore, is one wherein G and G¹ are as defined above and in which the remaining variables have the following definitions:

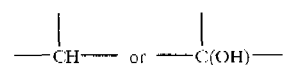
[0296] Ar¹ is phenyl or R¹⁰-substituted phenyl, wherein R¹⁰ is halogeno;

[0297] Ar² is phenyl or R¹¹-phenyl, wherein R¹¹ is 1 to 3 substituents independently selected from the group consisting of C₁-C₆ alkoxy and halogeno;

[0298] Q is a bond and R¹ is lower alkylene; Q, with the 3-position ring carbon of the azetidinone, forms the group

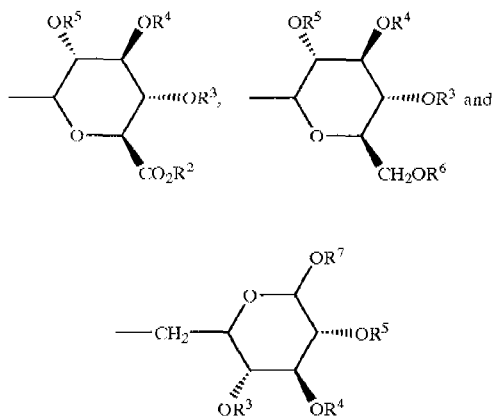


[0299] wherein preferably R¹³ and R¹⁴ are each ethylene and a and b are each 1, and wherein R¹² is



[0300] Q is a bond and R¹ is —O—CH₂—CH(OH)—; Q is a bond and R¹ is —CH(OH)—(CH₂)₂—; or Q is a bond and R¹ is —CH(OH)—CH₂—S(O)₀₋₂—.

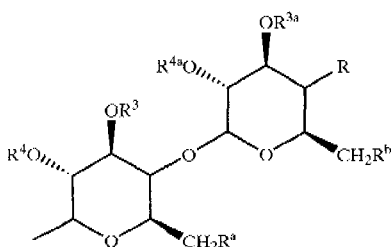
[0301] Preferred variables for G and G¹ groups of the formulac



[0302] are as follows:

[0303] R², R³, R⁴, R⁵, R⁶ and R⁷ are independently selected from the group consisting of H, (C₁-C₆)alkyl, benzyl and acetyl.

[0304] Preferred variables for group G or G¹ of the formula:



[0305] are as follows:

[0306] R³, R^{3a}, R⁴ and R^{4a} are selected from the group consisting of H, (C₁-C₆)alkyl, benzyl and acetyl;

[0307] R, R^a and R^b are independently selected from the group consisting of H, —OH, halogeno, —NH₂, azido, (C₁-C₆)alkoxy(C₁-C₆)alkoxy and —W—R³⁰,

[0308] wherein W is —O—C(O)— or —O—C(O)—NR³¹—, R³¹ is H and R³⁰ is (C₁-C₆)alkyl, —C(O)—(C₁-C₄)alkoxy-(C₁-C₆)alkyl, T, T—(C₁-C₆)alkyl, or T or T—(C₁-C₆)alkyl wherein T is substituted by one or two halogeno or (C₁-C₆)alkyl groups.

[0309] Preferred R³⁰ substituents are selected from the group consisting of: 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl, 2-methylphenyl, 2-thienylmethyl, 2-methoxy-carbonyl ethyl, thiazol-2-yl-methyl, 2-furyl, 2-methoxycarbonylbutyl and phenyl.

[0310] Preferred combinations of R, R^a and R^b are as follows:

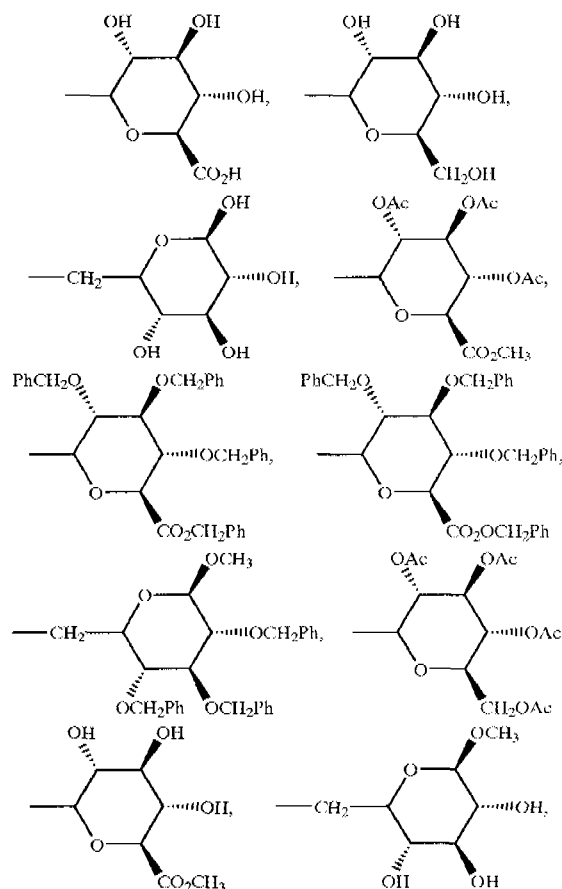
[0311] 1) R, R^a and R^b are independently —OH or —O—C(O)—NH—R³⁰, especially wherein R^a is —OH and R and R^b are —O—C(O)—NH—R³⁰ and R³⁰ is selected from the preferred substituents identified above, or wherein R and R^a are each —OH and R^b is —O—C(O)—NH—R³⁰ wherein R³⁰ is 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl;

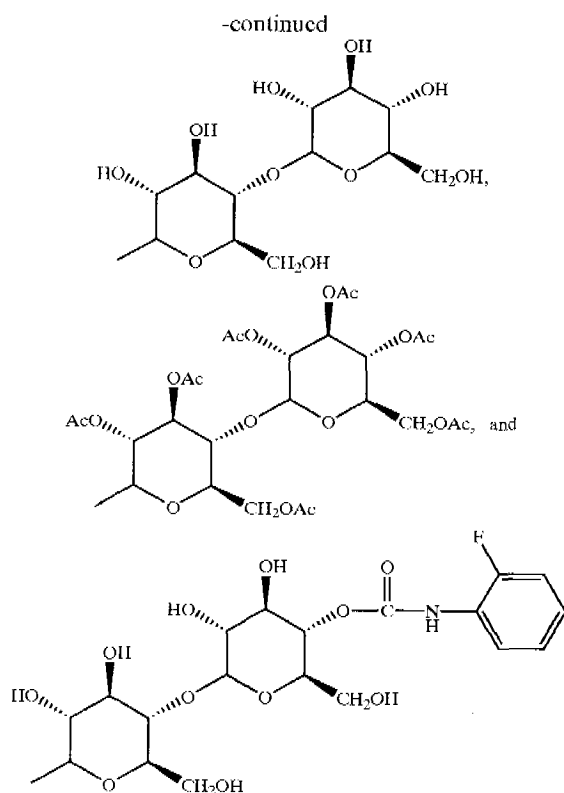
[0312] 2) R^a is —OH, halogeno, azido or (C₁-C₆)alkoxy(C₁-C₆)alkoxy, R^b is H, halogeno, azido or (C₁-C₆)alkoxy(C₁-C₆)alkoxy, and R is —O—C(O)—NH—R³⁰, especially compounds wherein R^a is —OH, R^b is H and R³⁰ is 2-fluorophenyl;

[0313] 3) R, R^a and R^b are independently —OH or —O—C(O)—R³⁰ and R³⁰ is (C₁-C₆)alkyl, T, or T substituted by one or two halogeno or (C₁-C₆)alkyl groups, especially compounds wherein R is —OH and R^a and R^b are —O—C(O)—R³⁰ wherein R³⁰ is 2-furyl; and

[0314] 4) R, R^a and R^b are independently —OH or halogeno. Three additional classes of preferred compounds are those wherein the C^{1'} anomeric oxy is beta, wherein the C^{2'} anomeric oxy is beta, and wherein the R group is alpha.

[0315] G and G¹ are preferably selected from:

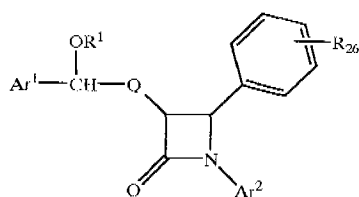




[0316] wherein Ac is acetyl and Ph is phenyl.

[0317] Preferably, R^{26} is H or OH, more preferably H. The —O—G substituent is preferably in the 4-position of the phenyl ring to which it is attached.

[0318] In another embodiment, sterol inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (IX) below:



(IX)

[0319] or isomers of the compounds of Formula (IX), or pharmaceutically acceptable salts or solvates of the compounds of Formula (IX) or of the isomers of the compounds of Formula (IX), or prodrugs of the compounds of Formula (IX) or of the isomers, salts or solvates of the compounds of Formula (IX), wherein

[0320] R^{26} is selected from the group consisting of:

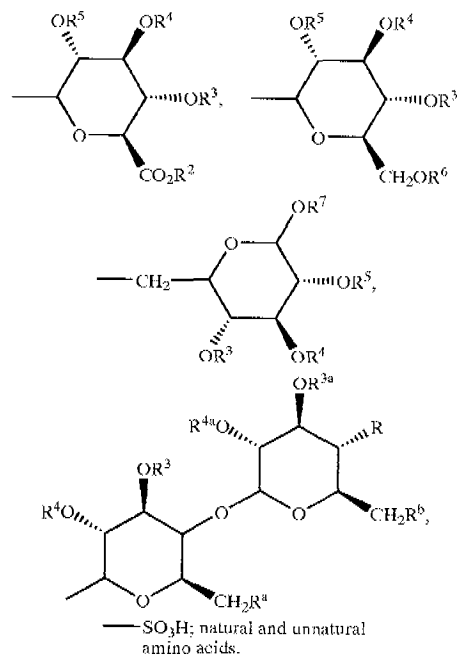
[0321] a) OH;

[0322] b) OCH_3 ;

[0323] c) fluorine and

[0324] d) chlorine.

[0325] R^1 is selected from the group consisting of



[0326] —SO₃H; natural and unnatural amino acids.

[0327] R , R^a and R^b are independently selected from the group consisting of H, —OH, halogeno, —NH₂, azido, (C₁–C₆)alkoxy(C₁–C₆)–alkoxy and —W— R^{30} ;

[0328] W is independently selected from the group consisting of —NH—C(O)—, —O—C(O)—, —O—C(O)—N(R^{31})—, —NH—C(O)—N(R^{31})— and —O—C(S)—N(R^{31})—;

[0329] R^2 and R^6 are independently selected from the group consisting of H, (C₁–C₆)alkyl, aryl and aryl(C₁–C₆)alkyl;

[0330] R^3 , R^4 , R^5 , R^7 , R^{3a} and R^{4a} are independently selected from the group consisting of H, (C₁–C₆)alkyl, aryl(C₁–C₆)alkyl, —C(O)(C₁–C₆)alkyl and —C(O)aryl;

[0331] R^{30} is independently selected from the group consisting of R^{32} -substituted T, R^{32} -substituted-T—(C₁–C₆)alkyl, R^{32} -substituted-(C₂–C₄)alkenyl, R^{32} -substituted-(C₁–C₆)alkyl, R^{32} -substituted-(C₃–C₇)cycloalkyl and R^{32} -substituted-(C₃–C₇)cycloalkyl(C₁–C₆)alkyl;

[0332] R^{31} is independently selected from the group consisting of H and (C₁–C₄)alkyl;

[0333] T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

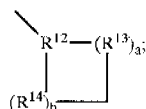
[0334] R^{32} is independently selected from 1-3 substituents independently selected from the group consisting of H, halogeno, (C_1-C_4) alkyl, $-\text{OH}$, phenoxy, $-\text{CF}_3$, $-\text{NO}_2$, (C_1-C_4) alkoxy, methylenedioxy, oxo, (C_1-C_4) alkylsulfanyl, (C_1-C_4) alkylsulfenyl, (C_1-C_4) alkylsulfonyl, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})-\text{NH}(C_1-C_4)\text{alkyl}$, $-\text{C}(\text{O})-\text{N}((C_1-C_4)\text{alkyl})_2$, $-\text{C}(\text{O})-(C_1-C_4)\text{alkyl}$, $-\text{C}(\text{O})-(C_1-C_4)\text{alkoxy}$ and pyrrolidinylcarbonyl; or R^{32} is a covalent bond and R^{31} , the nitrogen to which it is attached and R^{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a (C_1-C_4) alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

[0335] Ar^1 is aryl or R^{10} -substituted aryl;

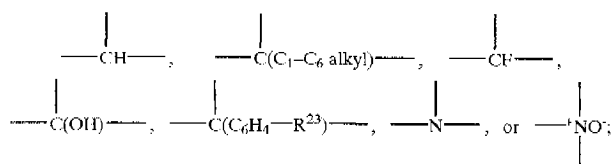
[0336] Ar^2 is aryl or R^{11} -substituted aryl;

[0337] Q is $-(\text{CH}_2)_q-$, wherein q is 2-6, or, with the 3-position ring carbon of the azetidinone,

[0338] forms the spiro group



[0339] R^{12} is



[0340] R^{13} and R^{14} are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(C_1-C_6\text{ alkyl})-$, $-\text{C}(\text{di-}(C_1-C_6\text{ alkyl}))$, $-\text{CH}=\text{CH}-$ and $-\text{C}(C_1-C_6\text{ alkyl})=\text{CH}-$; or R^{12} together with an adjacent R^{13} , or R^{12} together with an adjacent R^{14} , form a $-\text{CH}=\text{CH}-$ or a $-\text{CH}=\text{C}(C_1-C_6\text{ alkyl})-$ group;

[0341] a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^{13} is $-\text{CH}=\text{CH}-$ or $-\text{C}(C_1-C_6\text{ alkyl})=\text{CH}-$, a is 1; provided that when R^{14} is $-\text{CH}=\text{CH}-$ or $-\text{C}(C_1-C_6\text{ alkyl})=\text{CH}-$, b is 1; provided that when a is 2 or 3, the R^{13} 's can be the same or different; and provided that when b is 2 or 3, the R^{14} 's can be the same or different;

[0342] R^{10} and R^{11} are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C_1-C_6) alkyl, $-\text{OR}^{19}$, $-\text{O}(\text{CO})\text{R}^{19}$, $-\text{O}(\text{CO})\text{OR}^{21}$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^{19}$, $-\text{O}(\text{CO})\text{NR}^{19}\text{R}^{20}$, $-\text{NR}^{19}\text{R}^{20}$, $-\text{NR}^{19}(\text{CO})\text{R}^{20}$, $-\text{NR}^{19}(\text{CO})\text{OR}^{21}$, $-\text{NR}^{19}(\text{CO})\text{NR}^{20}\text{R}^{25}$, $-\text{NR}^{19}\text{SO}_2\text{R}^{21}$, $-\text{COOR}^{19}$,

$-\text{CONR}^{19}\text{R}^{20}$, $-\text{COR}^{19}$, $-\text{SO}_2\text{NR}^{19}\text{R}^{20}$, $\text{S}(\text{O})_{0-2}\text{R}^{21}$, $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^{19}$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^{19}\text{R}^{20}$, $-(C_1-C_6\text{ alkylene})-\text{COOR}^{19}$, $-\text{CH}=\text{CH}-\text{COOR}^{19}$, $-\text{CF}_3$, $-\text{CN}$,

[0343] $-\text{NO}_2$ and halogen;

[0344] Ar^1 can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

[0345] R^{19} and R^{20} are independently selected from the group consisting of H, (C_1-C_6) alkyl, aryl and aryl-substituted (C_1-C_6) alkyl;

[0346] R^{21} is (C_1-C_6) alkyl, aryl or R^{24} -substituted aryl;

[0347] R^{22} is H, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, $-\text{C}(\text{O})\text{R}^{19}$ or $-\text{COOR}^{19}$;

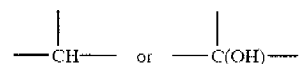
[0348] R^{23} and R^{24} are independently 1-3 groups independently selected from the group consisting of H, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, $-\text{COOH}$, NO_2 , $-\text{NR}^{19}\text{R}^{20}$, $-\text{OH}$ and halogeno; and

[0349] R^{25} is H, $-\text{OH}$ or (C_1-C_6) alkoxy.

[0350] Ar^2 is preferably phenyl or R^{11} -phenyl, especially $(4-R^{11})$ -substituted phenyl. Preferred definitions of R^{11} are lower alkoxy, especially methoxy, and halogeno, especially fluoro.

[0351] Ar^1 is preferably phenyl or R^{10} -substituted phenyl, especially $(4-R^{10})$ -substituted phenyl. A preferred definition of R^{10} is halogeno, especially fluoro.

[0352] Preferably Q is a lower alkyl or a spiro group as defined above, wherein preferably R^{13} and R^{14} are each ethylene and R^{12} is



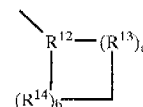
[0353] A preferred compound of formula IX, therefore, is one wherein R^1 is as defined above and in which the remaining variables have the following definitions:

[0354] Ar^1 is phenyl or R^{10} -substituted phenyl, wherein R^{10} is halogeno;

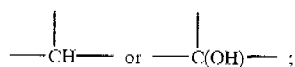
[0355] Ar^2 is phenyl or R^{11} -phenyl, wherein R^{11} is 1 to 3 substituents independently selected from the group consisting of C_1-C_6 alkoxy and halogeno;

[0356] Q is a lower alkyl (i.e. C-1 to C-2) with $Q=\text{C}-2$ being preferred, or Q , with the

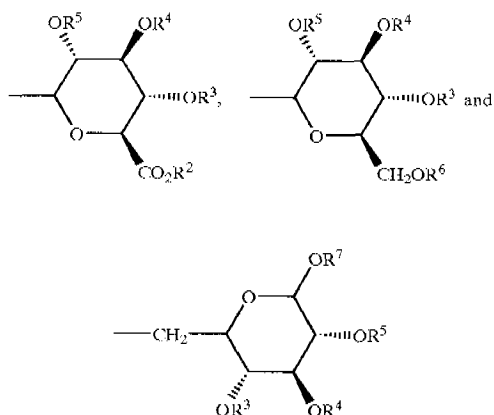
[0357] 3-position ring carbon of the azetidinone, forms the group



[0358] wherein preferably R^{13} and R^{14} are each ethylene and a and b are each 1, and wherein R^{12} is



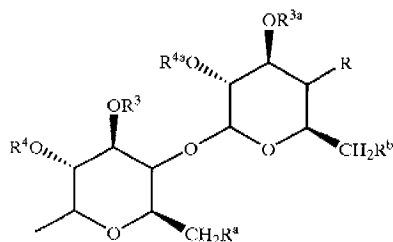
[0359] Preferred variables for R^1 groups of the formula



[0360] are as follows:

[0361] R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are independently selected from the group consisting of H, (C_1-C_6) alkyl, benzyl and acetyl.

[0362] Preferred variables for group R^1 of the formula



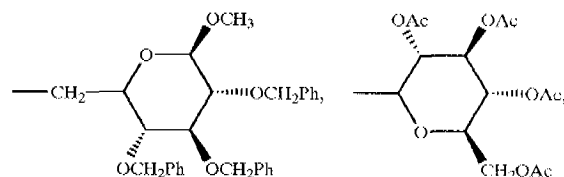
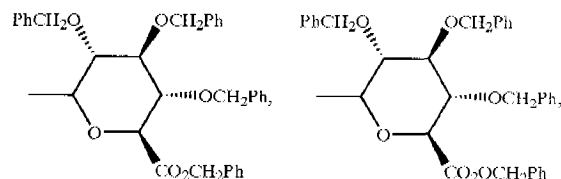
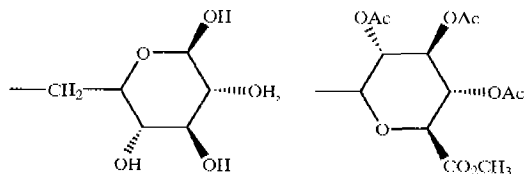
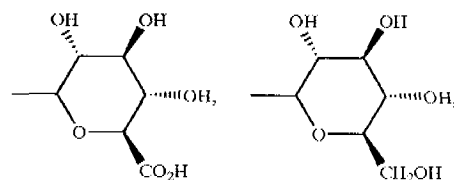
[0363] are as follows:

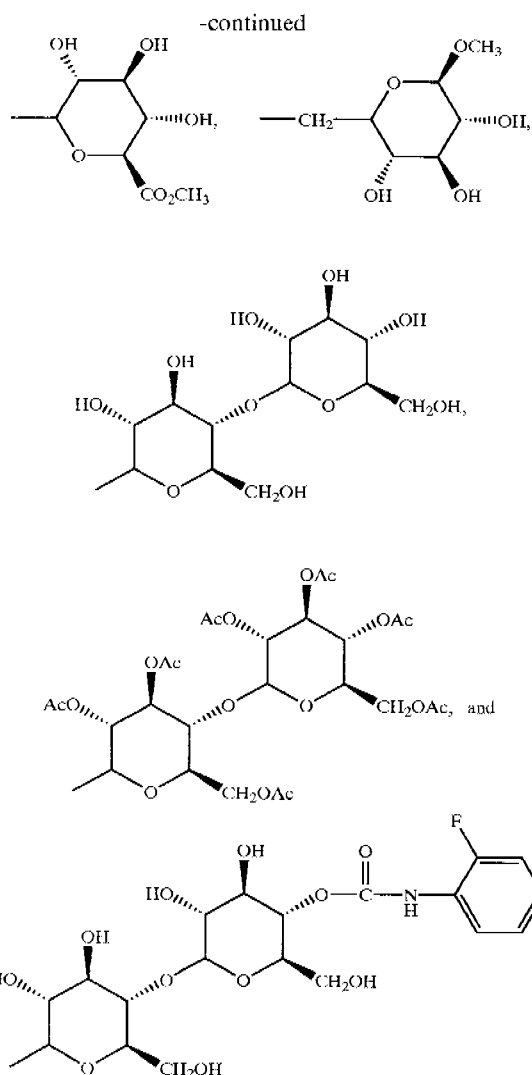
[0364] R^3 , R^{3a} , R^4 and R^{4a} are selected from the group consisting of H, (C_1-C_6) alkyl, benzyl and acetyl;

[0365] R , R^a and R^b are independently selected from the group consisting of H, $-\text{OH}$, halogeno, $-\text{NH}_2$, azido, (C_1-C_6) alkoxy, (C_1-C_6) alkoxy and $-\text{W}-R^{30}$, wherein W is $-\text{O}-\text{C}(\text{O})-$ or $-\text{O}-\text{C}(\text{O})-\text{NR}^{31}-$, R^{31} is H and R^{30} is (C_1-C_6) alkyl, $-\text{C}(\text{O})-(C_1-C_4)$ alkoxy, (C_1-C_6) alkyl, T, T- (C_1-C_6) alkyl, or T or T- (C_1-C_6) alkyl wherein T is substituted by one or two halogeno or (C_1-C_6) alkyl groups.

[0366] Preferred R^{30} substituents are 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl, 2-methylphenyl,

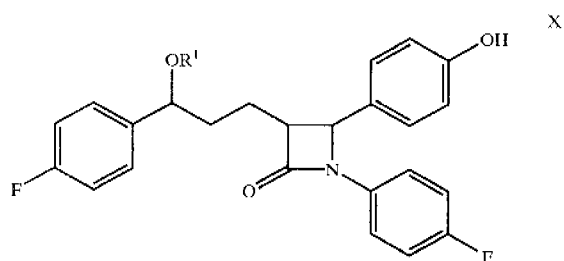
2-thienylmethyl, 2-methoxy-carbonyl-ethyl, thiazol-2-yl-methyl, 2-furyl, 2-methoxycarbonylbutyl and phenyl. Preferred combinations of R, R^a and R^b are as follows: (1) R, R^a and R^b are independently $-\text{OH}$ or $-\text{O}-\text{C}(\text{O})-\text{NH}-R^{30}$, especially wherein R^a is $-\text{OH}$ and R and R^b are $-\text{O}-\text{C}(\text{O})-\text{NH}-R^{30}$ and R^{30} is selected from the preferred substituents identified above, or wherein R and R^a are $-\text{OH}$ and R^b is $-\text{O}-\text{C}(\text{O})-\text{NH}-R^{30}$ wherein R^{30} is 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl; (2) R^a is $-\text{OH}$, halogeno, azido or (C_1-C_6) alkoxy, R^b is H, halogeno, azido or (C_1-C_6) alkoxy, and R is $-\text{O}-\text{C}(\text{O})-\text{NH}-R^{30}$, especially compounds wherein R^a is $-\text{OH}$, R^b is H and R^{30} is 2-fluorophenyl; (3) R, R^a and R^b are independently $-\text{OH}$ or $-\text{O}-\text{C}(\text{O})-R^{30}$ and R^{30} is (C_1-C_6) alkyl, T, or T substituted by one or two halogeno or (C_1-C_6) alkyl groups, especially compounds wherein R is $-\text{OH}$ and R^a and R^b are $-\text{O}-\text{C}(\text{O})-R^{30}$ wherein R^{30} is 2-furyl; and (4) R, R^a and R^b are independently $-\text{OH}$ or halogeno. Three additional classes of preferred are compounds are those wherein the C^1 anomeric oxy is beta, wherein the C^2 anomeric oxy is beta, and wherein the R group is alpha. R^1 is preferably selected from:





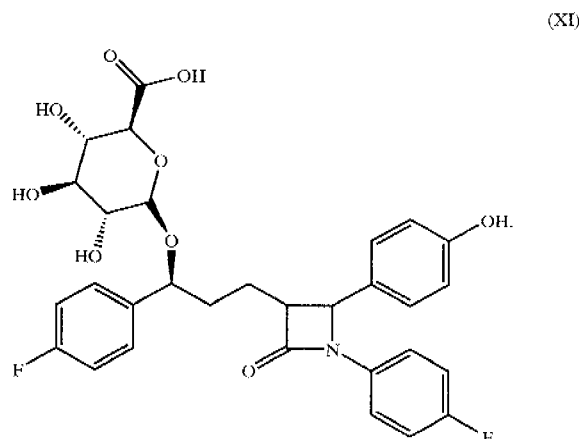
[0367] wherein Ac is acetyl and Ph is phenyl.

[0368] An example of a useful compound of this invention is one represented by the formula X:



[0369] or pharmaceutically acceptable salts or solvates of the compound of Formula (X), or prodrugs of the compound of Formula (X) or of the salts or solvates of the compound of Formula (X), wherein R^1 is defined as above.

[0370] A more preferred compound is one represented by formula XI:



[0371] or pharmaceutically acceptable salts or solvates of the compound of Formula (XI), or prodrugs of the compound of Formula (XI) or of the salts or solvates of the compound of Formula (XI).

[0372] In another embodiment, compositions, pharmaceutical compositions, therapeutic combinations, kits and methods of treatment as described above are provided which comprise: (a) a first amount of at least one cardiovascular agent; and (b) a second amount of at least one sterol absorption inhibitor, or pharmaceutically acceptable salt or solvate thereof, or prodrug of the sterol absorption inhibitor or of the salt or solvate of the sterol absorption inhibitor, wherein the first amount and the second amount together in their totality (whether administered concurrently or consecutively) comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering of a concentration or level of a sterol in plasma of a mammal. Suitable sterol absorption inhibitors include substituted azetidinone compounds or substituted β -lactam compounds such as any of the compounds discussed above in Formulae I-XI, isomers of the substituted azetidinone compounds or substituted β -lactam compounds, salts or solvates of the substituted azetidinone compounds or substituted β -lactam compounds or of the isomers of the substituted azetidinone compounds or substituted β -lactam compounds or prodrugs of the substituted azetidinone compounds or substituted β -lactam compounds or of the isomers, salts or solvates of the substituted azetidinone compounds or substituted β -lactam compounds. Other useful substituted azetidinone compounds include N-sulfonyl-2-azetidinones such as are disclosed in U.S. Pat. No. 4,983,597 and ethyl 4-(2-oxoazetidin-4-yl)phenoxy-alkanoates such as are disclosed in Ram et al., Indian J. Chem. Sect. B. 29B, 12 (1990), p. 1134-7, which are incorporated by reference herein.

[0373] The compounds of Formulae I-XI can be prepared by known methods, including the methods discussed above and, for example, WO 93/02048 describes the preparation of compounds wherein $-R^1-Q-$ is alkylene, alkenylene or alkylene interrupted by a hetero atom, phenylene or cycloalkylene; WO 94/17038 describes the preparation of compounds wherein Q is a spirocyclic group; WO 95/08532 describes the preparation of compounds wherein $-R^1-$

Q— is a hydroxy-substituted alkylene group; PCT/US95/03196 describes compounds wherein —R¹—Q— is a hydroxy-substituted alkylene attached to the Ar¹ moiety through an —O— or S(O)₀₋₂— group; and U.S. Ser. No. 08/463,619, filed Jun. 5, 1995, describes the preparation of compounds wherein —R¹—Q— is a hydroxy-substituted alkylene group attached the azetidinone ring by a —S(O)₀₋₂— group.

[0374] The daily dose of the sterol absorption inhibitor(s) can range from about 0.1 to about 1000 mg per day, preferably about 0.25 to about 50 mg/day, and more preferably is about 10 mg, 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.

[0375] For administration of pharmaceutically acceptable salts of the above compounds, the weights indicated above refer to the weight of the acid equivalent or the base equivalent of the therapeutic compound derived from the salt.

[0376] In one embodiment of the present invention, the compositions or therapeutic combinations can further comprise one or more pharmacological or therapeutic agents or drugs such as cholesterol biosynthesis inhibitors and/or lipid-lowering agents discussed below.

[0377] Non-limiting examples of cholesterol biosynthesis inhibitors for use in the compositions, therapeutic combinations and methods of the present invention include competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol biosynthesis, squalene synthase inhibitors, squalene epoxidase inhibitors and mixtures thereof. Non-limiting examples of suitable HMG CoA reductase inhibitors include statins such as lovastatin (for example MEVACOR® which is available from Merck & Co.), pravastatin (for example PRAVACHOL® which is available from Bristol Meyers Squibb), fluvastatin, simvastatin (for example ZOCOR® which is available from Merck & Co.), atorvastatin, cerivastatin, rosuvastatin, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate, CI-981 and pitavastatin (such as NK-104 of Nega Kowa of Japan); 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 squalestan 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]benzenemethanamine hydrochloride) and other sterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors include lovastatin, pravastatin and simvastatin. The most preferred HMG CoA reductase inhibitor is simvastatin.

[0378] Generally, a total daily dosage of cholesterol biosynthesis inhibitor(s) can range from about 0.1 to about 160 mg per day, and preferably about 0.2 to about 80 mg/day in single or 2-3 divided doses.

[0379] In another preferred embodiment, the composition or treatment comprises the compound of Formula (II) in combination with one or more cardiovascular agents and one or more cholesterol biosynthesis inhibitors. Preferably the

cholesterol biosynthesis inhibitor comprises one or more HMG CoA reductase inhibitors, such as, for example, lovastatin, pravastatin and/or simvastatin.

[0380] In another alternative embodiment, the compositions or treatments of the present invention can further comprise nicotinic acid (niacin) and/or derivatives thereof coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above.

[0381] As used herein, "nicotinic acid derivative" means a compound comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions and tautomers, where available. Examples of nicotinic acid derivatives include niceritol, nicofuranose and acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide). Nicotinic acid and its derivatives inhibit hepatic production of VLDL and its metabolite LDL and increases HDL and apo A-1 levels. An example of a suitable nicotinic acid product is NIASPAN® (niacin extended-release tablets) which are available from Kos.

[0382] Generally, a total daily dosage of nicotinic acid or a derivative thereof can range from about 500 to about 10,000 mg/day, preferably about 1000 to about 8000 mg/day, and more preferably about 3000 to about 6000 mg/day in single or divided doses.

[0383] In another alternative embodiment, the compositions or treatments of the present invention can further comprise one or more AcylCoA:Cholesterol O-acyltransferase ("ACAT") Inhibitors, which can reduce LDL and VLDL levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. ACAT is an enzyme responsible for esterifying excess intracellular cholesterol and may reduce the synthesis of VLDL, which is a product of cholesterol esterification, and overproduction of apo B-100-containing lipoproteins.

[0384] Non-limiting examples of useful ACAT inhibitors include avasimibe ([2,4,6-tris(1-methylethyl)phenyl]acetyl)sulfamic acid, 2,6-bis(1-methylethyl)phenyl ester, formerly known as CI-1011, HI-004, lecimibide (DuP-128) and CL-277082 (N-(2,4-difluorophenyl)-N-[[4-(2,2-dimethylpropyl)phenyl]methyl]-N-heptylurea). See P. Chang et al., "Current, New and Future Treatments in Dyslipidaemia and Atherosclerosis", *Drugs* 2000 July;60(1): 55-93, which is incorporated by reference herein.

[0385] In another alternative embodiment, the compositions or treatments of the present invention can further comprise probucol or derivatives thereof (such as AGI-1067 and other derivatives disclosed in U.S. Pat. Nos. 6,121,319 and 6,147,250), which can reduce LDL levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above.

[0386] Generally, a total daily dosage of probucol or derivatives thereof can range from about 10 to about 2000 mg/day, and preferably about 500 to about 1500 mg/day in single or 24 divided doses.

[0387] In another alternative embodiment, the compositions or treatments of the present invention can further comprise low-density lipoprotein (LDL) receptor activators, coadministered with or in combination with the cardiovas-

cular agent(s) and sterol absorption inhibitor(s) discussed above. Non-limiting examples of suitable LDL-receptor activators include HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity. See M. Huettinger et al., "Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the LDL Receptor Pathway", *Arterioscler. Thromb.* 1993; 13:1005-12.

[0388] Generally, a total daily dosage of LDL receptor activator(s) can range from about 1 to about 1000 mg/day in single or 24 divided doses.

[0389] In another alternative embodiment, the compositions or treatments of the present invention can further comprise fish oil, which contains Omega 3 fatty acids (3-PUFA), which can reduce VLDL and triglyceride levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. Generally, a total daily dosage of fish oil or Omega 3 fatty acids can range from about 1 to about 30 grams per day in single or 24 divided doses.

[0390] In another alternative embodiment, the compositions or treatments of the present invention can further comprise natural water soluble fibers, such as psyllium, guar, oat and pectin, which can reduce cholesterol levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. Generally, a total daily dosage of natural water soluble fibers can range from about 0.1 to about 10 grams per day in single or 24 divided doses.

[0391] In another alternative embodiment, the compositions or treatments of the present invention can further comprise plant sterols, plant stanols and/or fatty acid esters of plant stanols, such as sitostanol ester used in BENECOL® margarine, which can reduce cholesterol levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. Generally, a total daily dosage of plant sterols, plant stanols and/or fatty acid esters of plant stanols can range from about 0.5 to about 20 grams per day in single or 24 divided doses.

[0392] In another alternative embodiment, the compositions or treatments of the present invention can further comprise antioxidants, such as probucol, tocopherol, ascorbic acid, β -carotene and selenium, or vitamins such as vitamin B₆ or vitamin B₁₂, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. Generally, a total daily dosage of antioxidants or vitamins can range from about 0.05 to about 10 grams per day in single or 24 divided doses.

[0393] In another alternative embodiment, the compositions, therapeutic combinations or methods of the present invention can further comprise one or more bile acid sequestrants (insoluble anion exchange resins), coadministered with or in combination with the cardiovascular agents and sterol absorption inhibitor(s) discussed above.

[0394] Bile acid sequestrants bind bile acids in the intestine, interrupting the enterohepatic circulation of bile acids and causing an increase in the faecal excretion of steroids. Use of bile acid sequestrants is desirable because of their non-systemic mode of action. Bile acid sequestrants can lower intrahepatic cholesterol and promote the synthesis of

apo B/E (LDL) receptors which bind LDL from plasma to further reduce cholesterol levels in the blood.

[0395] Non-limiting examples of suitable bile acid sequestrants include cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN™ or QUESTRAN LIGHTS® cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, such as COLESTID® tablets which are available from Pharmacia), colestevlam hydrochloride (such as WelChol® Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) which are available from Sankyo), water soluble derivatives such as 3,3-iodene, N-(cycloalkyl) alkylamines and polyglusam, insoluble quaternized polystyrenes, saponins and mixtures thereof. Other useful bile acid sequestrants are disclosed in PCT Patent Applications Nos. WO 97/11345 and WO 98157652, and U.S. Pat. Nos. 3,692,895 and 5,703,188 which are incorporated herein by reference. Suitable inorganic cholesterol sequestrants include bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

[0396] Generally, a total daily dosage of bile acid sequestrant(s) can range from about 1 to about 50 grams per day, and preferably about 2 to about 16 grams per day in single or 2-4 divided doses.

[0397] Also useful with the present invention are compositions or therapeutic combinations that can further comprise at least one (one or more) activators for peroxisome proliferator-activated receptors (PPAR). These activators act as agonists for the peroxisome proliferator-activated receptors. Three subtypes of PPAR have been identified, and these are designated as peroxisome proliferator-activated receptor alpha (PPAR α), peroxisome proliferator-activated receptor gamma (PPAR γ) and peroxisome proliferator-activated receptor delta (PPAR δ). It should be noted that PPAR δ is also referred to in the literature as PPAR β and as NUC1, and each of these names refers to the same receptor.

[0398] PPAR α regulates the metabolism of lipids. PPAR α is activated by fibrates and a number of medium and long-chain fatty acids, and it is involved in stimulating β -oxidation of fatty acids. The PPAR γ receptor subtypes are involved in activating the program of adipocyte differentiation and are not involved in stimulating peroxisome proliferation in the liver. PPAR δ has been identified as being useful in increasing high density lipoprotein (HDL) levels in humans. See, e.g., WO 97/28149.

[0399] PPAR α activator compounds are useful for, among other things, lowering triglycerides, moderately lowering LDL levels and increasing HDL levels. Useful examples of PPAR α activators include the fibrates discussed above.

[0400] Other examples of PPAR α activators useful with the practice of the present invention include suitable fluorophenyl compounds as disclosed in U.S. No. 6,028,109 which is incorporated herein by reference; certain substituted phenylpropionic compounds as disclosed in WO 00/75103 which is incorporated herein by reference; and PPAR α activator compounds as disclosed in WO 98/43081 which is incorporated herein by reference.

[0401] Non-limiting examples of PPAR γ activator include suitable derivatives of glitazones or thiazolidinediones, such as, troglitazone (such as REZULIN® troglitazone (-5-[[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl] methyl]-2,4-thiazolidinedione) commercially available from Parke-Davis); rosiglitazone (such as AVANDIA® rosiglitazone maleate (-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (Z) -2-butenedioate) (1:1) commercially available from SmithKline Beecham) and pioglitazone (such as ACTOS™ pioglitazone hydrochloride (5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4- thiazolidinedione monohydrochloride) commercially available from Takeda Pharmaceuticals). Other useful thiazolidinediones include ciglitazone, englitazone, darglitazone and BRI. 49653 as disclosed in WO 98/05331 which is incorporated herein by reference; PPAR γ activator compounds disclosed in WO 00/76488 which is incorporated herein by reference; and PPAR γ activator compounds disclosed in U.S. Pat. No. 5,994,554 which is incorporated herein by reference.

[0402] Other useful classes of PPAR γ activator compounds include certain acetylphenols as disclosed in U.S. Pat. No. 5,859,051 which is incorporated herein by reference; certain quinoline phenyl compounds as disclosed in WO 99/20275 which is incorporated herein by reference; aryl compounds as disclosed by WO 99/138845 which is incorporated herein by reference; certain 1,4-disubstituted phenyl compounds as disclosed in WO 00/63161; certain aryl compounds as disclosed in WO 01/00579 which is incorporated herein by reference; benzoic acid compounds as disclosed in WO 01/12612 & WO 01/12187 which are incorporated herein by reference; and substituted 4-hydroxy-phenylallic acid compounds as disclosed in WO 97/131907 which is incorporated herein by reference.

[0403] PPAR δ compounds are useful for, among other things, lowering triglyceride levels or raising HDL levels. Non-limiting examples of PPAR δ activators include suitable thiazole and oxazole derivatives, such as C.A.S. Registry No. 317318-324, as disclosed in WO 01/00603 which is incorporated herein by reference; certain fluoro, chloro or thio phenoxy phenylacetic acids as disclosed in WO 97/28149 which is incorporated herein by reference; suitable non- β -oxidizable fatty acid analogues as disclosed in U.S. Pat. No. 5,093,365 which is incorporated herein by reference; and PPAR δ compounds as disclosed in WO 99/104815 which is incorporated herein by reference.

[0404] Moreover, compounds that have multiple functionality for activating various combinations of PPAR α , PPAR γ and PPAR δ are also useful with the practice of the present invention. Non-limiting examples include certain substituted aryl compounds as disclosed in U.S. Pat. No. 6,248,781; WO 00/23416; WO 00/23415; WO 00/23425; WO 00/23445; WO 00/23451; and WO 00/63153, all of which are incorporated herein by reference, are described as being useful PPAR α and/or PPAR γ activator compounds. Other non-limiting examples of useful PPAR α and/or PPAR γ activator compounds include activator compounds as disclosed in WO 97/25042 which is incorporated herein by reference; activator compounds as disclosed in WO 00/63190 which is incorporated herein by reference; activator compounds as disclosed in WO 01/21181 which is incorporated herein by reference; biaryl-oxa(thia)zole compounds as disclosed in WO 01/16120 which is incorporated

herein by reference; compounds as disclosed in WO 00/63196 and WO 00/63209 which are incorporated herein by reference; substituted 5-aryl-2,4-thiazolidinediones compounds as disclosed in U.S. Pat. No. 6,008,237 which is incorporated herein by reference; arylthiazolidinedione and aryloxazolidinedione compounds as disclosed in WO 00/178312 and WO 00/78313G which are incorporated herein by reference; GW2331 or (2-(4-[difluorophenyl]-1-heptylureido)ethyl)phenoxy)-2-methylbutyric compounds as disclosed in WO 98/05331 which is incorporated herein by reference; aryl compounds as disclosed in U.S. Pat. No. 6,166,049 which is incorporated herein by reference; oxazole compounds as disclosed in WO 01/17994 which is incorporated herein by reference; and dithiolane compounds as disclosed in WO 01/25225 and WO 01/25226 which are incorporated herein by reference.

[0405] Other useful PPAR activator compounds include substituted benzylthiazolidine-2,4-dione compounds as disclosed in WO 01/14349, WO 01/14350 and WO 01/04351 which are incorporated herein by reference; mercaptocarboxylic compounds as disclosed in WO 00/50392 which is incorporated herein by reference; ascofuranone compounds as disclosed in WO 00/53563 which is incorporated herein by reference; carboxylic compounds as disclosed in WO 99/46232 which is incorporated herein by reference; compounds as disclosed in WO 99/12534 which is incorporated herein by reference; benzene compounds as disclosed in WO 99/15520 which is incorporated herein by reference; o-anisamide compounds as disclosed in WO 01/21578 which is incorporated herein by reference; and PPAR activator compounds as disclosed in WO 01/40192 which is incorporated herein by reference.

[0406] The peroxisome proliferator-activated receptor(s) activator(s) are administered in a therapeutically effective amount to treat the specified condition, for example in a daily dose preferably ranging from about 50 to about 3000 mg per day, and more preferably about 50 to about 2000 mg per day, given in a single dose or 24 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on such factors as the potency of the compound administered, the age, weight, condition and response of the patient.

[0407] The compositions or treatments of the present invention can further comprise one or more ileal bile acid transport ("IBAT") inhibitors (or apical sodium co-dependent bile acid transport ("ASBT") inhibitors) coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. The IBAT inhibitors can inhibit bile acid transport to reduce LDL cholesterol levels. Non-limiting examples of suitable IBAT inhibitors include benzothiepinines such as therapeutic compounds comprising a 2,3,4,5-tetrahydro-1-benzothiepine 1,1-dioxide structure such as are disclosed in PCT Patent Application WO 00/38727 which is incorporated herein by reference.

[0408] Generally, a total daily dosage of IBAT inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.1 to about 50 mg/day in single or 24 divided doses.

[0409] The compositions or treatments of the present invention can further comprise one or more Cholesteryl Ester Transfer Protein ("CETP") Inhibitors coadministered

with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. CETP is responsible for the exchange or transfer of cholesteryl ester carrying HDL and triglycerides in VLDL.

[0410] Non-limiting examples of suitable CETP inhibitors are disclosed in PCT Patent Application No. WO 00/38721 and U.S. Pat. No. 6,147,090, which are incorporated herein by reference. Pancreatic cholesteryl ester hydrolase (PCEH) inhibitors such as WAY-121898 also can be coadministered with or in combination with the peroxisome proliferator-activated receptor(s) activator and sterol absorption inhibitor(s) discussed above.

[0411] Generally, a total daily dosage of CETP inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.5 to about 20 mg/kg body weight/day in single or divided doses.

[0412] The compositions or treatments of the present invention can further comprise probucol or derivatives thereof (such as AGI-1067 and other derivatives disclosed in U.S. Pat. Nos. 6,121,319 and 6,147,250), which can reduce LDL and HDL levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above.

[0413] The compositions or treatments of the present invention can further comprise monocyte and macrophage inhibitors such as polyunsaturated fatty acids (PUFA), thyroid hormones including throxine analogues such as CGS-26214 (a thyroxine compound with a fluorinated ring), gene therapy and use of recombinant proteins such as recombinant apo E. Generally, a total daily dosage of these agents can range from about 0.01 to about 1000 mg/day in single or 2-4 divided doses.

[0414] Also useful with the present invention are compositions or therapeutic combinations which further comprise hormone replacement agents and compositions. Useful hormone agents and compositions for hormone replacement therapy of the present invention include androgens, estrogens, progestins, their pharmaceutically acceptable salts and derivatives. Combinations of these agents and compositions are also useful.

[0415] The dosage of androgen and estrogen combinations vary, desirably from about 1 mg to about 4 mg androgen and from about 1 mg to about 3 mg estrogen. Examples include, but are not limited to, androgen and estrogen combinations such as the combination of esterified estrogens (sodium estrone sulfate and sodium equilin sulfate) and methyltestosterone (17-hydroxy-17-methyl-, (17B)- androst-4-en-3-one) available from Solvay Pharmaceuticals, Inc., Marietta, Ga., under the tradename Estratest.

[0416] Estrogens and estrogen combinations may vary in dosage from about 0.01 mg up to 8 mg, desirably from about 0.3 mg to about 3.0 mg. Examples of useful estrogens and estrogen combinations include:

[0417] (a) the blend of nine (9) synthetic estrogenic substances including sodium estrone sulfate, sodium equilin sulfate, sodium 17 α -dihydroequilin sulfate, sodium 17 α -estradiol sulfate, sodium 17 β -dihydroequilin sulfate, sodium 17 α -dihydroequilenin sulfate, sodium 17 β -dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17 β -estradiol

sulfate; available from Duramed Pharmaceuticals, Inc., Cincinnati, Ohio, under the tradename Cenestin;

[0418] (b) ethinyl estradiol (19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol; available by Schering Plough Corporation, Kenilworth, N.J., under the tradename Estinyl;

[0419] (c) esterified estrogen combinations such as sodium estrone sulfate and sodium equilin sulfate; available from Solvay under the tradename Estratab and from Monarch Pharmaceuticals, Bristol, Tenn., under the tradename Menest;

[0420] (d) estropipate (piperazine estra-1,3,5(10)-trien-17-one, 3-(sulfoxy)-estrone sulfate); available from Pharmacia & Upjohn, Peapack, N.J., under the tradename Ogen and from Women First Health Care, Inc., San Diego, Calif., under the tradename Ortho-Est; and

[0421] (e) conjugated estrogens (17 α -dihydrocquin, 17 α -estradiol, and 17 β -dihydroequilin); available from Wyeth-Ayerst Pharmaceuticals, Philadelphia, Pa., under the tradename Premarin.

[0422] Progestins and estrogens may also be administered with a variety of dosages, generally from about 0.05 to about 2.0 mg progestin and about 0.001 mg to about 2 mg estrogen, desirably from about 0.1 mg to about 1 mg progestin and about 0.01 mg to about 0.5 mg estrogen. Examples of progestin and estrogen combinations that may vary in dosage and regimen include:

[0423] (a) the combination of estradiol (estra-1, 3, 5(10)-triene-3, 17 β -diol hemihydrate) and norethindrone (17 β -acetoxy-19-nor-17 α -pregn-4-en-20-yn-3-one); which is available from Pharmacia & Upjohn, Peapack, N.J., under the tradename Activella;

[0424] (b) the combination of levonorgestrel (d(-)-13 β -ethyl-17 α -ethinyl-17 β -hydroxygon-4-en-3-one) and ethinyl estradiol; available from Wyeth-Ayerst under the tradename Alesse, from Watson Laboratories, Inc., Corona, Calif., under the tradenames Levora and Trivora, Monarch Pharmaceuticals, under the tradename Nordette, and from Wyeth-Ayerst under the tradename Triphasil;

[0425] (c) the combination of ethynodiol diacetate (19-nor-17 α -pregn-4-en-20-yne-3 β , 17-diol diacetate) and ethinyl estradiol; available from G.D. Searle & Co., Chicago, Ill., under the tradename Demulen and from Watson under the tradename Zovia;

[0426] (d) the combination of desogestrel (13-ethyl-11-methylene-18,19-dinor-17 α -pregn-4-en-20-yn-17-ol) and ethinyl estradiol; available from Organon under the tradenames Desogen and Mircette, and from Ortho-McNeil Pharmaceutical, Raritan, N.J., under the tradename Ortho-Cept;

[0427] (e) the combination of norethindrone and ethinyl estradiol; available from Parke-Davis, Morris Plains, N.J., under the tradenames Estrostep and femhrt, from Watson under the tradenames Micro-

gestin, Necon, and Tri-Norinyl, from Ortho-McNeil under the tradenames Modicon and Ortho-Novum, and from Warner Chilcott Laboratories, Rockaway, N.J., under the tradename Ovcon;

[0428] (f) the combination of norgestrel (($\pm$)-13-ethyl-17-hydroxy-18, 19-dinor-17 α -preg-4-en-20-yn-3-one) and ethinyl estradiol; available from Wyeth-Ayerst under the tradenames Ovral and Lo/Ovral, and from Watson under the tradenames Oggestrel and Low-Ogestrel;

[0429] (g) the combination of norethindrone, ethinyl estradiol, and mestranol (3-methoxy-19-nor-17 α -pregna-1,3,5(10)-trien-20-yn-17-ol); available from Watson under the tradenames Brevicon and Norinyl;

[0430] (h) the combination of 17 β -estradiol (estra-1,3,5(10)-trien-3,17 β -diol) and micronized norgestimate (17 α -17-(Acetyloxy)-13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one-3-oxime); available from Ortho-McNeil under the tradename Ortho-Prefest;

[0431] (i) the combination of norgestimate (18,19-dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 α)-(+)-) and ethinyl estradiol; available from Ortho-McNeil under the tradenames Ortho Cyclen and Ortho Tri-Cyclen; and

[0432] j) the combination of conjugated estrogens (sodium estrone sulfate and sodium equilin sulfate) and medroxyprogesterone acetate (20-dione, 17-(acetyloxy)-6-methyl-, (6 α)-pregn-4-ene-3); available from Wyeth-Ayerst under the tradenames Premphase and Prempro.

[0433] In general, a dosage of progestins may vary from about 0.05 mg to about 10 mg or up to about 200 mg if micro-sized progesterone is administered. Examples of progestins include norethindrone; available from ESI Lederle, Inc., Philadelphia, Pa., under the tradename Aygestin, from Ortho-McNeil under the tradename Micronor, and from Watson under the tradename Nor-QD; norgestrel; available from Wyeth-Ayerst under the tradename Ovrette; micronized progesterone (pregn-4-ene-3,20-dione); available from Solvay under the tradename Prometrium; and medroxyprogesterone acetate; available from Pharmacia & Upjohn under the tradename Provera.

[0434] The compositions, therapeutic combinations or methods of the present invention can further comprise one or more obesity control medications. Different obesity control medications include, but are not limited to, drugs that reduce energy intake or suppress appetite, drugs that increase energy expenditure and nutrient-partitioning agents. Suitable obesity control medications include, but are not limited to, noradrenergic agents (such as diethylpropion, mazindol, phenylpropanolamine, phentermine, phendimetrazine, phendamine tartrate, methamphetamine, phendimetrazine and tartrate); serotonergic agents (such as sibutramine, fenfluramine, dexfenfluramine, fluoxetine, fluvoxamine and paroxetine); thermogenic agents (such as ephedrine, caffeine, theophylline, and selective β 3-adrenergic agonists); an α -blocking agent; a kainite or AMPA receptor antagonist; a leptin-lipolysis stimulated receptor; a phosphodiesterase enzyme inhibitor; a compound having nucleotide sequences of the mahogany gene; a fibroblast growth factor-

10 polypeptide; a monoamine oxidase inhibitor (such as bexloxtone, moclobemide, brofaromine, phenoxathine, esuprone, befol, toloxatone, pirlindol, amiflamine, sercloreline, bazinaprine, lazabemide, milacemide and caroxazone); a compound for increasing lipid metabolism (such as evodiamine compounds); and a lipase inhibitor (such as orlistat). Generally, a total dosage of the above-described obesity control medications can range from 1 to 3,000 mg/day, desirably from about 1 to 1,000 mg/day and more desirably from about 1 to 200 mg/day in single or 2-4 divided doses.

[0435] The compositions, therapeutic combinations or methods of the present invention can further comprise one or more blood modifiers which are chemically or structurally different from the sterol absorption inhibitors (such as compounds (I-XI) above) and the cardiovascular agents discussed above, for example, they contain one or more different atoms, have a different arrangement of atoms or a different number of one or more atoms than the sterol absorption inhibitor(s) and the cardiovascular agents discussed above. Different blood modifiers include but are not limited to anti-coagulants (argatroban, bivalirudin, dalteparin sodium, desirudin, dicumarol, lyapolate sodium, nafamostat mesylate, phenprocoumon, tinzaparin sodium, warfarin sodium); antithrombotic (anagrelide hydrochloride, bivalirudin, cilostazol, dalteparin sodium, danaparoid sodium, dazoxiben hydrochloride, efegatran sulfate, enoxaparin sodium, fluretofen, ifetroban, ifetroban sodium, lamifiban, lotrafiban hydrochloride, napsagatran, orbofiban acetate, roxifiban acetate, sibrafiban, tinzaparin sodium, tirfenagrel, abciximab, zolimomab aritox); fibrinogen receptor antagonists (roxifiban acetate, fradafiban, orbofiban, lotrafiban hydrochloride, tirofiban, xemilofiban, monoclonal antibody 7E3, sibrafiban); platelet inhibitors (cilostazol, clopidogrel bisulfate, epoprostenol, epoprostenol sodium, ticlopidine hydrochloride, aspirin, ibuprofen, naproxen, sulindac, idomethacin, mefenamate, doxicam, diclofenac, sulfapyrazone, piroxicam, dipyridamole); platelet aggregation inhibitors (acadesine, beraprost, beraprost sodium, ciprostone calcium, itazigrel, lifarizine, lotrafiban hydrochloride, orbofiban acetate, oxagrelate, fradafiban, orbofiban, tirofiban, xemilofiban); hemorrhologic agents (pentoxifylline); lipoprotein associated coagulation inhibitor; Factor VIIa inhibitors (4H-31-benzoxazin-4-ones, 4H-3,1-benzoxazin-4-thiones, quinazolin-4-ones, quinazolin-4-thiones, benzothiazin-4-ones, imidazolyI-boronic acid-derived peptide analogues TFPI-derived peptides, naphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl} amide trifluoroacetate, dibenzofuran-2-sulfonic acid {1-[3-(aminomethyl)-benzyl]-5-oxo-pyrrolidin-3-yl}-amide, toluene-4-sulfonic acid {1-[3-(aminoiminomethyl)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl}-amide trifluoroacetate, 3,4-dihydro-1H-isoquinoline-2-sulfonic acid {1-[3-(aminoiminomethyl)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl}-amide trifluoroacetate); Factor Xa inhibitors (disubstituted pyrazolines, disubstituted triazolines, substituted n-[(aminomethyl)phenyl] propylamides, substituted n-[(aminomethyl)phenyl] propylamides, tissue factor pathway inhibitor (TFPI), low molecular weight heparins, heparinoids, benzimidazolines, benzoxazolinones, benzopiperazinones, indanones, dibasic (amidinoaryl) propanoic acid derivatives, amidinophenyl-pyrrolidines, amidinophenyl-pyrrolines, amidinophenyl-

isoxazolidines, amidinoindoles, amidinoazoles, bis-arylsulfonylaminobenzamide derivatives, peptidic Factor Xa inhibitors).

[0436] The compositions, therapeutic combinations or methods of the present invention can further comprise one or more antidiabetic medications for reducing blood glucose levels in a human. Different antidiabetic medications include, but are not limited to, drugs that reduce energy intake or suppress appetite, drugs that increase energy expenditure and nutrient-partitioning agents. Suitable antidiabetic medications include, but are not limited to, sulfonylurea (such as acetohexamide, chlorpropamide, glimepiride, glipizide, glyburide, glimepiride, tolazamide, and tolbutamide), meglitinide (such as repaglinide and nateglinide), biguanide (such as metformin and buformin), thiazolidinedione (such as troglitazone, rosiglitazone, pioglitazone, ciglitazone, englitazone, and darglitazone), alpha-glucosidase inhibitor (such as acarbose, miglitol, camiglibose, and voglibose), certain peptides (such as amlintide, pramlintide, exendin, and GLP-1 agonistic peptides), and orally administrable insulin or insulin composition for intestinal delivery thereof. Generally, a total dosage of the above-described antidiabetic medications can range from 0.1 to 1,000 mg/day in single or 2-4 divided doses.

[0437] Mixtures of any of the pharmacological or therapeutic agents described above can be used in the compositions and therapeutic combinations of these other embodiments of the present invention.

[0438] The compositions and therapeutic combinations of the present invention can be administered to a mammal in need of such treatment in a therapeutically effective amount to treat vascular conditions such as hypertension. The compositions and treatments can be administered by any suitable means that produce contact of these compounds with the site of action in the body, for example in the plasma, liver or small intestine of a mammal.

[0439] The daily dosage for the various compositions and therapeutic combinations described above can be administered to a patient in a single dose or in multiple subdoses, as desired. Subdoses can be administered 2 to 6 times per day, for example. Sustained release dosages can be used. Where the cardiovascular agents and sterol absorption inhibitor(s) are administered in separate dosages, the number of doses of each component given per day may not necessarily be the same, e.g., one component may have a greater duration of activity and will therefore need to be administered less frequently.

[0440] The pharmaceutical treatment compositions and therapeutic combinations of the present invention can further comprise one or more pharmaceutically acceptable carriers, one or more excipients and/or one or more additives. Non-limiting examples of pharmaceutically acceptable carriers include solids and/or liquids such as ethanol, glycerol, water and the like. The amount of carrier in the treatment composition can range from about 5 to about 99 weight percent of the total weight of the treatment composition or therapeutic combination. Non-limiting examples of suitable pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders such as starch, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifi-

ers and the like. The amount of excipient or additive can range from about 0.1 to about 90 weight percent of the total weight of the treatment composition or therapeutic combination. One skilled in the art would understand that the amount of carrier(s), excipients and additives (if present) can vary.

[0441] The treatment compositions of the present invention 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 and conventional techniques. Several examples of preparation of dosage formulations are provided below.

[0442] The following formulations exemplify some of the dosage forms of this invention. In each formulation, the term "Active Compound I" designates a sterol absorption inhibitor and the term "Active Compound II" designates a cardiovascular agent described herein above.

EXAMPLE

[0443]

No.	Tablets	
	Ingredient	mg/tablet
1	Active Compound I	10
2	Lactose monohydrate NF	55
3	Microcrystalline cellulose	20
4	Povidone (K29-32) USP	4
5	Croscarmellose sodium NF	8
6	Sodium lauryl sulfate	2
7	Magnesium stearate NF	1
Total		100

[0444] In the present invention, the above-described tablet can be coadministered with a tablet, capsule, etc. comprising a dosage of Active Compound II, for example a cardiovascular agent as described above.

[0445] Method of Manufacture

[0446] Mix Item No. 4 with purified water in suitable mixer to form binder solution. Spray the binder solution and then water over Items 1, 2, 6 and a portion of Item 5 in a fluidized bed processor to granulate the ingredients. Continue fluidization to dry the damp granules. Screen the dried granules and blend with Item No. 3 and the remainder of Item 5. Add Item No. 7 and mix. Compress the mixture to appropriate size and weight on a suitable tablet machine.

[0447] For coadministration in separate tablets or capsules, representative formulations comprising a cholesterol absorption inhibitor such as are discussed above are well known in the art and representative formulations comprising a cardiovascular agent such as are discussed above are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for sterol absorption inhibitor may readily be modified using the knowledge of one skilled in the art.

[0448] Since the present invention relates to reducing the plasma sterol (especially cholesterol) concentrations or levels by treatment with a combination of active ingredients or treating vascular conditions, stroke or obesity wherein the active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: a pharmaceutical composition comprising at least one cardiovascular agent and a separate pharmaceutical composition comprising at least one sterol absorption inhibitor as described above. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g., oral and parenteral) or are administered at different dosage intervals.

[0449] The treatment compositions and therapeutic combinations of the present invention can inhibit the intestinal absorption of cholesterol in mammals, as shown in the Example below, and can be useful in the treatment and/or prevention of vascular conditions, such as vascular inflammation, atherosclerosis, hypercholesterolemia and sitosterolemia, stroke, obesity and lowering of plasma levels of cholesterol in mammals, in particular in humans.

[0450] In another embodiment of the present invention, the compositions and therapeutic combinations of the present invention can inhibit sterol absorption or reduce plasma concentration of at least one sterol selected from the group consisting of phytosterols (such as sitosterol, campesterol, stigmasterol and avenasterol), 5α -stanols (such as cholestanol, 5α -campestanol, 5α -sitostanol), cholesterol and mixtures thereof. The plasma concentration can be reduced by administering to a mammal in need of such treatment an effective amount of at least one treatment composition or therapeutic combination comprising at least one cardiovascular agent and at least one sterol absorption inhibitor described above. The reduction in plasma concentration of sterols can range from about 1 to about 70 percent, and preferably about 10 to about 50 percent. Methods of measuring serum total blood cholesterol and total LDL cholesterol are well known to those skilled in the art and for example include those disclosed in PCT WO 99/38498 at page 11, incorporated by reference herein. Methods of determining levels of other sterols in serum are disclosed in H. Gylling et al., "Serum Sterols During Stanol Ester Feeding in a Mildly Hypercholesterolemic Population", J. Lipid Res. 40: 593-600 (1999), incorporated by reference herein.

[0451] Illustrating the invention is the following example which, however, are not to be considered as limiting the invention to their details. Unless otherwise indicated, all parts and percentages in the following examples, as well as throughout the specification, are by weight.

EXAMPLE

PREPARATION OF COMPOUND OF FORMULA (II)

[0452] Step 1):

[0453] To a solution of (S)-4-phenyl-2-oxazolidinone (41 g, 0.25 mol) in CH_2Cl_2 (200 ml), was added 4-dimethylaminopyridine (2.5 g, 0.02 mol) and triethylamine (84.7 ml,

0.61 mol) and the reaction mixture was cooled to 0°C . Methyl-4-(chloroformyl)butyrate (50 g, 0.3 mol) was added as a solution in CH_2Cl_2 (375 ml) dropwise over 1 h, and the reaction was allowed to warm to 22°C . After 17 h, water and H_2SO_4 (2N, 100 ml), was added, the layers were separated, and the organic layer was washed sequentially with NaOH (10%), NaCl (sat'd) and water. The organic layer was dried over MgSO_4 and concentrated to obtain a semicrystalline product.

[0454] Step 2):

[0455] To a solution of TiCl_4 (18.2 ml, 0.165 mol) in CH_2Cl_2 (600 ml) at 0°C ., was added titanium isopropoxide (16.5 ml, 0.055 mol). After 15 min., the product of Step 1 (49.0 g, 0.17 mol) was added as a solution in CH_2Cl_2 (100 ml). After 5 min., diisopropylethylamine (DIPEA) (65.2 ml, 0.37 mol) was added and the reaction mixture was stirred at 0°C . for 1 h, the reaction mixture was cooled to -20°C ., and 4-benzyloxybenzylidene(4-fluoro)aniline (114.3 g, 0.37 mol) was added as a solid. The reaction mixture was stirred vigorously for 4 h at -20°C ., then acetic acid was added as a solution in CH_2Cl_2 dropwise over 15 min., the reaction mixture was allowed to warm to 0°C ., and H_2SO_4 (2N) was added. The reaction mixture was stirred an additional 1 h, the layers were separated, washed with water, separated and the organic layer was dried. The crude product was crystallized from ethanol/water to obtain the pure intermediate.

[0456] Step 3):

[0457] To a solution of the product of Step 2 (8.9 g, 14.9 mmol) in toluene (100 ml) at 50°C ., was added N,O-bis(trimethylsilyl)acetamide (BSA) (7.50 ml, 30.3 mmol). After 0.5 h, solid TBAF (0.39 g, 1.5 mmol) was added and the reaction mixture stirred at 50°C . for an additional 3 h. The reaction mixture was cooled to 22°C ., CH_3OH (10 ml), was added. The reaction mixture was washed with HCl (1 N), NaHCO_3 (1 N) and NaCl (sat'd.), and the organic layer was dried over MgSO_4 .

[0458] Step 4):

[0459] To a solution of the product of Step 3 (0.94 g, 2.2 mmol) in CH_3OH (3 ml), was added water (1 ml) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (102 mg, 2.4 mmole). The reaction mixture was stirred at 22°C . for 1 h and then additional $\text{LiOH}\cdot\text{H}_2\text{O}$ (54 mg, 1.3 mmole) was added. After a total of 2 h, HCl (1 N) and EtOAc was added, the layers were separated, the organic layer was dried and concentrated in vacuo. To a solution of the resultant product (0.91 g, 2.2 mmol) in CH_2Cl_2 at 22°C ., was added ClCOCOCI (0.29 ml, 3.3 mmol) and the mixture stirred for 16 h. The solvent was removed in vacuo.

[0460] Step 5):

[0461] To an efficiently stirred suspension of 4-fluorophenylzinc chloride (4.4 mmol) prepared from 4-fluorophenylmagnesium bromide (1 M in THF, 4.4 ml, 4.4 mmol) and ZnCl_2 (0.6 g, 4.4 mmol) at 4°C ., was added tetrakis(triphenylphosphine)palladium (0.25 g, 0.21 mmol) followed by the product of Step 4 (0.94 g, 2.2 mmol) as a solution in THF (2 ml). The reaction was stirred for 1 h at 0°C . and then for 0.5 h at 22°C . HCl (1 N, 5 ml) was added and the mixture was extracted with EtOAc. The organic layer was concentrated to an oil and purified by silica gel chromatography to obtain 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(R)-(3-oxo-3-phenylpropyl)-2-azetidinone:

[0462] HRMS calc'd for $C_{24}H_{19}F_2NO_3=408.1429$, found 408.1411.

[0463] Step 6):

[0464] To the product of Step 5 (0.95 g, 1.91 mmol) in THF (3 ml), was added (R)-tetrahydro-1-methyl-3,3-diphenyl-1H, 3H-pyrrolo-[1,2-c][1,3,2] oxazaborole (120 mg, 0.43 mmol) and the mixture was cooled to -20°C . After 5 min, borohydride-dimethylsulfide complex (2M in THF, 0.85 ml, 1.7 mmol) was added dropwise over 0.5 h. After a total of 1.5 h, CH_3OH was added followed by HCl (1 N) and the reaction mixture was extracted with EtOAc to obtain 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone (compound 6A-1) as an oil. ^1H in $CDCl_3$, δ H 3=4.68, J=2.3 Hz, Cl (M⁺H) 500.

[0465] Use of (S)-tetra-hydro-1-methyl-3,3-diphenyl-1H, 3H-pyrrolo-[1,2-c][1,3,2] oxazaborole gives the corresponding 3(R)-hydroxypropyl azetidinone (compound 6B-1). ^1H in $CDCl_3$, δ H 3=4.69, J=2.3 Hz, Cl (M⁺H) 500.

[0466] To a solution of compound 6A-1 (0.4 g, 0.8 mmol) in ethanol (2 ml), was added 10% Pd/C (0.03 g) and the reaction mixture was stirred under a pressure (60 psi) of H_2 gas for 16 h. The reaction mixture was filtered and the solvent was concentrated to obtain compound 6A. Mp $164-166^\circ\text{C}$; Cl (M⁺H) 410. $[\alpha]_D^{25}=-28.1^\circ$ (c 3, CH_3OH) Elemental analysis calc'd for $C_{24}H_{21}F_2NO_3$: C 70.41; H 5.17; N 3.42; found C 70.25; H 5.19; N 3.54.

[0467] Similarly treat compound 6B-1 to obtain compound 6B.

[0468] Mp $129.5-132.5^\circ\text{C}$; Cl (M⁺H) 410. Elemental analysis calc'd for $C_{24}H_{21}F_2NO_3$: C 70.41; H 5.17; N 3.42; found C 70.30; H 5.14; N 3.52.

[0469] Step 640 (Alternative):

[0470] To a solution of the product of Step 5 (0.14 g, 0.3 mmol) in ethanol (2 ml), was added 10% Pd/C (0.03 g) and the reaction was stirred under a pressure (60 psi) of H_2 gas for 16 h. The reaction mixture was filtered and the solvent was concentrated to afford a 1:1 mixture of compounds 6A and 6B.

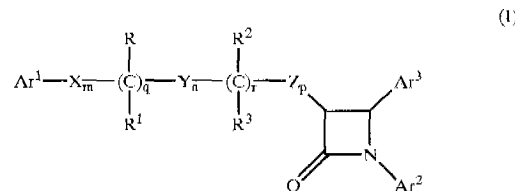
[0471] It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications which are within the spirit and scope of the invention, as defined by the appended claims.

Therefore, we claim:

1. A composition comprising:

- at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate thereof or prodrug of the at least one sterol absorption inhibitor or of the salt or solvate thereof; and
- at least one cardiovascular agent for treating vascular conditions which is different from the at least one sterol absorption inhibitor.

2. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (I):



or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or prodrugs of the compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4 -substituted aryl;

Ar^3 is aryl or R^5 -substituted aryl;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, $-CH$ (lower alkyl)- and $-C$ (dilower alkyl)-;

R and R^2 are independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^6$ and $-O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

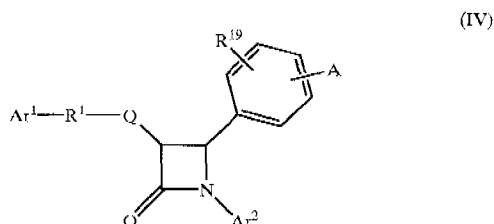
R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^6$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^6$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, $-(lower\ alkylene)COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, $-CN$, $-NO_2$ and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^6$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^6$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, $-(lower\ alkylene)COOR^6$ and $-CH=CH-COOR^6$;

R^6 , R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

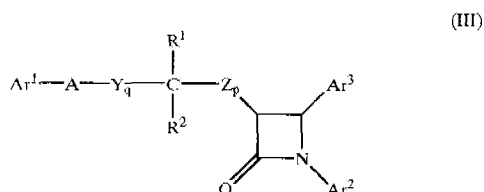
R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

3. The composition according to claim 2, wherein the sterol absorption inhibitor is represented by Formula (II) below:



or pharmaceutically acceptable salts or solvates thereof, or prodrugs of the compound of Formula (II) or of the salts or solvates thereof.

4. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (III):



or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (III) or of the isomers thereof, or prodrugs of the compounds of Formula (III) or of the isomers, salts or solvates thereof, wherein, in Formula (III) above:

Ar¹ is R³-substituted aryl;

Ar² is R⁴-substituted aryl;

Ar³ is R⁵-substituted aryl;

Y and Z are independently selected from the group consisting of —CH₂—, —CH(lower alkyl)— and —C(dilower alkyl)—;

A is selected from —O—, —S—, —S(O)— or —S(O)₂—;

R¹ is selected from the group consisting of —OR⁶, —O(CO)R⁶, —O(CO)OR⁹ and —O(CO)NR⁶R⁷; R² is selected from the group consisting of hydrogen, lower alkyl and aryl; or R¹ and R² together are =O;

q is 1, 2 or 3;

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

R⁵ is 1-3 substituents independently selected from the group consisting of —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)₁₋₅OR⁹, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂-lower alkyl, —NR⁶SO₂-aryl, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₀₋₂-alkyl, S(O)₀₋₂-aryl, —O(CH₂)₁₋₁₀—COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, -(lower alkylene)-COOR⁶, and

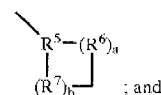
—CH=CH—COOR⁶;

R³ and R⁴ are independently 1-3 substituents independently selected from the group consisting of R⁵ hydrogen, p-lower alkyl, aryl, —NO₂, —CF₃ and p-halogeno;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl.

5. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (IV):



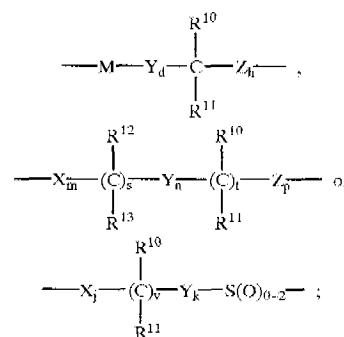
or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IV) or of the isomers thereof, or prodrugs of the compounds of Formula (IV) or of the isomers, salts or solvates thereof, wherein, in Formula (IV) above:

A is selected from the group consisting of R²-substituted heterocycloalkyl, R²-substituted heteroaryl, R²-substituted benzofused heterocycloalkyl, and R²-substituted benzofused heteroaryl;

Ar¹ is aryl or R³-substituted aryl;

Ar² is aryl or R⁴-substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group



and

R¹ is selected from the group consisting of:

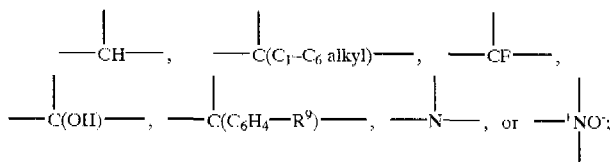
—(CH₂)_q—, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

—(CH₂)_e—G—(CH₂)_r—, wherein G is —O—, —C(O)—, phenylene, —NR⁸— or —S(O)₀₋₂—, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

—(C₂-C₆ alkenylene)—; and

—(CH₂)_f—V—(CH₂)_g—, wherein V is C₃-C₆ cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

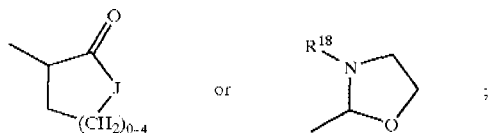
R⁵ is selected from:



R⁶ and R⁷ are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{C}_1-\text{C}_6 \text{ alkyl})-$, $-\text{C}(\text{di}(\text{C}_1-\text{C}_6) \text{ alkyl})-$, $-\text{CH}=\text{CH}-$ and $-\text{C}(\text{C}_1-\text{C}_6 \text{ alkyl})=\text{CH}-$; or R⁵ together with an adjacent R⁶, or R⁵ together with an adjacent R⁷, form a $-\text{CH}=\text{CH}-$ or a $-\text{CH}=\text{C}(\text{C}_1-\text{C}_6 \text{ alkyl})-$ group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R⁶ is $-\text{CH}=\text{CH}-$ or $-\text{C}(\text{C}_1-\text{C}_6 \text{ alkyl})=\text{CH}-$, a is 1; provided that when R⁷ is $-\text{CH}=\text{CH}-$ or $-\text{C}(\text{C}_1-\text{C}_6 \text{ alkyl})=\text{CH}-$, b is 1; provided that when a is 2 or 3, the R⁶'s can be the same or different; and provided that when b is 2 or 3, the R⁷'s can be the same or different;

and when Q is a bond, R¹ also can be selected from:



where M is $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$ or $-\text{S}(\text{O})_2-$;

X, Y and Z are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{C}_1-\text{C}_6 \text{ alkyl})-$ and $-\text{C}(\text{di}(\text{C}_1-\text{C}_6) \text{ alkyl})-$;

R¹⁰ and R¹² are independently selected from the group consisting of $-\text{OR}^{14}$, $-\text{O}(\text{CO})\text{R}^{14}$, $-\text{O}(\text{CO})\text{OR}^{16}$ and $-\text{O}(\text{CO})\text{NR}^{14}\text{R}^{15}$;

R¹¹ and R¹³ are independently selected from the group consisting of hydrogen, $(\text{C}_1-\text{C}_6) \text{ alkyl}$ and aryl; or R¹⁰ and R¹¹ together are $=\text{O}$, or R¹² and R¹³ together are $=\text{O}$;

d is 1, 2 or 3;

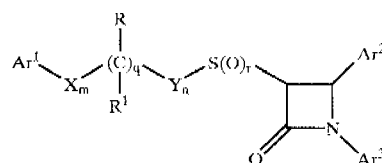
h is 0, 1, 2, 3 or 4;

s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4; provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

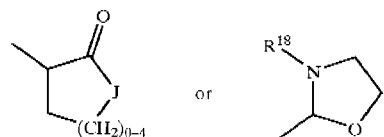
v is 0 or 1;

j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

R² is 1-3 substituents on the ring carbon atoms selected from the group consisting of hydrogen, $(\text{C}_1-\text{C}_{10}) \text{ alkyl}$, $(\text{C}_2-\text{C}_{10}) \text{ alkenyl}$, $(\text{C}_2-\text{C}_{10}) \text{ alkynyl}$, $(\text{C}_3-\text{C}_6) \text{ cycloalkyl}$, $(\text{C}_3-\text{C}_6) \text{ cycloalkenyl}$, R¹⁷-substituted aryl, R¹⁷-substituted benzyl, R¹⁷-substituted benzyloxy, R¹⁷-substituted aryloxy, halogeno, $-\text{NR}^{14}\text{R}^{15}$, $\text{NR}^{14}\text{R}^{15}(\text{C}_1-\text{C}_6 \text{ alkylene})-$, $\text{NR}^{14}\text{R}^{15}\text{C}(\text{O})(\text{C}_1-\text{C}_6 \text{ alkylene})-$, $-\text{NH}-\text{C}(\text{O})\text{R}^{16}$, OH, $\text{C}_1-\text{C}_6 \text{ alkoxy}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{COR}^{14}$, hydroxy $(\text{C}_1-\text{C}_6) \text{ alkyl}$, $(\text{C}_1-\text{C}_6) \text{ alkoxy}(\text{C}_1-\text{C}_6) \text{ alkyl}$, NO_2 , $-\text{S}(\text{O})_{0-2}\text{R}^{16}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$ and $-(\text{C}_1-\text{C}_6 \text{ alkylene})\text{COOR}^{14}$; when R² is a substituent on a heterocycloalkyl ring, R² is as defined, or is $=\text{O}$ or



and, where R² is a substituent on a substitutable ring nitrogen, it is hydrogen, $(\text{C}_1-\text{C}_6) \text{ alkyl}$, aryl, $(\text{C}_1-\text{C}_6) \text{ alkoxy}$, aryloxy, $(\text{C}_1-\text{C}_6) \text{ alkylcarbonyl}$, arylcarbonyl, hydroxy, $-(\text{CH}_2)_{1-6}\text{CONR}^{18}\text{R}^{18}$,



wherein J is $-\text{O}-$, $-\text{NH}-$, $-\text{NR}^{18}-$ or $-\text{CH}_2-$;

R³ and R⁴ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of $(\text{C}_1-\text{C}_6) \text{ alkyl}$, $-\text{OR}^{14}$, $-\text{O}(\text{CO})\text{R}^{14}$, $-\text{O}(\text{CO})\text{OR}^{16}$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^{14}$, $-\text{O}(\text{CO})\text{NR}^{14}\text{R}^{15}$, $-\text{NR}^{14}\text{R}^{15}$, $-\text{NR}^{14}(\text{CO})\text{R}^{15}$, $-\text{NR}^{14}(\text{CO})\text{OR}^{16}$, $-\text{NR}^{14}(\text{CO})\text{NR}^{15}\text{R}^{19}$, $\text{NR}^{14}\text{SO}_2\text{R}^{16}$, $-\text{COOR}^{14}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{COR}^{14}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $\text{S}(\text{O})_{0-2}\text{R}^{16}$, $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^{14}$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^{14}\text{R}^{16}$, $-(\text{C}_1-\text{C}_6 \text{ alkylene})-\text{COOR}^{14}$, $-\text{CH}=\text{CH}-\text{COOR}^{14}$, $-\text{Cl}$, $-\text{CN}$, $-\text{NO}_2$ and halogeno;

R⁸ is hydrogen, $(\text{C}_1-\text{C}_6) \text{ alkyl}$, aryl $(\text{C}_1-\text{C}_6) \text{ alkyl}$, $-\text{C}(\text{O})\text{R}^{14}$ or $-\text{COOR}^{14}$;

R⁹ and R¹⁷ are independently 1-3 groups independently selected from the group consisting of hydrogen, $(\text{C}_1-\text{C}_6) \text{ alkyl}$, $(\text{C}_1-\text{C}_6) \text{ alkoxy}$, $-\text{COOH}$, NO_2 , $-\text{NR}^{14}\text{R}^{15}$, OH and halogeno;

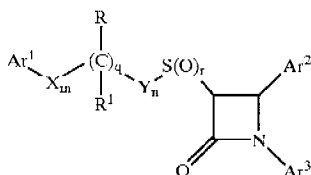
R¹⁴ and R¹⁵ are independently selected from the group consisting of hydrogen, $(\text{C}_1-\text{C}_6) \text{ alkyl}$, aryl and aryl-substituted $(\text{C}_1-\text{C}_6) \text{ alkyl}$;

R¹⁶ is $(\text{C}_1-\text{C}_6) \text{ alkyl}$, aryl or R¹⁷-substituted aryl;

R¹⁸ is hydrogen or $(\text{C}_1-\text{C}_6) \text{ alkyl}$; and

R¹⁹ is hydrogen, hydroxy or $(\text{C}_1-\text{C}_6) \text{ alkoxy}$.

6. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is represented by formula (V):



or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (V) or of the isomers thereof, or prodrugs of the compounds of Formula (V) or of the isomers, salts or solvates thereof, wherein, in Formula (V) above:

Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

X and Y are independently selected from the group consisting of —CH₂—, —CH(lower alkyl)— and —C(dilower alkyl)—;

R is —OR⁶, —O(CO)R⁶, —O(CO)OR⁹ or —O(CO)NR⁶R⁷; R¹ is hydrogen, lower alkyl or aryl; or R and R¹ together are =O;

q is 0 or 1;

r is 0, 1 or 2;

m and n are independently 0, 1, 2, 3, 4 or 5; provided that the sum of m, n and q is 1, 2, 3, 4 or 5;

R⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)₁₋₅OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₀₋₂R⁹, —O(CH₂)₁₋₁₀—COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —(lower alkylene)COOR⁶ and —CH=CH—COOR⁶;

R⁵ is 1-5 substituents independently selected from the group consisting of —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)₁₋₅OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₀₋₂R⁹, —O(CH₂)₁₋₁₀—COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —CF₃, —CN, —NO₂, halogen,

—(lower alkylene)COOR⁶ and —CH=CH—COOR⁶;

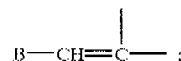
R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl; and

R¹⁰ is 1-5 substituents independently selected from the group consisting of lower alkyl, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)₁₋₅OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, —S(O)₀₋₂R⁹, —O(CH₂)₁₋₁₀—COOR⁶,

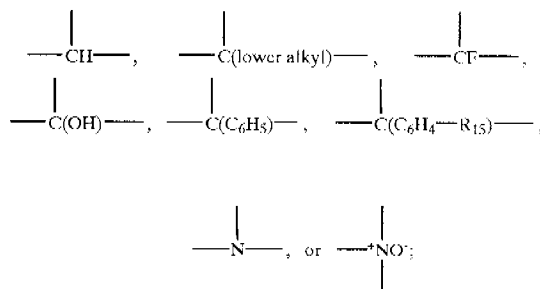
—O(CH₂)₁₋₁₀CONR⁶R⁷, —CF₃, —CN, —NO₂ and halogen.

7. The composition according to claim 1, where the at least one sterol absorption inhibitor is represented by Formula (VI):



or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VI) or of the isomers thereof, or prodrugs of the compounds of Formula (VI) or of the isomers, salts or solvates thereof, wherein:

R₁ is



R² and R³ are independently selected from the group consisting of: —CH₂—, —CH(lower alkyl)—, —C(dilower alkyl)—, —CH=CH— and —C(lower alkyl)=CH—; or R₁ together with an adjacent R², or R₁ together with an adjacent R³, 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 R₂ is —CH=CH— or —C(lower alkyl)=CH—, v is 1; provided that when R₃ is —CH=CH— or —C(lower alkyl)=CH—, u is 1; provided that when v is 2 or 3, the R₂'s can be the same or different; and provided that when u is 2 or 3, the R₃'s can be the same or different;

R₄ is selected from B—(CH₂)_mC(O)—, wherein m is 0, 1, 2, 3, 4 or 5;

B—(CH₂)_q—, wherein q is 0, 1, 2, 3, 4, 5 or 6;

B—(CH₂)_e—Z—(CH₂)_r—, wherein Z is —O—, —C(O)—, phenylene, —N(R₈)— 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—(C₂—C₆ alkenylene)—;

B—(C₄—C₆ alkadienylene)—;

B—(CH₂)_t—Z—(C₂—C₆ 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;

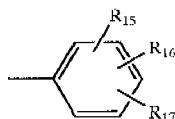
B—(CH₂)_f—V—(CH₂)_g—, wherein V is C₃—C₆ cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6;

B—(CH₂)_t—V—(C₂-C₆ alkenylene)- or

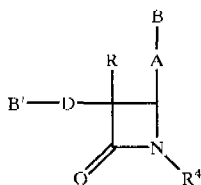
B—(C₂-C₆ alkenylene)-V—(CH₂)_t—, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

B—(CH₂)_a—Z—(CH₂)_b—V—(CH₂)_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; or T—(CH₂)_s—, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

R₁ and R₄ together form the group

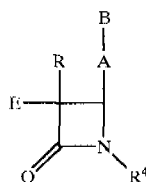


B is selected from indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing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



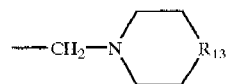
(VIIA)

and



(VIIB)

W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxyalkoxyalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, —CF₃, —OCF₃, benzyl, R₇-benzyl, benzyloxy, R₇-benzyloxy, phenoxy, R₇-phenoxy, dioxolanyl, NO₂, —N(R₈)(R₉), N(R₈)(R₉)-lower alkylene-, N(R₈)(R₉)-lower alkylenyloxy-, OH, halogeno, —CN, —N₃, —NHC(O)OR₁₀, —NHCO(R₁₀)R₁₀, R₁₁O₂SNH—, (R₁₁O₂S)₂N—, —S(O)₂NH₂, —S(O)₀₋₂R₈, tert-butyltrimethylsilyloxymethyl, —C(O)R₁₂, —COOR₁₉, —CON(R₈)(R₉), —CH=CHC(O)R₁₂, —lower alkylene-C(O)R₁₂, R₁₀C(O)(lower alkylenyloxy)-, N(R₈)(R₉)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)OR₁₀, —C(O)R₁₀, OH, N(R₈)(R₉)-lower alkylene-, N(R₈)(R₉)-lower alkylenyloxy-, —S(O)₂NH₂ and 2-(trimethylsilyl)-ethoxymethyl;

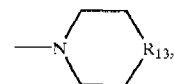
R₇ is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, —COOH, NO₂, —N(R₈)(R₉), OH, and halogeno;

R₈ and R₉ are independently selected from H or lower alkyl;

R₁₀ is selected from lower alkyl, phenyl, R₇-phenyl, benzyl or R₇-benzyl;

R₁₁ is selected from OH, lower alkyl, phenyl, benzyl, R₇-phenyl or R₇-benzyl;

R₁₂ is selected from H, OH, alkoxy, phenoxy, benzyloxy,



—N(R₈)(R₉), lower alkyl, phenyl or R⁷-phenyl;

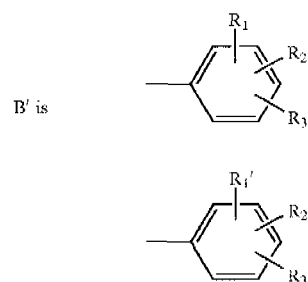
R¹³ is selected from —O—, —CH₂—, —NH—, —N(lower alkyl)- or —NC(O)R₁₀;

R₁₅, R₁₆ and R₁₇ are independently selected from the group consisting of H and the groups defined for W; or R₁₅ is hydrogen and R₁₆ and R₁₇, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

R₁₉ is H, lower alkyl, phenyl or phenyl lower alkyl; and

R₂₀ and R₂₁ 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.

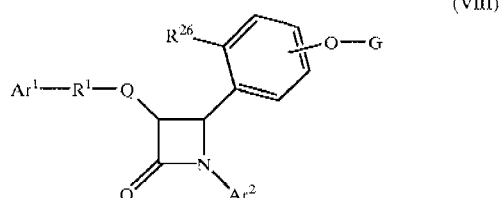
8. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (VIIA) or (VIIB):



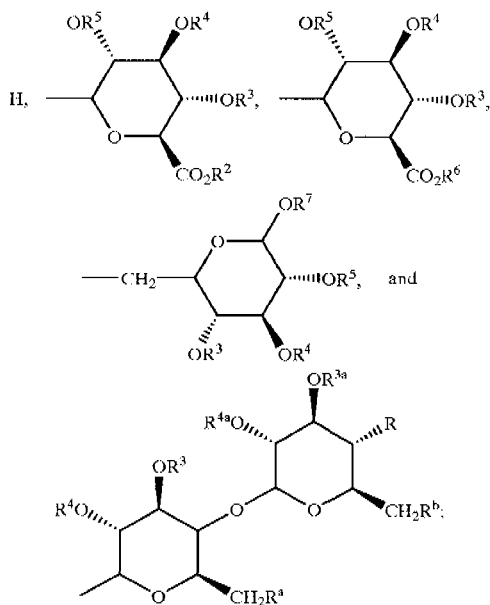
or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VIIA) or Formula (VIIB) or of the isomers thereof, or prodrugs of the compounds of Formula (VIIA) or Formula (VIIB) or of the isomers, salts or solvates thereof, wherein in Formula (VIIA) and Formula (VIIB):

A is $-\text{CH}=\text{CH}-$, $-\text{C}=\text{C}-$ or $-(\text{CH}_2)_p-$ wherein p is 0, 1 or 2;

B is



B' is



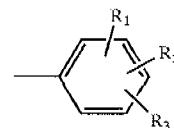
D is $-(\text{CH}_2)_m\text{C}(\text{O})-$ or $-(\text{CH}_2)_q-$ wherein m is 1, 2, 3 or 4 and q is 2, 3 or 4;

E is C_{10} to C_{20} alkyl or $-\text{C}(\text{O})-(\text{C}_9 \text{ to } \text{C}_{10})\text{-alkyl}$, wherein the alkyl is straight or branched, saturated or containing one or more double bonds;

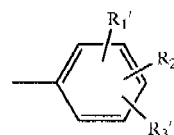
R is hydrogen, $\text{C}_1\text{-C}_{15}$ alkyl, straight or branched, saturated or containing one or more double bonds, or $\text{B}-(\text{CH}_2)_r-$, wherein r is 0, 1, 2, or 3;

R_1 , R_2 , R_3 , R_1' , R_2' , and R_3' are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, carboxy, NO_2 , NH_2 , OH, halogeno, lower alkylamino, dilower alkylamino, $-\text{NH}-\text{C}(\text{O})\text{OR}_5$, $\text{R}_6\text{O}_2\text{SNH}-$ and $-\text{S}(\text{O})_2\text{NH}_2$;

R_4 is



B' is

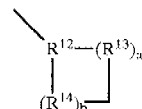


wherein n is 0, 1, 2 or 3;

R_5 is lower alkyl; and

R_6 is OH, lower alkyl, phenyl, benzyl or substituted phenyl wherein the substituents are 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, carboxy, NO_2 , NH_2 , OH, halogeno, lower alkylamino and dilower alkylamino.

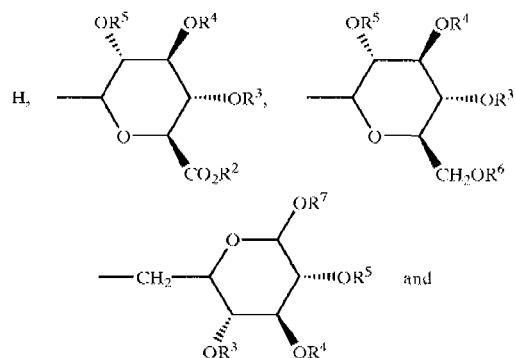
9. The composition according to claim 1, wherein the at least one sterol absorption inhibitor represented by Formula (VIII):

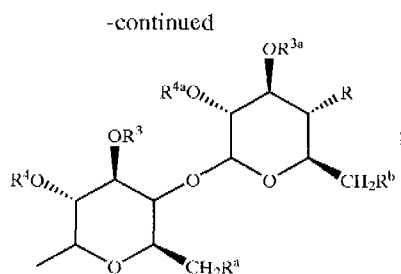


or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VII) or of the isomers thereof, or prodrugs of the compounds of Formula (VIII) or of the isomers, salts or solvates thereof, wherein, in Formula (VIII) above,

R^{26} is H or OG^1 ;

G and G^1 are independently selected from the group consisting of





provided that when R^{26} is H or OH, G is not H;

R , R^a and R^b are independently selected from the group consisting of H, —OH, halogeno, —NH₂, azido, (C₁–C₆)alkoxy(C₁–C₆)alkoxy or —W—R³⁰;

W is independently selected from the group consisting of —NH—C(O)—, —O—C(O)—, —O—C(O)—N(R³¹)—, —NH—C(O)—N(R³¹)— and —O—C(S)—N(R³¹)—;

R^2 and R^6 are independently selected from the group consisting of H, (C₁–C₆)alkyl, aryl and aryl(C₁–C₆)alkyl;

R^3 , R^4 , R^5 , R^7 , R^{3a} and R^{4a} are independently selected from the group consisting of H, (C₁–C₆)alkyl, aryl(C₁–C₆)alkyl, —C(O)(C₁–C₆)alkyl and —C(O)aryl;

R^{30} is selected from the group consisting of R^{32} -substituted T,

R^{32} -substituted-T—(C₁–C₆)alkyl, R^{32} -substituted-(C₂–C₄)alkenyl,

R^{32} -substituted-(C₁–C₆)alkyl, R^{32} -substituted-(C₃–C₇)cycloalkyl and

R^{32} -substituted-(C₃–C₇)cycloalkyl(C₁–C₆)alkyl;

R^{31} is selected from the group consisting of H and (C₁–C₄)alkyl;

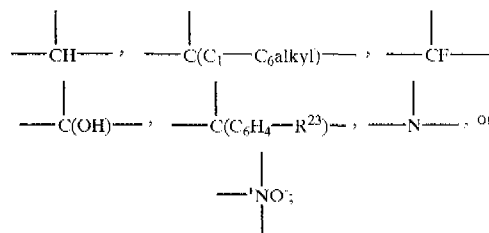
T is selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R^{32} is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C₁–C₄)alkyl, —OH, phenoxy, —Cl₃, —NO₂, (C₁–C₄)alkoxy, methylenedioxy, oxo, (C₁–C₄)alkylsulfanyl, (C₁–C₄)alkylsulfinyl, (C₁–C₄)alkylsulfonyl, —N(CH₃)₂, —C(O)—NH(C₁–C₄)alkyl, —C(O)—N((C₁–C₄)alkyl)₂, —C(O)—(C₁–C₄)alkyl, —C(O)—(C₁–C₄)alkoxy and pyrrolidinylcarbonyl; or R^{32} is a covalent bond and R^{31} , the nitrogen to which it is attached and R^{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolyl or morpholyl group, or a (C₁–C₄)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolyl or morpholyl group;

Ar¹ is aryl or R¹⁰-substituted aryl;

Ar² is aryl or R¹¹-substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group



and

R^1 is selected from the group consisting of

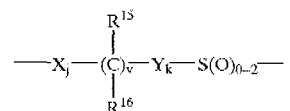
—(CH₂)_q—, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

—(CH₂)_e—E—(CH₂)_r—, wherein E is —O—, —C(O)—, phenylene, —NR²²— or —S(O)₀₋₂—, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

—(C₂–C₆)alkenylene—; and

—(CH₂)_f—V—(CH₂)_g—, wherein V is C₃–C₆ cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

R^{12} is



R^{13} and R^{14} are independently selected from the group consisting of —CH₂—, —CH(C₁–C₆ alkyl)—, —C(di-(C₁–C₆) alkyl)—, —CH=CH— and —C(C₁–C₆ alkyl)=CH—; or R^{12} together with an adjacent R^{13} , or R^{12} together with an adjacent R^{14} , form a —CH=CH— or a —CH=C(C₁–C₆ alkyl)— group;

a and b are independently 0, 1, 2 or 3, provided both are not zero;

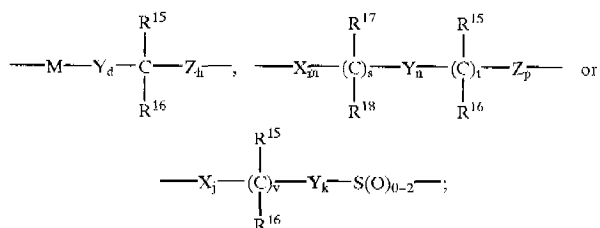
provided that when R^{13} is —CH=CH— or —C(C₁–C₆ alkyl)=CH—, a is 1;

provided that when R^{14} is —CH=CH— or —C(C₁–C₆ alkyl)=CH—, b is 1;

provided that when a is 2 or 3, the R^{13} 's can be the same or different; and

provided that when b is 2 or 3, the R^{14} 's can be the same or different;

and when Q is a bond, R^1 also can be:



M is ---O--- , ---S--- , ---S(O)--- or $\text{---S(O)}_2\text{---}$;

X, Y and Z are independently selected from the group consisting of $\text{---CH}_2\text{---}$, $\text{---CH(C}_1\text{---C}_6\text{)alkyl---}$ and $\text{---C(di-C}_1\text{---C}_6\text{)alkyl---}$;

R^{10} and R^{11} are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of $(\text{C}_1\text{---C}_6)\text{alkyl}$, ---OR^{19} , ---O(CO)R^{19} , ---O(CO)OR^{20} , $\text{---O(CH}_2\text{)}_{1-50}\text{R}^{19}$, $\text{---O(CO)NR}^{19}\text{R}^{20}$, $\text{---NR}^{19}\text{R}^{20}$, $\text{---NR}^{19}(\text{CO)R}^{20}$, $\text{---NR}^{19}(\text{CO)OR}^{21}$, $\text{---NR}^{19}(\text{CO)NR}^{20}\text{R}^{25}$, $\text{---NR}^{19}\text{SO}_2\text{R}^{21}$, ---COOR^{19} , $\text{---CONR}^{19}\text{R}^{20}$, ---COR^{19} , $\text{---SO}_2\text{NR}^{19}\text{R}^{20}$, $\text{S(O)}_{0-2}\text{R}^{23}$, $\text{---O(CH}_2\text{)}_{1-10}\text{---COOR}^{19}$, $\text{---O(CH}_2\text{)}_{1-10}\text{CONR}^{19}\text{R}^{20}$, $(\text{C}_1\text{---C}_6\text{ alkylene)---COOR}^{19}$, $\text{---CH=CH---COOR}^{19}$, ---CF_3 , ---CN , ---NO_2 and halogen;

R^{15} and R^{17} are independently selected from the group consisting of ---OR^{19} , ---O(CO)R^{19} , ---O(CO)OR^{21} and $\text{---O(CO)NR}^{19}\text{R}^{20}$;

R^{16} and R^{18} are independently selected from the group consisting of H, $(\text{C}_1\text{---C}_6)\text{alkyl}$ and aryl; or R^{15} and R^{16} together are =O , or R^{17} and R^{18} together are =O ;

d is 1, 2 or 3;

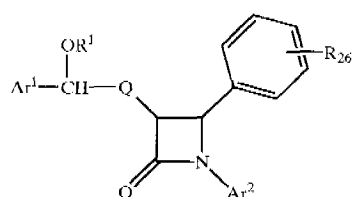
b is 0, 1, 2, 3 or 4;

s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4; provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6;

provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and t is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

j and k are independently 1-5, provided that the sum of j, k and v is 1-5; and when Q is a bond and R^1 is



(IX)

Ar^1 can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R^{19} and R^{20} are independently selected from the group consisting of H, $(\text{C}_1\text{---C}_6)\text{alkyl}$, aryl and aryl-substituted $(\text{C}_1\text{---C}_6)\text{alkyl}$;

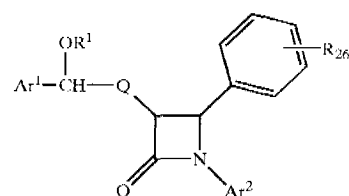
R^{21} is $(\text{C}_1\text{---C}_6)\text{alkyl}$, aryl or R^{24} -substituted aryl;

R^{22} is H, $(\text{C}_1\text{---C}_6)\text{alkyl}$, aryl $(\text{C}_1\text{---C}_6)\text{alkyl}$, ---C(O)R^{19} or ---COOR^{19} ;

R^{23} and R^{24} are independently 1-3 groups independently selected from the group consisting of H, $(\text{C}_1\text{---C}_6)\text{alkyl}$, $(\text{C}_1\text{---C}_6)\text{alkoxy}$, ---COOH , NO_2 , $\text{---NR}^{19}\text{R}^{20}$, ---OH and halogeno; and

R^{25} is H, ---OH or $(\text{C}_1\text{---C}_6)\text{alkoxy}$.

10. The composition according to claim 1, wherein the at least one sterol absorption inhibitor represented by Formula (IX):



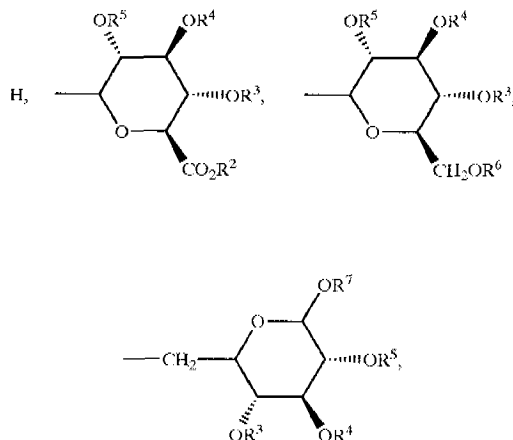
(IX)

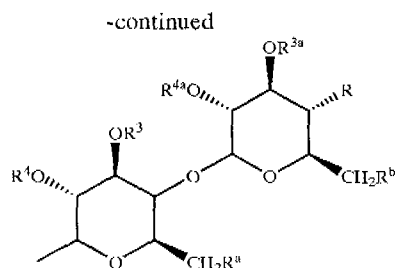
or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IX) or of the isomers thereof, or prodrugs of the compounds of Formula (IX) or of the isomers, salts or solvates thereof, wherein, in Formula (IX) above,

R^{26} is selected from the group consisting of:

- OH;
- OCH_3 ;
- fluorine and
- chlorine.

R^1 is selected from the group consisting of





—SO₃H; natural and unnatural amino acids.

R, R^a and R^b are independently selected from the group consisting of H, —OH, halogeno, —NH₂, azido, (C₁–C₆)alkoxy(C₁–C₆)-alkoxy and —W—R³⁰;

W is independently selected from the group consisting of —NH—C(O)—, —O—C(O)—, —O—C(O)—N(R³¹)—, —NH—C(O)—N(R³¹)— and —O—C(S)—N(R³¹)—;

R² and R⁶ are independently selected from the group consisting of H, (C₁–C₆)alkyl, aryl and aryl(C₁–C₆)alkyl;

R³, R⁴, R⁵, R⁷, R^{3a} and R^{4a} are independently selected from the group consisting of H, (C₁–C₆)alkyl, aryl(C₁–C₆)alkyl, —C(O)(C₁–C₆)alkyl and —C(O)aryl;

R³⁰ is independently selected from the group consisting of R³²-substituted —T, R³²-substituted—T—(C₁–C₆)alkyl, R³²-substituted—(C₂–C₄)alkenyl, R³²-substituted—(C₁–C₆)alkyl, R³²-substituted—(C₃–C₇)cycloalkyl and R³²-substituted—(C₃–C₇)cycloalkyl(C₁–C₆)alkyl;

R³¹ is independently selected from the group consisting of H and (C₁–C₄)alkyl;

T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

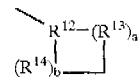
R³² is independently selected from 1-3 substituents independently selected from the group consisting of H, halogeno, (C₁–C₄)alkyl, —OH, phenoxy, —CF₃, —NO₂, (C₁–C₄)alkoxy, methylenedioxy, oxo, (C₁–C₄)alkylsulfanyl, (C₁–C₄)alkylsulfinyl, (C₁–C₄)alkylsulfonyl, —N(CH₃)₂, —C(O)—NH(C₁–C₄)alkyl, —C(O)—N((C₁–C₄)alkyl)₂, —C(O)—(C₁–C₄)alkyl, —C(O)—(C₁–C₄)alkoxy and pyrrolidinylcarbonyl; or R³² is a covalent bond and R³¹, the nitrogen to which it is attached and R³² form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolyl or morpholyl group, or a (C₁–C₄)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolyl or morpholyl group;

Ar¹ is aryl, R¹ 0-substituted aryl; pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

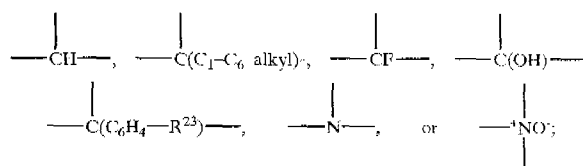
Ar² is aryl or R¹ 1-substituted aryl;

Q is —(CH₂)_q—, wherein q is 2-6, or, with the 3-position ring carbon of the azetidinone,

forms the spiro group



R¹² is



R¹³ and R¹⁴ are independently selected from the group consisting of —CH₂—, —CH(C₁–C₆ alkyl)—, —C(di-(C₁–C₆ alkyl))—, —CH=CH— and —C(C₁–C₆ alkyl)=CH—; or R¹² together with an adjacent R¹³, or R¹² together with an adjacent R¹⁴, form a —CH=CH— or a —CH=C(C₁–C₆ alkyl)— group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R¹³ is —CH=CH— or —C(C₁–C₆ alkyl)=CH—, a is 1; provided that when R¹⁴ is —CH=CH— or —C(C₁–C₆ alkyl)=CH—, b is 1; provided that when a is 2 or 3, the R¹³'s can be the same or different; and provided that when b is 2 or 3, the R¹⁴'s can be the same or different;

R¹⁰ and R¹¹ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C₁–C₆)alkyl, R¹⁹, —O(CO)R¹⁹, —O(CO)OR²¹, —O(CH₂)₁₋₅OR¹⁹, —O(CO)NR¹⁹, —NR¹⁹OR²⁰, —NR¹⁹(CO)R²⁰, —NR¹⁹(CO)OR²¹, —NR¹⁹(CO)NR²⁰R²⁵, —NR¹⁹SO₂R²¹, —COOR¹⁹, —CONR¹⁹R²⁰, —COR¹⁹, —SO₂NR¹⁹R²⁰, —S(O)₀₋₂R²¹, —O(CH₂)₁₋₁₀COOR¹⁹, —O(CH₂)₁₋₁₀CONR¹⁹R²⁰, —(C₁–C₆ alkyl)ene—COOR¹⁹, —CH=CH—COOR¹⁹, —CF₃, —CN, —NO₂ and halogen;

R¹⁹ and R²⁰ are independently selected from the group consisting of H, (C₁–C₆)alkyl, aryl and aryl-substituted (C₁–C₆)alkyl;

R²³ is (C₁–C₆)alkyl, aryl or R²⁴-substituted aryl;

R²² is H, (C₁–C₆)alkyl, aryl (C₁–C₆)alkyl, —C(O)R¹⁹ or —COOR¹⁹;

R²³ and R²⁴ are independently 1-3 groups independently selected from the group consisting of H, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, —COOH, NO₂, —NR¹⁹R²⁰, —OH and halogeno; and

R²⁵ is H, —OH or (C₁–C₆)alkoxy.

11. The composition according to claim 1, wherein the at least one cardiovascular agent for treating vascular conditions is selected from the group consisting of channel blockers, adrenergic blockers, adrenergic stimulants, angio-

tensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof.

12. The composition according to claim 11, wherein the at least one cardiovascular agent is an adrenergic blocker.

13. The composition according to claim 12, wherein the adrenergic blocker is an α -receptor inhibitor selected from the group consisting of fenpropirone hydrochloride, labetalol hydrochloride, prazosin, alfuzosin hydrochloride and combinations thereof.

14. The composition according to claim 12, wherein the adrenergic blocker is a β -receptor inhibitor selected from the group consisting of acebutolol, acebutolol hydrochloride, alprenolol hydrochloride, atenolol, bunolol hydrochloride, carteolol hydrochloride, celiprolol hydrochloride, cetamolol hydrochloride, cicloprolol hydrochloride, dexpropololol hydrochloride, diacetolol hydrochloride, dilevalol hydrochloride, esmolol hydrochloride, exaprolol hydrochloride, flestolol sulfate, labetalol hydrochloride, levobetaxolol hydrochloride, levobunolol hydrochloride, metolol hydrochloride, metoprolol, metoprolol tartrate, nadolol, pamatolol sulfate, penbutolol sulfate, practolol, propranolol hydrochloride, sotalol hydrochloride, timolol, timolol maleate, tiprenolol hydrochloride, tolamolol, bisoprolol, bisoprolol fumarate, nebivolol and combinations thereof.

15. The composition according to claim 12, wherein the adrenergic blocker is selected from the group consisting of bretylium tosylate, dihydroergotamine mesylate, phentolamine mesylate, solipertine tartrate, zolertine hydrochloride, carvedilol, labetalol hydrochloride and combinations thereof.

16. The composition according to claim 11, wherein the at least one cardiovascular agent is a calcium channel blocker.

17. The composition according to claim 16, wherein the calcium channel blocker is selected from the group consisting of elenitazem maleate, amlodipine besylate, isradipine, nimodipine, felodipine, nilvadipine, nifedipine, teludipine hydrochloride, diltiazem hydrochloride, belfosdil, verapamil hydrochloride, fostedil and combinations thereof.

18. The composition according to claim 11, wherein the at least one cardiovascular agent is an angiotensin-converting enzyme (ACE) inhibitor.

19. The composition according to claim 18, wherein the angiotensin-converting enzyme inhibitor is selected from the group consisting of benazepril hydrochloride, benazeprilat, captopril, delapril hydrochloride, fosinopril sodium, libenzapril, moexipril hydrochloride, pentopril, perindopril, quinapril hydrochloride, quinaprilat, ramipril, spirapril hydrochloride, spiraprilat, teprotide, enalapril maleate, lisinopril, zofenopril calcium, perindopril erbumine and combinations thereof.

20. The composition according to claim 11, wherein the at least one cardiovascular agent is an adrenergic stimulant.

21. The composition according to claim 20, wherein the adrenergic stimulant is selected from the group consisting of the combination product of chlorothiazide and methyl dopa, the combination product of methyl dopa hydrochlorothiazide and methyl dopa, clonidine hydrochloride, clonidine, the combination product of chlorthalidone and clonidine hydrochloride, guanfacine hydrochloride, and combinations thereof.

22. The composition according to claim 11, wherein the at least one cardiovascular agent is an antihypertensive agent.

23. The composition according to claim 22, wherein the antihypertensive agent is selected from the group consisting of althiazide, benzthiazide, captopril, carvedilol, chlorothiazide sodium, clonidine hydrochloride, cyclothiazide, delapril hydrochloride, dilevalol hydrochloride, doxazosin mesylate, fosinopril sodium, guanfacine hydrochloride, methyl dopa, metoprolol succinate, moexipril hydrochloride, monatepil maleate, pelanserine hydrochloride, phenoxybenzamine hydrochloride, prazosin hydrochloride, primidolol, quinapril hydrochloride, quinaprilat, ramipril, terazosin hydrochloride, candesartan, candesartan cilexetil, telmisartan, amlodipine besylate, amlodipine maleate, bevantolol hydrochloride and combinations thereof.

24. The composition according to claim 11, wherein the at least one cardiovascular agent is an angiotensin II receptor antagonist.

25. The composition according to claim 24, wherein the angiotensin II receptor antagonist is selected from the group consisting of candesartan, irbesartan, losartan potassium, candesartan cilexetil, telmisartan and combinations thereof.

26. The composition according to claim 11, wherein the at least one cardiovascular agent is an anti-anginal agent.

27. The composition according to claim 26, wherein the anti-anginal agent is selected from the group consisting of amlodipine besylate, amlodipine maleate, betaxolol hydrochloride, bevantolol hydrochloride, butopropazine hydrochloride, carvedilol, cinepazet maleate, metoprolol succinate, molsidomine, monatepil maleate, primidolol, ranolazine hydrochloride, tofisfen, verapamil hydrochloride and combinations thereof.

28. The composition according to claim 11, wherein the at least one cardiovascular agent is a coronary vasodilator.

29. The composition according to claim 28, wherein the coronary vasodilator is selected from the group consisting of fostedil, azaclozine hydrochloride, chromonar hydrochloride, clonitrate, diltiazem hydrochloride, dipyridamole, droperidolamine, erythritol tetranitrate, isosorbide dinitrate, isosorbide mononitrate, lidoflazine, mioslazine hydrochloride, mixidine, molsidomine, nicorandil, nifedipine, nisoldipine, nitroglycerine, oxprenolol hydrochloride, pentaeritrol, perhexiline maleate, prenylamine, propatyl nitrate, terodiline hydrochloride, tolamolol, verapamil and combinations thereof.

30. The composition according to claim 11, wherein the at least one cardiovascular agent is a diuretic.

31. The composition according to claim 30, wherein the diuretic is selected from the group consisting of the combination product of hydrochlorothiazide and spironolactone and the combination product of hydrochlorothiazide and triamterene.

32. The composition according to claim 1, wherein the at least one cardiovascular agent is labetalol hydrochloride.

33. The composition according to claim 1, wherein the at least one cardiovascular agent for treating vascular conditions is administered to a mammal in an amount ranging from about 50 to about 3000 milligrams of cardiovascular agent per day.

34. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is administered to a mammal in an amount ranging from about 0.1 to about 1000 milligrams of sterol absorption inhibitor per day.

35. The composition according to claim 1, further comprising at least one cholesterol biosynthesis inhibitor.

36. The composition according to claim 35, wherein the at least one cholesterol biosynthesis inhibitor comprises at least one HMG CoA reductase inhibitor.

37. The composition according to claim 36 wherein the at least one HMG CoA reductase inhibitor comprises lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, rosuvastatin, rivastatin, cerivastatin and mixtures thereof.

38. The composition according to claim 37, wherein the at least one HMG CoA reductase inhibitor comprises simvastatin.

39. The composition according to claim 1, further comprising at least one bile acid sequestrant.

40. The composition according to claim 1, further comprising at least one AcylCoA:Cholesterol O-acyltransferase Inhibitor.

41. The composition according to claim 1, further comprising probucol or a derivative thereof.

42. The composition according to claim 1, further comprising at least one low-density lipoprotein receptor activator.

43. The composition according to claim 1, further comprising at least one Omega 3 fatty acid.

44. The composition according to claim 1, further comprising at least one natural water soluble fiber.

45. The composition according to claim 1, further comprising at least one antioxidant or vitamin.

46. A pharmaceutical composition for the treatment or prevention of vascular conditions, obesity, diabetes or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 1 and a pharmaceutically acceptable carrier.

47. A method of treating or preventing vascular conditions, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment:

(a) an effective amount of at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate thereof or prodrug of the at least one sterol absorption inhibitor or of the salt or solvate thereof; and

(b) an effective amount of at least one cardiovascular agent which is different from the sterol absorption inhibitor.

48. The method according to claim 47, wherein the vascular condition is hyperlipidemia.

49. A therapeutic combination comprising:

(a) a first amount of at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate thereof or prodrug of the at least one sterol absorption inhibitor or of the salt or solvate thereof; and

(b) a second amount of at least one cardiovascular agent different from the at least one sterol absorption inhibitor.

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, obesity, diabetes or lowering a concentration of a sterol in plasma of a mammal.

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(54) **MEDICINAL COMPOSITIONS FOR PREVENTING OR TREATING HEART FAILURE**

(57) The present invention relates to pharmaceutical compositions, which contain a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522

and an angiotensin II receptor antagonist and optionally further contain a calcium channel blocker.

Description

[Technical field]

- 5 **[0001]** The present invention relates to pharmaceutical compositions for the prevention or treatment of cardiac failure, the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease, said pharmaceutical compositions containing a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522 and an angiotensin II receptor antagonist and optionally further containing a calcium channel blocker.
- 10 **[0002]** The present invention also relates to methods for the prevention or treatment of cardiac failure, the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease, said methods comprising administering to a warm-blooded animal (particularly a human) in need of such treatment or prevention a pharmacologically effective amount of a pharmaceutical composition that contains a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522 and an angiotensin
- 15 II receptor antagonist and optionally further contains a calcium channel blocker.

[Technical background]

- 20 **[0003]** HMG-CoA reductase inhibitors such as pravastatin are well known as an anti-hyperlipidemic agent (for example, U.S. Patent Nos. 4346227, 4444784, 4231938, 5856336, 5260440 and the like) and such medicaments have been placed on the market.
- [0004]** Angiotensin II receptor antagonists are well known as an antihypertensive agent (for example, U.S. Patent Nos. 5138069, 5196444, 5616599 and the like) and a lot of such medicaments have been placed on the market.
- 25 **[0005]** Calcium channel blockers are well known as an antihypertensive agent (for example, U.S. Patent Nos. 3485847, 3985758, 4572909 and the like) and a lot of such medicaments have been placed on the market.
- [0006]** A pharmaceutical agent containing an angiotensin II acceptor antagonist and a pyridine derivative having HMG-CoA reductase inhibitory activity (particularly for circulatory system disease, Japanese Patent Application Publication number No. Hei 9-323940), a pharmaceutical composition containing an angiotensin II acceptor antagonist and a HMG-CoA reductase inhibitor (particularly a drug for arteriosclerosis, Japanese Patent Application Publication
- 30 No. Hei 10-81633), a pharmaceutical composition containing amlodipine and atorvastatin (particularly a heart disease risk factor inhibitor, WO Publication No. 99/11259), a pharmaceutical composition containing atorvastatin and an antihypertensive agent (particularly a heart disease risk factor inhibitor, WO Publication No. 99/11260), a pharmaceutical composition containing amlodipine and a statin derivative (particularly a heart disease risk factor inhibitor, WO Publication No. 99/11263) and the like are known as combination agents comprising these medicaments.
- 35 **[0007]** A pharmaceutical composition for the prevention or treatment of cardiac failure, the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease, said pharmaceutical compositions containing a particular HMG-CoA reductase inhibitor such as pravastatin and an angiotensin II receptor antagonist have not previously been disclosed.

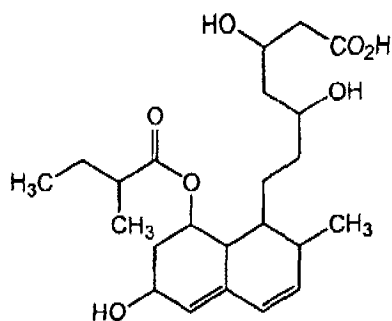
40 [Disclosure of the invention]

- [0008]** The inventors have made a great effort to study pharmaceutical compositions containing a HMG-CoA reductase inhibitor, angiotensin II receptor antagonist and/or a calcium channel blocker for many years and found that a pharmaceutical composition containing particular pharmaceutical agents exhibit excellent left ventricular hypertrophy
- 45 inhibition activity and are useful pharmaceutical compositions for the prevention or treatment of cardiac failure, the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease.
- [0009]** The present invention provides pharmaceutical compositions for the prevention or treatment of cardiac failure, the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease, said pharmaceutical compositions containing a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522 and an angiotensin II receptor antagonist and optionally further containing a calcium channel blocker.
- 50 **[0010]** The present invention also relates to methods for the prevention or treatment of cardiac failure, the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease, said methods comprising administering to a warm-blooded animal (particularly a human) in need of such treatment or prevention a pharmacologically effective amount of a pharmaceutical composition that contains a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522 and an angiotensin
- 55 II receptor antagonist and optionally further contains a calcium channel blocker.
- [0011]** The pharmaceutical composition of the present invention, which is for the prevention or treatment of cardiac

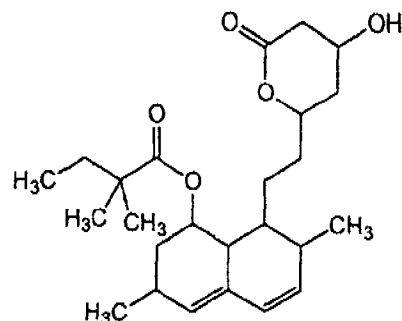
failure, the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease, contains as active ingredients a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522 and an angiotensin II receptor antagonist and optionally further contains a calcium channel blocker.

[0012] An active ingredient of the pharmaceutical composition is a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522; preferably pravastatin, simvastatin, pitavastatin or ZD-4522; more preferably pravastatin, simvastatin or ZD-4522; still more preferably pravastatin or simvastatin; and most preferably pravastatin.

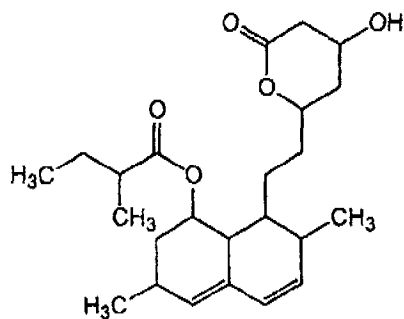
[0013] The chemical formulae of the HMG-CoA reductase inhibitors are shown below:



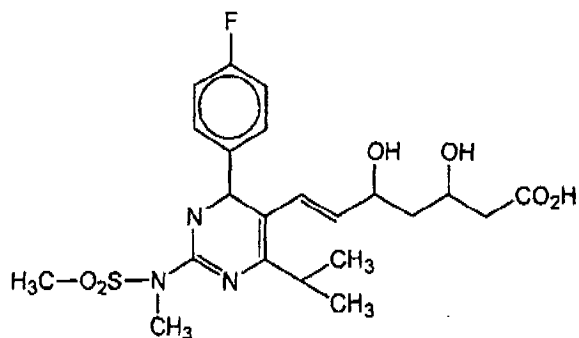
Pravastatin



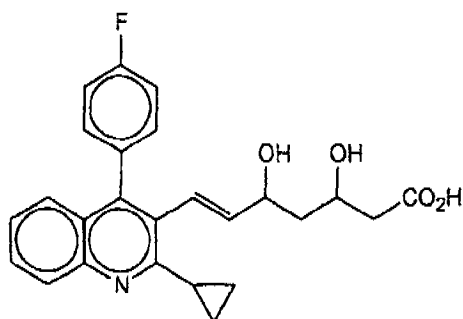
Simvastatin



Lovastatin



ZD-4522
(Rosuvastatin)



Pitavastatin

[0014] Pravastatin is disclosed in the specifications of Japanese Patent Application Publication No. Sho 57-2240, U.S. Patent No. 4346227 and the like and is (+)-(3R,5R)-3,5-dihydroxy-7-[(1S, 2S, 6S, 8S, 8aR)-6-hydroxy-2-methyl-8-[(S)-2-methylbutyryloxy]-1,2,6,7,8,8a-hexahydro-1-naphthyl]heptanoic acid. In the present invention the term "pravastatin" is intended to include its lactone ring closure form and its pharmacologically acceptable salts (the sodium salt of pravastatin and the like).

[0015] Simvastatin is disclosed in the specifications of Japanese Patent Application Publication No. Sho 56-122375, U.S. Patent No. 4444784 and the like and is (+)-(1S,3R,7S, 8S, 8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R, 4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthyl] 2,2-dimethylbutylate. In the present invention the term "lovastatin" is intended to include its lactone ring open form and pharmacologically acceptable salts of the lactone ring open form (the sodium salt and the like).

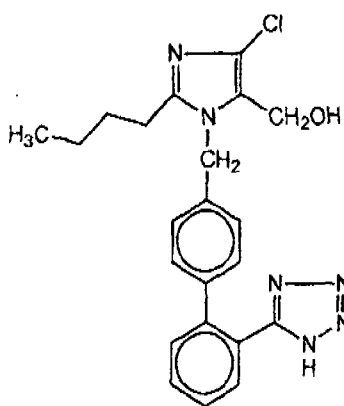
[0016] Lovastatin is disclosed in the specifications of Japanese Patent Application Publication No. Sho 57-163374, U.S. Patent No. 4231938 and the like and is (+)-(1S, 3R, 7S, 8S, 8aR)-1,2,3,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R, 4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthyl] (S)-2-methylbutylate. In the present invention the term "lovastatin" is intended to include its lactone ring open form and pharmacologically acceptable salts of the lactone ring open form (the sodium salt and the like).

[0017] Pitavastatin is disclosed in the specifications of Japanese Patent Application Publication No. Hei 1-279866, U.S. Patent No. 5856336 and the like and is (3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptanoic acid. In the present invention the term "pitavastatin" is intended to include its lactone ring closed form and its pharmacologically acceptable salts (the calcium salt and the like).

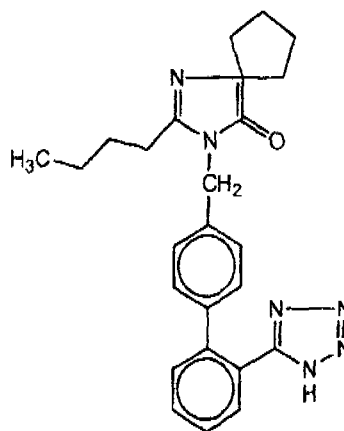
[0018] ZD-4522 (Rosuvastatin) is disclosed in the specifications of Japanese Patent Application Publication No. Hei 5-178841, U.S. Patent No. 5260440 and the like and is (+)-(3R,5S)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)pyridin-5-yl]-3,5-dihydroxy-6(E)-heptanoic acid. In the present invention the term "ZD-4522 (Rosuvastatin)" is intended to include its lactone ring closed form and its pharmacologically acceptable salts (the sodium salt, calcium salt and the like).

[0019] An active ingredient of the pharmaceutical composition of the present invention is an angiotensin II receptor antagonist. Typical examples of such antagonists are biphenyltetrazole compounds and biphenyl carboxylic acid compounds which are disclosed in the specifications of U.S. Patent No. 5138069, WO Publication No. 91/14679, European Patent Publication No. 433983, U.S. Patent Nos. 5354766, 5196444, 5616599, European Patent Publication No. 502314 and the like; preferably biphenyltetrazole compounds; yet more preferably losartan, irbesartan, valsartan, candesartan, olmesartan or telmisartan; more preferably losartan, irbesartan, valsartan, candesartan or olmesartan; yet more preferably losartan, candesartan or olmesartan; still more preferably losartan or olmesartan; and most preferably olmesartan.

[0020] The chemical formulae of typical angiotensin II receptor antagonists are shown below:

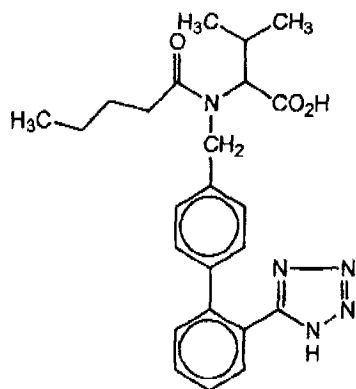


Losartan

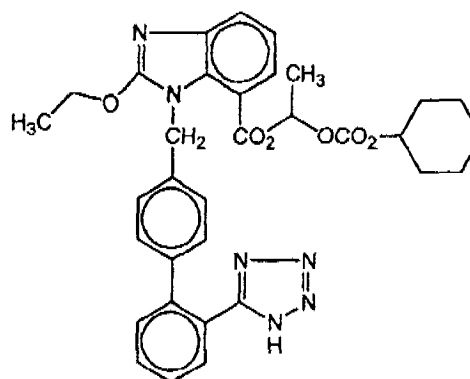


Irbesartan

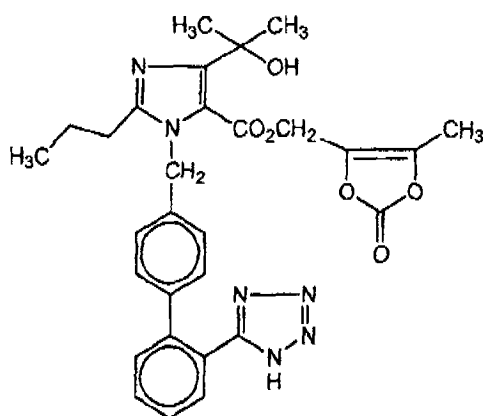
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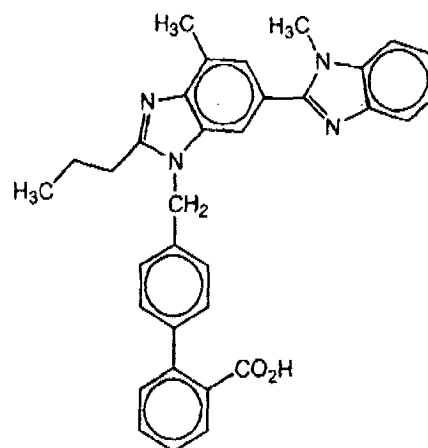
Valsartan



Candesartan



Olmesartan



Telmisartan

[0021] Losartan (DUP-753) is disclosed in the specifications of Japanese Patent Application Publication No. Sho 63-23868, U.S. Patent No. 5138069 and the like and is 2-butyl-4-chloro-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-imidazole-5-methanol. In the present invention the term "losartan" is intended to include its pharmacologically acceptable salts (losartan potassium and the like).

[0022] Irbesartan (SR-47436) is disclosed in the specifications of Japanese Patent Application Publication (Kohyo) No. Hei 4-506222, WO Publication No. 91/14679 and the like and is 2-N-butyl-4-spirocyclopentane-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-2-imidazoline-5-one. In the present invention the term "irbesartan" is intended to include its pharmacologically acceptable salts.

[0023] Valsartan (CGP-48933) is disclosed in the specifications of Japanese Patent Application Publication No. Hei 4-235149, European Patent Publication No. 433983 and the like and is (S)-N-valeryl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]valine. In the present invention the term "valsartan" is intended to include its pharmacologically acceptable esters and salts.

[0024] Candesartan (TCV-116) is disclosed in the specifications of Japanese Patent Application Publication No. Hei 4-364171, U.S. Patent No. 5196444 and the like and is 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-benzimidazole-7-carboxylate. In the present invention the term "candesartan" is intended to include its carboxylic acid derivatives, pharmacologically acceptable ester derivatives (TCV-116 and the like) of the carboxylic acid derivatives and pharmacologically acceptable salts of candesartan.

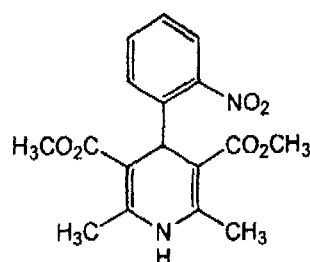
[0025] Olmesartan (CS-866) is disclosed in the specifications of Japanese Patent Application Publication No. Hei 5-78328, U.S. Patent No. 5616599 and the like and is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazole-5-carboxylate. In the present invention the term "olmesartan" is intended to include its carboxylic acid derivatives, pharmacologically acceptable ester derivatives (CS-866 and the like) of the carboxylic acid derivatives and pharmacologically acceptable salts of olmesartan.

[0026] Telmisartan (BIBR-277) is disclosed in the specifications of Japanese Patent Application Publication No. Hei 4-346978, U.S. Patent No. 5591762, European Patent Publication No. 502314 and the like and is 4'-[2-n-propyl-4-me-

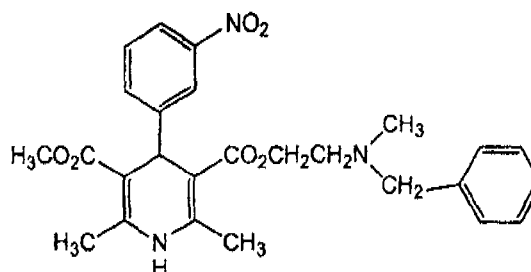
thyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)methyl]-biphenyl-2-carboxylate. In the present invention the term "telmisartan" is intended to include its carboxylic acid derivatives, pharmacologically acceptable ester derivatives (BIBR-277 and the like) of the carboxylic acid derivatives and pharmacologically acceptable salts of telmisartan.

[0027] An active ingredient of the pharmaceutical composition of the present invention is a calcium channel blocker. Typical examples of such blockers are nifedipine, nicardipine, amlodipine, azelnidipine, and manidipine which are disclosed in the specifications of U.S. Patent Nos. 3485847, 3985758, 4572909, 4772596, 4892875 and the like; preferably nicardipine, amlodipine or azelnidipine; more preferably amlodipine or azelnidipine.

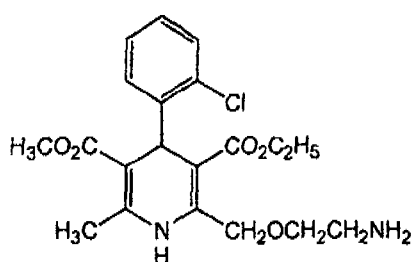
[0028] The chemical formulae of the typical calcium channel blockers are shown below:



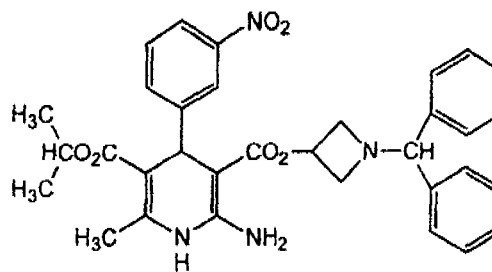
Nifedipine



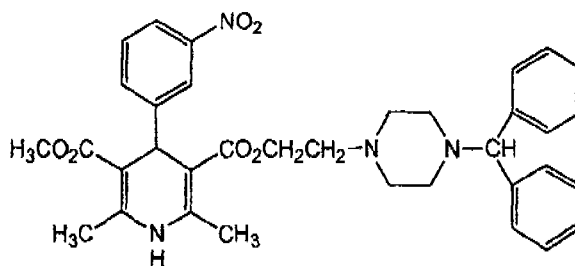
Nicardipine



Amlodipine



Azelnidipine



Manidipine

[0029] Nifedipine is disclosed in the specifications of U.S. Patent No. 3485847 and the like and is 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrophenyl)-1,4-dihydropyridine. In the present invention the term "nifedipine" is intended to include its pharmacologically acceptable salts (the hydrochloride and the like).

[0030] Nicardipine is disclosed in the specifications of U.S. Patent No. 3985758, Japanese Patent Application Publication No. Sho 49-108082 and the like and is 2,6-dimethyl-3-[2-(N-benzyl-N-methylamino)ethoxycarbonyl]-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine. In the present invention the term "nicardipine" is intended to include its pharmacologically acceptable salts (the hydrochloride and the like).

[0031] Amlodipine is disclosed in the specifications of U.S. Patent No. 4572909, Japanese Patent Application Publication No. Sho 58-167569 and the like and is 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-meth-

oxycarbonyl-6-methyl-1,4-dihydropyridine. In the present invention the term "amlodipine" is intended to include its pharmacologically acceptable salts (the hydrochloride and the like).

[0032] Azelnidipine is disclosed in the specifications of U.S. Patent No. 4772596, Japanese Patent Application Publication No. Sho 63-253082 and the like and is 2-amino-3-(1-diphenylmethyl-3-azetidinyloxycarbonyl)-5-isopropoxy-carbonyl-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine. In the present invention the term "azelnidipine" is intended to include its pharmacologically acceptable salts (the hydrochloride and the like).

[0033] Manidipine is disclosed in the specifications of U.S. Patent No. 4892875, Japanese Patent Application Publication No. Sho 58-201765 and the like and is 2,6-dimethyl-3-[2-(4-diphenylmethyl-1-piperazinyl)ethoxycarbonyl]-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine. In the present invention the term "manidipine" is intended to include its pharmacologically acceptable salts (the hydrochloride and the like).

[0034] When the HMG-CoA reductase inhibitors, angiotensin II receptor antagonists and/or calcium channel blockers described above have an asymmetric carbon(s), the present invention encompasses the optical isomers of these compounds and mixtures of said optical isomers. In addition the hydrates of the compounds described above are also encompassed in the present invention.

[0035] In the present invention the pharmaceutical composition contains one or more HMG-CoA reductase inhibitors selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522 and one or more angiotensin receptor antagonists. The pharmaceutical composition of this invention contains one or more HMG-CoA reductase inhibitors and one or more angiotensin receptor antagonists described above and, if necessary, may contain one or more calcium channel blockers.

[0036] Preferred pharmaceutical compositions includes:

(1) a pharmaceutical composition wherein the HMG-CoA reductase inhibitor is pravastatin, simvastatin, pitavastatin or ZD-4522;

(2) a pharmaceutical composition wherein the HMG-CoA reductase inhibitor is pravastatin, simvastatin or ZD-4522;

(3) a pharmaceutical composition wherein the HMG-CoA reductase inhibitor is pravastatin or simvastatin;

(4) a pharmaceutical composition wherein the HMG-CoA reductase inhibitor is pravastatin;

(5) a pharmaceutical composition wherein the angiotensin II receptor antagonist as an active ingredient is a biphenyltetrazole compound or a biphenyl carboxylic acid compound;

(6) a pharmaceutical composition wherein the angiotensin II receptor antagonist as an active ingredient is a biphenyltetrazole compound;

(7) a pharmaceutical composition wherein the angiotensin II receptor antagonist as an active ingredient is losartan, irbesartan, valsartan, candesartan, olmesartan or telmisartan;

(8) a pharmaceutical composition wherein the angiotensin II receptor antagonist as an active ingredient is losartan, irbesartan, valsartan, candesartan or olmesartan;

(9) a pharmaceutical composition wherein the angiotensin II receptor antagonist as an active ingredient is losartan, candesartan or olmesartan;

(10) a pharmaceutical composition wherein the angiotensin II receptor antagonist as an active ingredient is losartan or olmesartan;

(11) a pharmaceutical composition wherein the angiotensin II receptor antagonist as an active ingredient is losartan;

(12) a pharmaceutical composition wherein the angiotensin II receptor antagonist as an active ingredient is olmesartan;

(13) a pharmaceutical composition wherein the calcium channel blocker as an active ingredient is nifedipine, nicardipine, amlodipine, azelnidipine or manidipine;

(14) a pharmaceutical composition wherein the calcium channel blocker as an active ingredient is nicardipine, amlodipine or azelnidipine; or

(15) a pharmaceutical composition wherein the calcium channel blocker as an active ingredient is amlodipine or azelnidipine.

Preferred pharmaceutical compositions also includes a pharmaceutical composition that contains a HMG-CoA reductase inhibitor arbitrarily selected from the group consisting of (1), (2), (3) and (4) and an angiotensin II receptor antagonist arbitrarily selected from the group consisting of (5), (6), (7), (8), (9), (10), (11) and (12) and may contain a calcium channel blocker arbitrarily selected from the group consisting of (13), (14) and (15). Examples of such a pharmaceutical composition include, for example:

(16) a pharmaceutical composition wherein the HMG-CoA reductase inhibitor as an active ingredient is pravastatin, simvastatin, pitavastatin, or ZD-4522 and the angiotensin II receptor antagonist as an active ingredient is a biphenyltetrazole compound, said pharmaceutical composition optionally further containing a calcium channel blocker as an active ingredient such as nifedipine, nicardipine, amlodipine, azelnidipine or manidipine;

(17) a pharmaceutical composition wherein the HMG-CoA reductase inhibitor as an active ingredient is pravastatin, simvastatin, or ZD-4522 and the angiotensin II receptor antagonist as an active ingredient is a biphenyltetrazole

compound, said pharmaceutical composition optionally further containing a calcium channel blocker as an active ingredient such as nifedipine, nicardipine, amlodipine, azelnidipine or manidipine;

(18) a pharmaceutical composition wherein the HMG-CoA reductase inhibitor as an active ingredient is pravastatin, simvastatin, pitavastatin, or ZD-4522 and the angiotensin II receptor antagonist as an active ingredient is losartan, irbesartan, valsartan, candesartan, olmesartan or telmisartan, said pharmaceutical composition optionally further containing a calcium channel blocker as an active ingredient such as nifedipine, nicardipine, amlodipine, azelnidipine or manidipine;

(19) a pharmaceutical composition wherein the HMG-CoA reductase inhibitor as an active ingredient is pravastatin, simvastatin or ZD-4522 and the angiotensin II receptor antagonist as an active ingredient is losartan, irbesartan, valsartan, candesartan or olmesartan, said pharmaceutical composition optionally further containing a calcium channel blocker as an active ingredient such as nifedipine, nicardipine, amlodipine, azelnidipine or manidipine;

(20) a pharmaceutical composition wherein the HMG-CoA reductase inhibitor as an active ingredient is pravastatin or simvastatin and the angiotensin II receptor antagonist as an active ingredient is losartan, candesartan or olmesartan, said pharmaceutical composition optionally further containing a calcium channel blocker as an active ingredient such as nicardipine, amlodipine or azelnidipine;.

(21) a pharmaceutical composition wherein the HMG-CoA reductase inhibitor as an active ingredient is pravastatin and the angiotensin II receptor antagonist as an active ingredient is losartan or olmesartan, said pharmaceutical composition optionally further containing a calcium channel blocker as an active ingredient such as amlodipine or azelnidipine; or

(22) a pharmaceutical composition wherein the HMG-CoA reductase inhibitor as an active ingredient is pravastatin and the angiotensin II receptor antagonist as an active ingredient is olmesartan, said pharmaceutical composition optionally further containing a calcium channel blocker as an active ingredient such as amlodipine or azelnidipine.

[Advantages of the invention]

[0037] The pharmaceutical composition of this invention which contains an HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin, and ZD-4522 and an angiotensin II receptor antagonist and, if necessary, may further contain a calcium channel blocker exhibits excellent left ventricular hypertrophy inhibition activity and low toxicity and is a useful pharmaceutical composition for the prevention or treatment of cardiac failure in a warm-blooded animal (particularly a human), or for the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease in a warm-blooded animal (particularly a human).

[Industrial applicability]

[0038] The pharmaceutical composition which contains a particular HMG-CoA reductase inhibitor such as pravastatin and the like and a particular angiotensin II receptor antagonist and, if necessary, may further contain a calcium channel blocker has superior activity to each single pharmaceutical agent alone and to a combined pharmaceutical agent which does not contain a particular HMG-CoA reductase inhibitor such as pravastatin. Such excellent activity can also be obtained even if all these two or three pharmaceutical agents do not exist in the body at the same time. Such activity can be obtained even if the blood concentrations of these pharmaceutical agents are lower to some extent than that obtained on administration at the same time.

[0039] According to a presumption, when a pharmaceutical agent of this invention is taken into the living body and reaches its receptor site, it will turn on a switch of the living body. When the blood concentration of said pharmaceutical agent of the pharmaceutical composition becomes very low after the administration of said pharmaceutical agent and said pharmaceutical agent at such low concentration might not exhibit any pharmacological activity, the switch has already been turned on and said pharmaceutical agent of the pharmaceutical composition still exhibits activity for the prevention or treatment of cardiac failure or activity for the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease. Under these conditions, when another pharmaceutical agent(s) is administered, an excellent pharmacological activity can be obtained by the combined effect of its activity for the prevention and treatment of cardiac failure, the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease and the pharmacological effect of the pharmaceutical agent which has already been administered.

[0040] Administration of the pharmaceutical agents contained in the pharmaceutical composition at the same time is clinically convenient and a particular HMG-CoA reductase inhibitor such as pravastatin and the like and an angiotensin II receptor antagonist and, if necessary, a calcium channel blocker can be administered in a unit dosage form which combines these pharmaceutical agents.

[0041] When these pharmaceutical agents cannot be blended at the same time in a formulation technique, these

pharmaceutical agents can each be administered in single unit dosage forms of said pharmaceutical agents at the same time or in a single unit dosage form of a pharmaceutical agent and a unit dosage form comprising a combination of the other pharmaceutical agents at the same time.

[0042] As mentioned above, the excellent activity of the pharmaceutical composition can be obtained even if these pharmaceutical agents are not administered at the same time. These pharmaceutical agents can each be administered in single unit dosage forms of said pharmaceutical agents at appropriate time intervals after administration of the first unit dosage form or in a single unit dosage form of a pharmaceutical agent and a unit dosage form comprising a combination of the other pharmaceutical agents at appropriate time intervals after administration of the unit dosage form. The maximum time intervals in which the excellent pharmacological activity can be obtained by administration of these pharmaceutical agents can be determined by clinical or animal testing of these pharmaceutical agents.

[0043] In general a particular HMG-CoA reductase inhibitor such as pravastatin and the like, an angiotensin II acceptor antagonist and a calcium channel blocker employed in this invention are orally administered. Each of these pharmaceutical agents can be prepared in a single unit dosage form respectively or these pharmaceutical agents are blended and are formulated in a unit dosage form. Examples of such dosage forms include powders, granules, tablets, capsules and the like and these dosage forms can be prepared by conventional formulation techniques. These dosage forms can be prepared, if necessary, using additives such as excipients, lubricating agents, binding agents, disintegrating agents, stabilizing agents, corrigents, diluting agents and the like by techniques known to those skilled in the art.

[0044] The excipients are selected from organic excipients, for example, sugar derivatives such as lactose, sucrose, glucose, mannitol and sorbitol; starch derivatives such as corn starch, potato starch, α -starch and dextrin; cellulose derivatives such as crystalline cellulose; acacia; dextran; pullulan; and inorganic excipients, for example, silicate derivatives such as light silicic acid anhydride, synthetic aluminum silicate, calcium silicate and magnesium aluminosilicate; phosphate derivatives such as calcium hydrogenphosphate; carbonate derivatives such as calcium carbonate; sulfate derivatives such as calcium sulfate; and the like. One or more of the excipients mentioned hereinbefore can be employed in this invention. Preferred excipients are the sugar derivatives and particularly lactose.

[0045] The lubricating agents are selected from metal stearates such as stearic acid, calcium stearate and magnesium stearate; talc; colloidal silica; waxes such as beeswax and spermaceti; boric acid; adipic acid; sulfates such as sodium sulfate; glycol; fumaric acid; sodium benzoate; DL-leucine; sodium salts of aliphatic acids; lauryl sulfates such as sodium lauryl sulfate and magnesium lauryl sulfate; silicic acids such as silicic acid anhydride and silicic acid hydrates and starch derivatives as mentioned for the excipients. One or more of the lubricating agents mentioned hereinbefore can be employed in this invention. Preferred lubricating agents are the metal stearates and particularly magnesium stearate.

[0046] The binding agents are selected from hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, macrogol, and compounds as mentioned for excipients. One or more of the binding agents mentioned hereinbefore can be employed in this invention. The preferred binding agents is hydroxypropylcellulose.

[0047] The disintegrating agents are selected from cellulose derivatives such as low-substituted hydroxypropylcellulose, carboxymethylcellulose, calcium carboxymethylcellulose, and internally-cross-linked sodium carboxymethylcellulose; and chemically modified starch cellulose derivatives such as carboxymethylstarch, sodium carboxymethylstarch, and cross-linked polyvinylpyrrolidone. One or more of the disintegrating agents mentioned hereinbefore can be employed in this invention. Preferred disintegrating agents are cellulose derivatives and particularly low-substituted hydroxypropylcellulose.

[0048] If necessary, additives such as stabilizing agents, corrigents, diluents and the like can be employed in this invention.

[0049] The stabilizing agent is selected from para-oxybenzoic acid esters such as methylparaben and propylparaben; alcohols such as chlorobutanol, benzyl alcohol and phenylethyl alcohol; benzalkonium chloride; phenol derivatives such as phenol and cresol; thimerosal; dehydroacetic acid; and sorbic acid. One or more of the stabilizing agents mentioned hereinbefore can be employed in this invention.

[0050] The corrigents are, for example, sweetening, souring and flavoring agents which are conventionally used.

[0051] The dosage levels and ratios of a particular HMG-CoA reductase inhibitor, an angiotensin II receptor antagonist and a calcium channel blocker will vary depending on various factors such as the pharmacological activity of each of these pharmaceutical agents and the symptoms, age, body weight and the like of the patient. For example, in the case of the angiotensin II receptor antagonist, olmesartan exhibits different activity to losartan in in vivo activity tests using rats with elevated blood pressure. The difference of dosage levels of the two agents is theoretically about one order or more. The dosage level of a particular HMG-CoA reductase inhibitor such as pravastatin, which is usually used as anti-hyperlipidemic agent, for the prevention or treatment of cardiac failure, for the prevention of ischemic coronary heart disease or for the prevention of the recurrence of ischemic coronary heart disease may be less than that for hyperlipidemia. When an angiotensin II receptor antagonist is used together with a HMG-CoA reductase inhibitor, the dosage levels of these pharmaceutical agents may be further lower than those for normal use. When these pharmaceutical agents are used together with a calcium channel blocker, the dosage levels of these pharmaceutical

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agents may also be further lower than those for normal use. For example, when pravastatin is used as an anti-hyperlipidemic agent, the dosage level is in the range of 5 - 100 mg/day and when olmesartan is used as an antihypertensive agent, the dosage level is in the range of 0.1 - 200 mg/day; on the other hand when pravastatin and olmesartan is used as an agent for the prevention or treatment of cardiac failure, the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease, the dosage level of pravastatin may be in the range of 1 - 80 mg/day (preferably 10-40 mg/day) and that of olmesartan is in the range of 0.05 - 100 mg/day (preferably 10 - 40 mg/day).

[0052] As mentioned hereinbefore, the dosage levels of a particular HMG-CoA reductase inhibitor such as pravastatin and the like, an angiotensin II receptor antagonist and/or a calcium channel blocker in this invention vary over a wide range; the dosage level of a HMG-CoA reductase inhibitor is in the range of about 1 - 80 mg/day, that of an angiotensin II receptor is in the range of about 0.05-100 mg/day and that of a calcium channel blocker is in the range of about 1-100 mg/day.

[0053] The dosage ratio of these pharmaceutical agents will vary over a wide range; the general dosage ratio (by weight) of a particular HMG-CoA reductase inhibitor such as pravastatin, an angiotensin II receptor antagonist and/or a calcium channel blocker is in the range between 1:500:500 and 500:1:1.

[0054] The dosage levels of these pharmaceutical agents mentioned hereinbefore are administered once throughout the day at the same time or are separately administered respectively at appropriate time intervals once throughout the day. The dosage levels of these pharmaceutical agents mentioned hereinbefore are divided to form several subunits respectively. The subunits are administered several times throughout the day at the same time or are separately administered respectively at appropriate time intervals several times throughout the day.

[Best mode for carrying out the invention]

[0055] The present invention is further illustrated by Examples and Formulation examples, however the scope of the present invention is not limited to these examples.

Test Example 1

Ameliorating effects of the compounds on left ventricular hypertrophy.

[0056] Forty patients with hypertension and hyperlipidemia whose average diastolic and systolic blood pressures and total plasma cholesterol levels calculated from 3 determinations were 95-115 mmHg (DBP), 160-200 mmHg, and higher than 240 mg/dl, respectively were equally divided into 2 groups consisting of 20 patients per group; group 1-I (m/f: 14/6, average age, height and weight were 61 years, 166 cm, and 65 kg, respectively) and group 1-II (m/f: 14/6, average age, height, and weight were 64 years, 164 cm, and 64 kg, respectively). A further 20 hypertensive patients (m/f: 15/5) with average blood pressure as described above and normal cholesterol levels were recruited into a group 1-III (average age, height, and weight were 62 years, 165 cm, and 66 kg, respectively). Lastly, in order to obtain the normal mass of the left ventricle, 10 healthy volunteer subjects (m/f: 7/3; 60 years old, 168 cm and 70 kg) with normal blood pressure (> 140/90 mmHg) and normal plasma cholesterol levels were recruited into a control group.

[0057] Pravastatin (10 mg), losartan (50 mg) and amlodipine (5 mg) were concomitantly administered to patients in the 1-I group, once daily for 6 months. Patients in the 1-II group received losartan (50 mg) and amlodipine (5 mg) concomitantly and orally once daily and underwent diet therapy for 6 months. Patients in the 1-III group received losartan (50 mg) and amlodipine (5 mg) concomitantly once daily for 6 months.

[0058] In all subjects, the mass of the left ventricle (LV mass) and the mass index of the left ventricle (LV mass index) were calculated from the diameter of the left ventricle in diastolic phase (LV end-diastolic dimension; EDD), the ventricular septum thickness (VS), and the posterior wall thickness (PW) which were determined by Doppler color flow-mapping methods using a two-dimension echo-cardiography device (Hewlett-Packard, SONOS 2,000) and according to the following equation:

$$\text{LV mass (g)} = 0.80 \times \{1.04 \times [(EDD + VS + PW)^3 - EDD^3]\} + 0.6$$

$$\text{LV mass index} = \text{LV mass} / (\text{area of the body surface, g/cm}^2)$$

[0059] The calculated LV mass indexes are presented in Table 1. The LV mass index in the control group was 83 ± 10 g/m² throughout the study.

[Table 1]

Group	LV mass Index (g/m ²)	
	Before treatment	After treatment
1-I	143 ± 12	107 ± 13
1-II	142 ± 18	122 ± 11
1-III	142 ± 18	122 ± 11

[0060] Following treatment, the LV masses were reduced by 24%, 13%, and 13% in the 1-I (treated with pravastatin, losartan and amlodipine), 1-II (treated with diet therapy, losartan and amlodipine), and 1-III groups (losartan and amlodipine), respectively. Thus, patients in group 1-I (treated with pravastatin, losartan and amlodipine) showed the biggest reduction in LV mass.

[0061] Similarly to the results observed in test example 1, treatment with either a combination of pravastatin (10 mg) and losartan (50 mg) or of pravastatin (10 mg) with olmesartan (5 mg) shows excellent retraction in LV mass.

[0062] Furthermore, combination therapy of either pravastatin plus olmesartan or simvastatin plus olmesartan ameliorated LV hypertrophy in a stress-loaded LV hypertrophy model in rats.

Test Example 2

Suppression of hypertrophy of ventricular cells in the area adjacent to infarction.

(Preparation of the animal model)

[0063] Adult male Wistar rats weighing 250-300 g (normal plasma cholesterol levels) were used. Animals received a normal-sodium diet containing 0.32 wt% sodium prior to and throughout the experiment. Water was taken *ad libitum*. Five rats/cage were placed and bred in a breeding room controlled at a stable room temperature (22±1°C) and humidity and with a standard light-darkness cycle. Echocardiography was recorded through the esophagus 24 hr after ligation of the anterior descending branch of the left coronary artery (day 0), then the animals were randomly divided into the following 4 groups consisting of 10 animals per group: control group (vehicle administration), 2-I group (administration of pravastatin 5 mg/kg/day in drink-water), 2-II group (administration of CS-866 2 mg/kg/day), and 2-III group (pravastatin 5 mg/kg/day + CS-866 2 mg/kg/day).

[0064] Surgical procedures were carried out as follows: rats were anesthetized with an intraperitoneal injection of ketamine (90 mg/kg). Under anesthesia, air was inspired into the animals by an artificial respirator for small animals (Model 683, Harvard Apparatus, Boston, MA) through a polyethylene catheter of gauge 14. Left thoracotomy was performed and the heart exposed. The anterior descending branch of the left coronary artery was ligated with a silk thread (6-0) between the bifurcation of the pulmonary artery and the left atrium. Then the muscle and the skin were sewn to close the chest. The rats of the normal group underwent a similar procedure except for the ligation of the coronary artery, in which the thread was passed through beneath the coronary artery. Drugs were administered to the rats for 4 weeks starting on the day when they were grouped.

(Determination of the ventricular cells in adjacent areas to the infarction)

[0065] The rats were heparinized and the hearts were removed. The heart was warmed at 37°C, and perfused by modified Langendorff's method at a constant flow-rate of 8 ml/min. The cardiac and non-cardiac muscle cells were enzymatically separated using collagenase according to previously described methods (Stewart et al., 1994). For the perfusion fluid, oxygenated Krebs-Henseleit buffer solution (pH: 7.4) containing 138 mmol NaCl, 4.7 mmol KCl, 1.5 mmol CaCl₂, 1.2 mmol MgCl₂, 10.0 mmol glucose, 10.0 mmol pyruvic acid, 5 mmol HEPES, and 20 U/l insulin was used. After the solution described above was perfused for 5 min to equilibrate, the perfusing solution was changed to Krebs-Henseleit solution not containing Ca²⁺, and further perfused for five minutes. Then collagenase B (1 mg/ml, Boehringer Mannheim Corp., Indianapolis, IN, USA) was added to the perfusing solution. After perfusion with the solution containing collagenase B for 10-15 min, the polyethylene cannula was removed from the heart and the non-digested infarction area removed. The left ventricle involving the ventricular septum was recovered and dissected in oxygenated Kraft-Brule buffer solution (pH: 7.2) containing 70 mmol glutamic acid, 25 mmol KCl, 10 mmol K₂HPO₄, 10 mmol oxalic acid, 10 mmol laurine, 11 mmol glucose, 2 mmol pyruvic acid, 2 mmol ATP, 2 mmol creatine phosphate, 10 mmol HEPES and 5 mmol MgCl₂. The obtained cell suspension solution was filtrated to remove the massive tissue. The mass of the cardiac cells in the adjacent area to the infarction was traced for determination under a phase-contrast

microscope. The obtained masses of the cardiac muscle cells in adjacent areas to the infarction are presented in Table 2.

Table 2

Group	Mass of cardiac muscle cells in adjacent area to the infarction (μm^2)
normal	2,737
control	3,812
2-I group	3,053
2-II group	2,940
2-III group	2,442

[0066] From the present results, the size of the cardiac muscle cells in the adjacent area to the infarction was retracted by $760 \mu\text{m}^2$ in group 2-I (pravastatin-administered group), $872 \mu\text{m}^2$ in group 2-II (olmesartan-administered group), and $1,370 \mu\text{m}^2$ in group 2-III (pravastatin plus olmesartan-administered group) versus control rats. Thus the most significant ameliorating effects were observed in group 2-III (pravastatin plus olmesartan administered group). It is clear that combined administration of olmesartan and pravastatin significantly retracts the size of the affected cardiac muscle cells versus each compound used alone, and furthermore, combined administration decreases the sizes of the cells more significantly than that observed in the normal group.

Formulation example 1	tablet
losartan	50.0 mg
pravastatin sodium salt	10.0 mg
amlodipine	5.0 mg
lactose	108.0 mg
corn starch	25.0 mg
magnesium stearate	2.0mg
	<u>200.0 mg</u>

[0067] The powdery ingredients listed above are blended and tabletted using a tablet machine to give a tablet (200 mg).

Formulation example 2	tablet
losartan	50.0 mg
pravastatin sodium salt	10.0 mg
lactose	113.0 mg
corn starch	25.0 mg
magnesium stearate	2.0mg
	<u>200.0 mg</u>

[0068] The powdery ingredients listed above are blended and tabletted using a tablet machine to give a tablet (200 mg).

Formulation example 3	tablet
olmesartan	5.0 mg
pravastatin sodium salt	10.0 mg
lactose	158.0 mg
corn starch	25.0 mg
magnesium stearate	2.0 mg
	<u>200.0 mg</u>

[0069] The powdery ingredients listed above are blended and tabletted using a tablet machine to give a tablet (200

mg).

Claims

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1. A pharmaceutical composition for the prevention or treatment of cardiac failure, said pharmaceutical composition containing a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522 and an angiotensin II receptor antagonist and optionally further containing a calcium channel blocker.

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2. A pharmaceutical composition according to claim 1 wherein the HMG-CoA reductase inhibitor is pravastatin, simvastatin, pitavastatin or ZD-4522.

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3. A pharmaceutical composition according to claim 1 wherein the HMG-CoA reductase inhibitor is pravastatin, simvastatin or ZD-4522.

4. A pharmaceutical composition according to claim 1 wherein the HMG-CoA reductase inhibitor is pravastatin or simvastatin.

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5. A pharmaceutical composition according to claim 1 wherein the HMG-CoA reductase inhibitor is pravastatin.

6. A pharmaceutical composition for the prevention of ischemic coronary heart disease or for the prevention of the recurrence of ischemic coronary heart disease, said pharmaceutical composition containing a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522 and an angiotensin II receptor antagonist and optionally further containing a calcium channel blocker.

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7. A pharmaceutical composition according to claim 6 wherein the HMG-CoA reductase inhibitor is pravastatin, simvastatin, pitavastatin or ZD-4522.

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8. A pharmaceutical composition according to claim 6 wherein the HMG-CoA reductase inhibitor is pravastatin, simvastatin or ZD-4522.

9. A pharmaceutical composition according to claim 6 wherein the HMG-CoA reductase inhibitor is pravastatin or simvastatin.

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10. A pharmaceutical composition according to claim 6 wherein the HMG-CoA reductase inhibitor is pravastatin.

11. A method for the prevention or treatment of cardiac failure, said method comprising administering to a warm-blooded animal in need of such prevention or treatment a pharmacologically effective amount of a pharmaceutical composition that contains a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522 and an angiotensin II receptor antagonist and optionally further contains a calcium channel blocker.

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12. A method according to claim 11 wherein the HMG-CoA reductase inhibitor is pravastatin, simvastatin, pitavastatin or ZD-4522.

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13. A method according to claim 11 wherein the HMG-CoA reductase inhibitor is pravastatin, simvastatin or ZD-4522.

14. A method according to claim 11 wherein the HMG-CoA reductase inhibitor is pravastatin or simvastatin.

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15. A method according to claim 11 wherein the HMG-CoA reductase inhibitor is pravastatin.

16. A method for the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease, said method comprising administering to a warm-blooded animal in need of such prevention a pharmacologically effective amount of a pharmaceutical composition that contains a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522 and an angiotensin II receptor antagonist and optionally further contains a calcium channel blocker.

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17. A method according to claim 16 wherein the HMG-CoA reductase inhibitor is pravastatin, simvastatin, pitavastatin or ZD-4522.

18. A method according to claim 16 wherein the HMG-CoA reductase inhibitor is pravastatin, simvastatin or ZD-4522.

19. A method according to claim 16 wherein the HMG-CoA reductase inhibitor is pravastatin or simvastatin.

20. A method according to claim 16 wherein the HMG-CoA reductase inhibitor is pravastatin.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/07437

A. CLASSIFICATION OF SUBJECT MATTER Int.Cl. ⁷ A61K31/404, 31/22, 31/366, 31/41, 31/4184, 31/505, 31/47, 45/06, A61P9/10, 9/04, 43/00		
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) Int.Cl. ⁷ A61K31/404, 31/22, 31/366, 31/41, 31/4184, 31/505, 31/47, 45/06, A61P9/10, 9/04, 43/00		
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 practicable, search terms used) CAPLUS (STN), MEDLINE (STN), EMBASE (STN)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/37688 A2 (TAKEDA CHEMICAL INDUSTRIES LTD.),	1-10
Y	16 October, 1997 (16.10.97), & EP 914158 A2 & US 6107323 A & JP 9-323940 A	1-10
Y	WO 99/11260 A1 (PFIZER INC.), 11 March, 1999 (11.03.99), & EP 1009400 A1 & JP 2001-514223 A	1-10
Y	WO 95/26188 A1 (MERCK AND CO. INC.), 05 October, 1995 (05.10.95), & EP 754042 A1 & US 5663186 A & US 5663187 A & JP 9-510973 A	1-10
Y	WO 99/11263 A1 (PFIZER INC.), 11 March, 1999 (11.03.99), & EP 1003507 A1 & JP 2001-514224 A	1-10
Y	WO 99/11259 A1 (PFIZER INC.), 11 March, 1999 (11.03.99), & EP 1003503 A1 & JP 2001-514222 A	1-10
☒ Further documents are listed in the continuation of Box C. ☐ See patent family 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 06 November, 2001 (06.11.01)		Date of mailing of the international search report 20 November, 2001 (20.11.01)
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer
Facsimile No.		Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/07437

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 10-81633 A2 (SANKYO COMPANY, LIMITED), 31 March, 1998 (31.03.98), (No family)	1-10
P,X	WO 01/15674 A2 (AVENTIS PHARMA DEUTSCHLAND GMBH), 08 March, 2001 (08.03.01), (No family)	1-10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/07437

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.: 11-20
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 11 to 20 pertain to methods for treatment of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39 (iv) of the Regulations under the PCT, to search.
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 searched 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.



US005663187A

United States Patent [19]

Nelson et al.

[11] **Patent Number:** 5,663,187[45] **Date of Patent:** Sep. 2, 1997**[54] TREATMENT OF ATHEROSCLEROSIS WITH ANGIOTENSIN II RECEPTOR BLOCKING IMIDAZOLES**[75] Inventors: **Edward B. Nelson**, Lower Gwynedd;
Charles S. Sweet, Ambler, both of Pa.[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.[21] Appl. No.: **466,484**[22] Filed: **Jun. 6, 1995****Related U.S. Application Data**

[62] Division of Ser. No. 219,685, Mar. 29, 1994, abandoned.

[51] **Int. Cl.⁶** **A61K 31/41**; **A61K 31/35**;
..... **A61K 31/235**[52] **U.S. Cl.** **514/381**; **514/460**; **514/547**[58] **Field of Search** **514/381**, **460**,
..... **514/547****[56] References Cited****U.S. PATENT DOCUMENTS**

4,444,784	4/1984	Hoffman et al.	424/279
5,138,069	8/1992	Carini et al.	548/253
5,162,340	11/1992	Chakravarty et al.	514/309
5,214,153	5/1993	Chen et al.	548/252
5,218,125	6/1993	Chen et al.	548/252
5,225,428	7/1993	Kramer et al.	514/381

FOREIGN PATENT DOCUMENTS

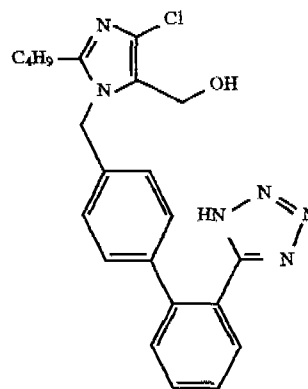
0 457 514 A1	11/1991	European Pat. Off.
0 475 206 A2	3/1992	European Pat. Off.
0 513 533 A2	11/1992	European Pat. Off.
0 535 463 A1	4/1993	European Pat. Off.
0 535 465 A1	4/1993	European Pat. Off.
0 539 713 A1	5/1993	European Pat. Off.
WO 92/04343	3/1992	WIPO
WO 92/20342	11/1992	WIPO
WO 93/04045	3/1993	WIPO
WO 93/04046	3/1993	WIPO
WO 93/15734	8/1993	WIPO
WO 94/04153	3/1994	WIPO

OTHER PUBLICATIONS

Mol et al., "Effects of Synvinolin (MK-733) on Plasma Lipids in Familial Hypercholesterolemia," *The Lancet*, Oct. 25, 1986, vol. II, pp. 936-939.
The Merck Manual, 1987, pp. 386-389.

Primary Examiner—Richard L. Raymond*Assistant Examiner*—Mary C. Cebulak*Attorney, Agent, or Firm*—Valerie J. Camara; Mark R. Daniel**[57] ABSTRACT**

A method of treatment for atherosclerosis and/or reducing cholesterol using an angiotensin II antagonist. This method of treatment can be used in conjunction with the treatment of hypertension. Substituted imidazoles such as



are useful as angiotensin II receptor antagonists for this method of treatment. A method of treatment for atherosclerosis and/or reducing cholesterol using an angiotensin II receptor antagonist in combination with an HMG-Co A reductase inhibitor. A method of treatment for atherosclerosis and/or reducing cholesterol using an angiotensin II receptor antagonist in combination with an HMG-Co A reductase inhibitor and an angiotensin converting enzyme inhibitor. Also within the scope of this invention are pharmaceutical compositions for this method of use.

2 Claims, No Drawings

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TREATMENT OF ATHEROSCLEROSIS WITH ANGIOTENSIN II RECEPTOR BLOCKING IMIDAZOLES

This is a division of application Ser. No. 08/219,685 filed Mar. 29, 1994, now abandoned.

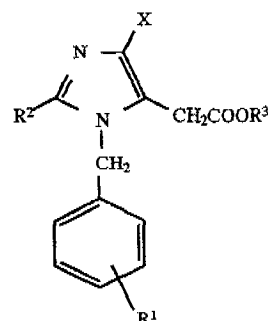
BACKGROUND OF THE INVENTION

This invention relates to a novel method of using an angiotensin II antagonist, such as substituted imidazole compounds, for the treatment of atherosclerosis and/or reducing cholesterol, alone or in conjunction with the treatment of hypertension. The invention also relates to using an angiotensin II antagonist in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (HMG-Co A reductase inhibitor). The invention also relates to using an angiotensin II antagonist in combination with an HMG-Co A reductase inhibitor and an angiotensin converting enzyme inhibitor. The invention also relates to compositions useful for this method of treatment.

The compounds of this invention are known to inhibit the action of the octapeptide hormone angiotensin II (II) and are useful therefore in alleviating angiotensin induced hypertension. The enzyme renin acts on a blood plasma α_2 -globulin, angiotensinogen, to produce angiotensin I, which is then converted by angiotensin converting-enzyme to AII. The latter substance is a powerful vasopressor agent which has been implicated as a causative agent for producing high blood pressure in various mammalian species, such as the rat, dog, and man. The angiotensin II antagonist compounds inhibit the action of AII at its receptors on target cells and thus prevent the increase in blood pressure produced by this hormone-receptor interaction. By administering an angiotensin II antagonist compound, such as a compound of formula I, to a species of mammal with atherosclerosis and/or high cholesterol and/or hypertension due to AII, the blood pressure is reduced. The compounds of formula I are also useful for the treatment of high cholesterol by reducing the total cholesterol. Administration of a compound of formula I with a diuretic such as furosemide or hydrochlorothiazide, either as a stepwise combined therapy (diuretic first) or as a physical mixture, enhances the anti-hypertensives effect of the compound, while also treating atherosclerosis and reducing cholesterol levels. Administration of an angiotensin II receptor antagonist, such as a compound of formula I, with an HMG-Co A reductase inhibitor, such as the compounds of formula II, either as a stepwise combined therapy or as a physical mixture, may enhance the treatment of atherosclerosis and/or the reduction of cholesterol levels, while also treating hypertension.

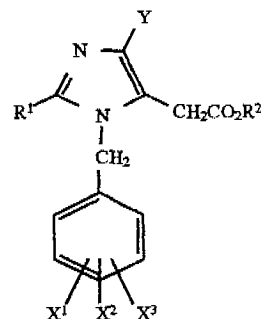
K. Matsumura, et. al., in U.S. Pat. No. 4,207,324 issued Jun. 10, 1980, discloses 1,2-disubstituted-4-haloimidazole-5-acetic acid derivatives of the formula:

2



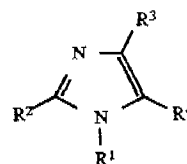
Wherein R^1 is hydrogen, nitro or amino; R^2 is phenyl, furyl or thienyl optionally substituted by halogen, lower alkyl, lower alkoxy or di-lower alkylamino; R^3 is hydrogen or lower alkyl and X is halogen; and their physiologically acceptable salts. These compounds have diuretic and hypotensive actions.

Furukawa, et al., in U.S. Pat. No. 4,355,040 issued Oct. 19, 1982, discloses hypotensive imidazole-5-acetic acid derivatives having the formula:



Wherein R^1 is lower alkyl, cycloalkyl, or phenyl optionally substituted; X^1 , X^2 , and X^3 are each hydrogen, halogen, nitro, amino, lower alkyl, lower alkoxy, benzyloxy, or hydroxy; Y is halogen and R^2 is hydrogen or lower alkyl; and salts thereof.

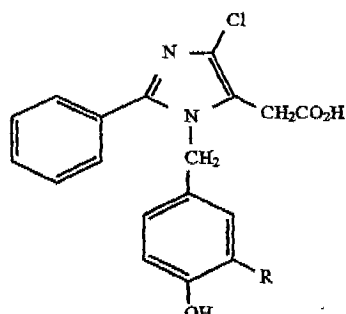
Furukawa, et al., in U.S. Pat. No. 4,340,598, issued Jul. 20, 1982, discloses hypotensive imidazole derivatives of the formula:



Wherein R^1 is lower alkyl or, phenyl C_{1-2} alkyl optionally substituted with halogen or nitro; R^2 is lower alkyl, cycloalkyl or phenyl optionally substituted; one of R^3 and R^4 is $-(CH_2)_nCOR^5$ where R^5 is amino, lower alkoxy or hydroxyl and n is 0, 1, 2 and the other of R^3 and R^4 is hydrogen or halogen; provided that R^1 is lower alkyl or phenethyl when R^3 is hydrogen, $n=1$ and R^5 is lower alkoxy or hydroxyl; and salts thereof.

Furukawa, et al., in European Patent Application 103,647 discloses 4-chloro-2-phenylimidazole-5-acetic acid derivatives useful for treating edema and hypertension of the formula:

3



Where R represents lower alkyl and salts thereof.

The metabolism and disposition of hypotensive agent 4-chloro-1-(4-methoxy-3-methylbenzyl)-2-phenyl-imidazole-5-acetic acid is disclosed by H. Torii in *Takeda Kenkyushoho*, 41, No 3/4, 180-191 (1982).

Frazee, et al., in European Patent Application 125,033-A discloses 1-phenyl(alkyl)-2-(alkyl)-thioimidazole derivatives which are inhibitors of dopamine- β -hydroxylase and are useful as antihypertensives, diuretics and cardiotonics.

European Patent Application 146,228 filed Oct. 16, 1984, by S. S. L. Parhi discloses a process for the preparation of 1-substituted-5-hydroxymethyl-2-mercaptoimidazoles.

A number of references disclose 1-benzyl-imidazoles such as U.S. Pat. Nos. 4,448,781 to Cross and Dickinson (issued May 15, 1984); 4,226,878 to Ilzuka, et al. (issued Oct. 7, 1980); 3,772,315 to Regel, et al. (issued Nov. 13, 1973); 4,379,927 to Vorbruggen, et al. (issued Apr. 12, 1983); amongst others.

Pals, et al., *Circulation Research*, 29, 673 (1971) describe the introduction of a sarcosine residue in position 1 and alanine in position 8 of the endogenous vasoconstrictor hormone AII to yield an (octa)peptide that blocks the effects of AII on the blood pressure of pithed rats. This analog, [Sar¹, Ala⁸] AII, initially called "P-113" and subsequently "Saralasin," was found to be one of the most potent competitive antagonists of the actions of AII, although, like most of the so-called peptide-AII-antagonists, it also possesses agonistic actions of its own. Saralasin has been demonstrated to lower arterial pressure in mammals and man when the (elevated) pressure is dependent on circulating AII (Pals et al., *Circulation Research*, 29, 673 (1971); Streeten and Anderson, *Handbook of Hypertension*, Vol. 5, Clinical Pharmacology of Antihypertensive Drugs, A. E. Doyle (Editor), Elsevier Science Publishers B. V., p. 246 (1984)). However, due to its agonistic character, saralasin generally elicits pressor effects when the pressure is not sustained by AII. Being a peptide, the pharmacological effects to saralasin are relatively short-lasting and are only manifest after parenteral administration, oral doses being ineffective. Although the therapeutic uses of peptide AII-blockers, like saralasin, are severely limited due to their oral ineffectiveness and short duration of action, their major utility is as a pharmaceutical standard.

Currently there are several A II antagonists in development. Among these development candidates, is losartan which is disclosed in a U.S. Pat. No. 5,138,069 issued to DuPont on Aug. 11, 1992. Losartan has been demonstrated to be an orally active A II antagonists, selective for the AT₁ receptor subtype.

Some known non-peptide antihypertensive agents act by inhibiting an enzyme, called angiotensin converting enzyme (ACE), which is responsible for conversion of angiotensin I to AII. Such agents are thus referred to as ACE inhibitors, or converting enzyme inhibitors (CEI's). Captopril and enalapril are commercially available CEI's. Based on experimental and clinical evidence, about 40% of hypertensive patients are non-responsive to treatment with CEI's. But when a diuretic such as furosemide or hydrochlorothiazide is given together with a CEI, the blood pressure of the majority of hypertensive patients is effectively normalized. Diuretic treatment converts the non-renin dependent state in regulating blood pressure to a renin-dependent State. Although the imidazoles of this invention act by a different mechanism, i.e., by blocking the AII receptor rather than by inhibiting the angiotensin converting enzyme, both mechanisms involve interference with the renin-angiotensin cascade. A combination of the CEI enalapril maleate and the diuretic hydrochlorothiazide is commercially available under the trademark Vaseretic® from Merck & Co. Publications which relate to the use of diuretics with CEI's to treat hypertension, in either a diuretic-first, stepwise approach or in physical combination, include Keeton, T. K. and Campbell, W. B., *Pharmacol. Rev.*, 31:81 (1981) and Weinberger, M. H., *Medical Clinics N. America*, 71:979 (1987). Diuretics have also been administered in combination with saralasin to enhance the antihypertensive effect.

Non-steroidal anti-inflammatory drugs (NSAID's) have been reported to induce renal failure in patients with renal under perfusion and high plasma level of AII (Dunn, M. J., *Hospital Practice*, 19:99, 1984). Administration of an AII blocking compound of this invention in combination with an NSAID (either stepwise or in physical combination) can prevent such renal failure. Saralasin has been shown to inhibit the renal vasoconstrictor effect of indomethacin and meclofenamate in dogs (Satoh, et al., *Circ. Res.* 36/37 (Suppl. D):I-89, 1975; Blasingham, et al., *Am J. Physiol.* 239:(F360, 1980). The CEI captopril has been demonstrated to reverse the renal vasoconstrictor effect of indomethacin in dogs with non-hypotensive hemorrhage. (Wong, et al., *J. Pharmacol. Exp. Ther.* 219:104, 1980).

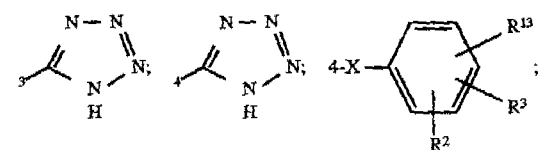
DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a novel method of treating atherosclerosis and/or reducing cholesterol alone or in conjunction with the treatment of hypertension using an angiotensin II receptor antagonist.

This invention relates to the use of the angiotensin II receptor antagonists as recited in European patent applications: EP 475,206, EP 497,150, EP 539,086, EP 539,713, EP 535,463, EP 535,465, EP 542,059, EP 497,121, EP 535,420, EP 407,342, EP 415,886, EP 424,317, EP 435,827, EP 433,983, EP 475,898, EP 490,820, EP 528,762, EP 324,377, EP 323,841, EP 420,237, EP 500,297, EP 426,021, EP 480,204, EP 429,257, EP 430,709, EP 434,249, EP 446,062, EP 505,954, EP 524,217, EP 514,197, EP 514,198, EP 514,193, EP 514,192, EP 450,566, EP 468,372, EP 485,929, EP 503,162, EP 533,058, EP 467,207, EP 399,731, EP 399,732, EP 412,848, EP 453,210, EP 456,442, EP 470,794, EP 470,795, EP 495,626, EP 495,627, EP 499,414, EP 499,416, EP 499,415, EP 511,791, EP 516,392, EP 520,723, EP 520,724, EP 539,066, EP 438,869, EP 505,893, EP 530,702, EP 400,835, EP 400,974, EP 401,030, EP 407,102, EP 411,766, EP 409,332, EP 412,594, EP 419,048, EP 480,659, EP 481,614, EP 490,587, EP 467,715, EP 479,479, EP 502,725, EP 503,838, EP 505,098, EP 505,111, EP 513,979, EP 507,594, EP 510,812, EP 511,767, EP 512,675, EP 512,676, EP 512,870, EP 517,357, EP 537,937, EP 534,706, EP 527,534, EP 540,356, EP 461,040, EP 540,039, EP 465,368, EP 498,723, EP 498,722, EP 498,721, EP 515,265, EP 503,785, EP 501,892, EP 519,831, EP 532,410,

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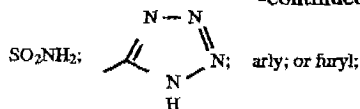
$$4\text{-CO}_2\text{H}; \quad 4\text{-CO}_2\text{R}^9; \quad \begin{array}{c} \text{O} \\ \parallel \\ \text{---O---S---OH} \\ \parallel \\ \text{OH} \end{array}; \quad \text{---SO}_3\text{H}; \quad \text{---C}(\text{CF}_3)_2\text{OH};$$
$$\begin{array}{ccccccc} \text{O} & & & & \text{O} & & \\ \parallel & & & & \parallel & & \\ -\text{O}-\text{P}-\text{OH}; & -\text{PO}_3\text{H}_2; & -\text{NH}-\text{P}-\text{OH}; & 4-\text{NHSO}_2\text{CH}_3; \\ | & & | & & & & \\ \text{OH} & & \text{OH} & & & & \end{array}$$
$$4\text{-NHSO}_2\text{CF}_3; \quad \text{---CONHOR}^{12}; \quad \text{---SO}_2\text{NH}_2; \quad \begin{array}{c} \text{OH} \quad \text{O} \\ | \quad || \\ \text{---C---P---OH;} \\ | \quad | \\ \text{R}^{27} \quad \text{OH} \end{array}$$




R² is H; Cl; Br; I; F; NO₂; CN; alkyl of 1 to 4 carbon atoms; acyloxy of 1 to 4 carbon atoms; alkoxy of 1 to 4 carbon atoms; 65 CO₂H; CO₂R⁹; HNSO₂CH₃; NHSO₂CF₃; CONHOR¹²;

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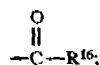
R³ is H; Cl, Br, I or F; alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms;

R⁴ is CN, NO₂ or CO₂R¹¹;

R⁵ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms alkenyl or alkynyl of 2 to 4 carbon atoms;

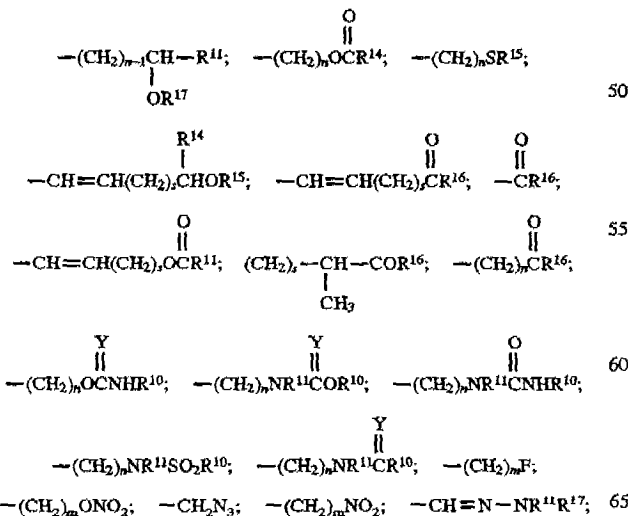
R⁶ is alkyl of 2 to 10 carbon atoms, alkenyl or alkynyl of 3 to 10 carbon atoms or the same groups substituted with F or CO₂R¹⁴; cycloalkyl of 3 to 8 carbon atoms, cycloalkylalkyl, of 4 to 10 carbon atoms; cycloalkylalkenyl or cycloalkylalkynyl 5 to 10 carbon atoms; (CH₂)₂Z(CH₂)_mR⁵ optionally substituted with F or CO₂R¹⁴; benzyl substituted on the phenyl ring with 1 or 2 halogens, alkoxy of 1 to 4 carbon atoms, alkyl of 1 to 4 carbon atoms or nitro;

R⁷ is H, F, Cl, Br, I, NO₂, C_vF_{2v+1}, where v=1-6, C₆F₅; CN;



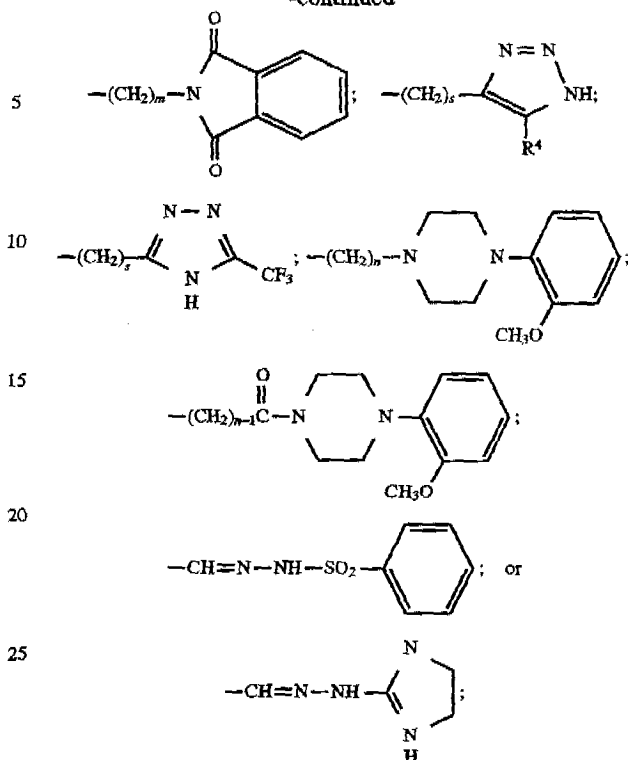
straight or branched alkyl of 1 to 6 carbon atoms; phenyl or phenylalkyl, where alkyl is 1 to 3 carbon atoms; or substituted phenyl or substituted phenylalkyl, where alkyl is 1 to 3 carbon atoms, substituted with one or two substituents selected from alkyl of 1 to 4 carbon atoms, F, Cl, Br, OH, OCH₃, CF₃, and COOR, where R is H, alkyl of 1 to 4 carbon atoms, or phenyl;

R⁸ is H, CN, alkyl of 1 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, or the same groups substituted with F; phenylalkenyl wherein the aliphatic portion is 2 to 6 carbon atoms; -(CH₂)_m-imidazol-1-yl; -(CH₂)_m-1,2,3-triazolyl optionally substituted with one or two group selected from CO₂CH₃ or alkyl of 1 to 4 carbon atoms; -(CH₂)_s tetrazolyl;

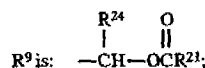


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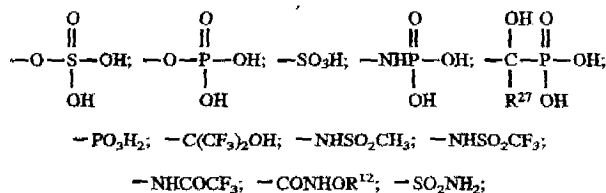


R¹⁰ is alkyl of 1 to 6 carbon atoms or perfluoroalkyl of 1 to 6 carbon atoms, 1-adamantyl, 1-naphthyl, 1-(1-naphthyl) ethyl, or (CH₂)₆C₆H₅;

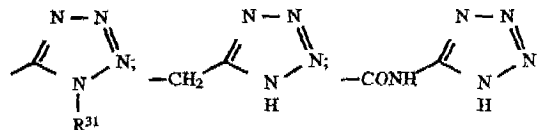
R¹¹ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R¹² is H, methyl or benzyl;

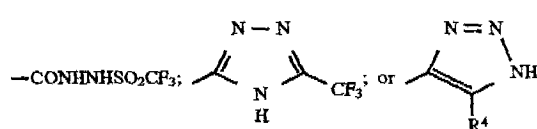
R¹³ is -CO₂H; -CO₂R⁹; -CH₂CO₂H; -CH₂CO₂R⁹;



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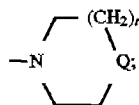
R¹⁴ is H, alkyl or perfluoroalkyl of 1 to 8 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R¹⁵ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl, benzyl, acyl of 1 to 4 carbon atoms, phenacyl;

R¹⁶ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, (CH₂)₆C₆H₅, OR¹⁷, or NR¹⁸R¹⁹;

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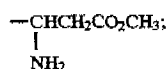
R^{17} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl; R^{18} and R^{19} independently are H, alkyl of 1 to 4 carbon atoms, phenyl, benzyl, α -methylbenzyl, or taken together with the nitrogen form a ring of the formula:



Q is NR^{20} , O or CH_2 ;

R^{20} is H, alkyl of 1-4 carbon atoms, or phenyl;

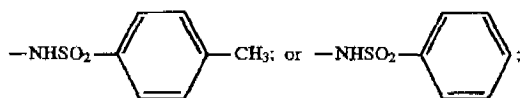
R^{21} is alkyl of 1 to 6 carbon atoms, $-NR^{22}R^{23}$, or



R^{22} and R^{23} independently are H, alkyl of 1 to 6 carbon atoms, benzyl, or are taken together as $(CH_2)_u$, where u is 3-6;

R^{24} is H, CH_3 or $-C_6H_5$;

R^{25} is $NR^{27}R^{28}$, OR^{28} , $NHCONH_2$, $NHCSNH_2$,



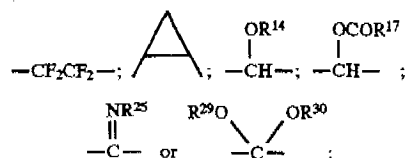
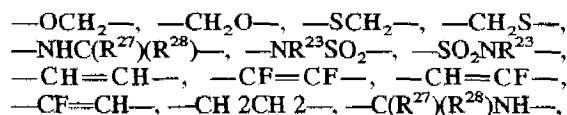
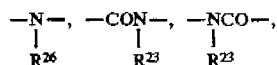
R^{26} is hydrogen, alkyl with from 1 to 6 carbon atoms, benzyl, or allyl;

R^{27} and R^{28} are independently hydrogen, alkyl with from 1 to 5 carbon atoms, or phenyl;

R^{29} and R^{30} are independently alkyl of 1-4 carbon atoms or taken together are $-(CH_2)_q$;

R^{31} is H, alkyl of 1 to 4 carbon atoms, $-CH_2CH=CH_2$ or $-CH_2C_6H_4R^{32}$;

X is a carbon-carbon single bond, $-CO-$, $-CH_2-$, $-O-$, $-S-$, $-NH-$,



Y is O or S;

Z is O, NR^{11} , or S;

m is 1 to 5;

n is 1 to 10;

p is 0 to 3;

q is 2 to 3;

r is 0 to 2;

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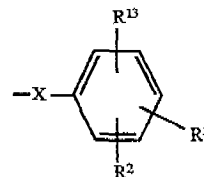
s is 0 to 5;

t is 0 or 1;

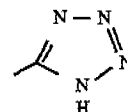
and pharmaceutically acceptable salts of these compounds; provided that:

(1) the R^1 group is not in the ortho position;

(2) when R^1 is

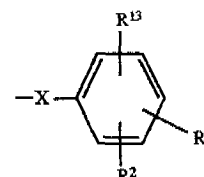


X is a single bond, and R^{13} is CO_2H , or



when R^{13} must be in the ortho or meta position; or when R^1 and X are as above and R^{13} is $NHSO_2CF_3$ of: $NHSO_2CH_3$, R^{13} must be ortho;

(3) when R^1 is

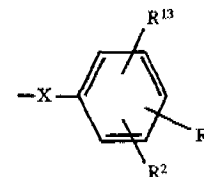


and X is other than a single bond, then R^{13} must be ortho except when $X=NR^{23}CO$ and R^{13} is $NHSO_2CF_3$ or $NHSO_2CH_3$, then R^{13} must be ortho or meta;

(4) when R^1 is 4- CO_2H or a salt thereof, R^6 cannot be S-alkyl;

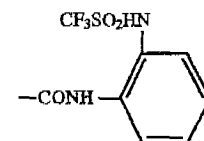
(5) when R^1 is 4- CO_2H or a salt thereof; the substituent on the 4-position of the imidazole cannot be CH_2OH , CH_2OCOCH_3 , or CH_2CO_2H ;

(6) when R^1 is



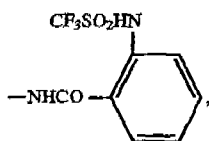
X is $-OCH_2-$, and R^{13} is 2- CO_2H , and R^7 is H then R^6 is not C_2H_5S ;

(7) when R^1 is

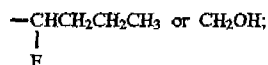


and R^6 is n-hexyl then R^7 and R^8 are not both hydrogen;

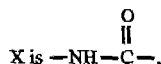
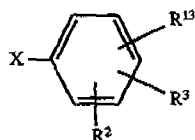
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(8) when R^1 is

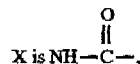
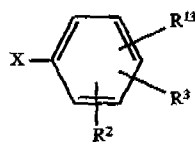
R^6 is not methoxybenzyl;
(9) the R^6 group



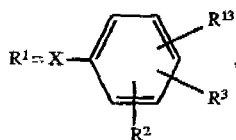
or CH_2OH ;
(10) when $r=0$, R^1 is



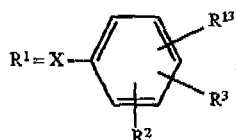
R^{13} is 2- $NHSO_2CF_3$ and R^6 is n-propyl, then R^7 and R^8 are not $-CO_2CH_3$;
(11) when $r=0$, R^1 is



R^{13} is 2-COOH, and R^6 is n-propyl, then R^7 and R^8 are not $-CO_2CH_3$;
(12) when $r=1$,



X is a single bond, R^7 is Cl, and R^8 is $-CHO$, then R^{13} is not 3-(tetrazol-5-yl);
(13) when $r=1$,



X is a single bond, R^7 is Cl, and R^8 is $-CHO$, then R^{13} is not 3-tetrazol-5-yl).
Preferred for their atherosclerotic, anticholesterolemic and antihypertensive activity are the compounds having the formula:

12

5

10

15 wherein:

 R^1 is $-CO_2H$; $-NHSO_2CF_3$;

20

25

30

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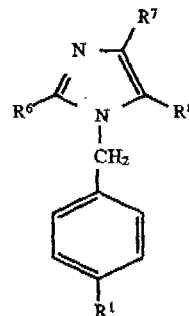
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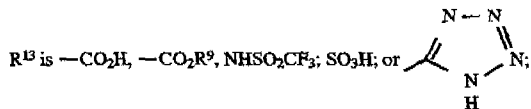
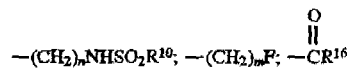
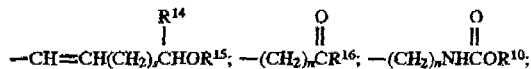
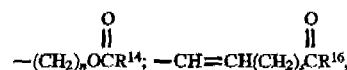
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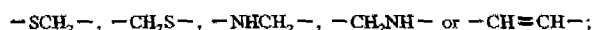
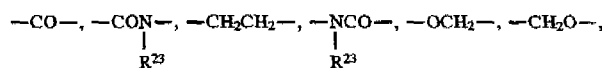


R^6 is alkyl of 3 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, alkynyl of 3 to 10 carbon atoms, cycloalkyl of 3 to 8 carbon atoms, benzyl substituted on the phenyl ring with up to two groups selected from alkoxy of 1 to 4 carbon atoms, halogen, alkyl of 1 to 4 carbon atoms, and nitro;

R^8 is phenylalkenyl wherein the aliphatic portion is 2 to 4 carbon atoms, $-(CH_2)_m$ -imidazol-1-yl, $-(CH_2)_m$ -1,2,3-triazolyl optionally substituted with one or two groups selected from CO_2CH_3 or alkyl of 1 to 4 carbon atoms, $(CH_2)_m$ -tetrazolyl, $-(CH_2)_nOR^{11}$;

 $NHSO_2CF_3$; SO_3H ;

R^{16} is H, alkyl of 1 to 5 carbon atoms, OR^{17} , or $NR^{18}R^{19}$;
X is carbon-carbon single bond,



and pharmaceutically acceptable salts of these compounds.

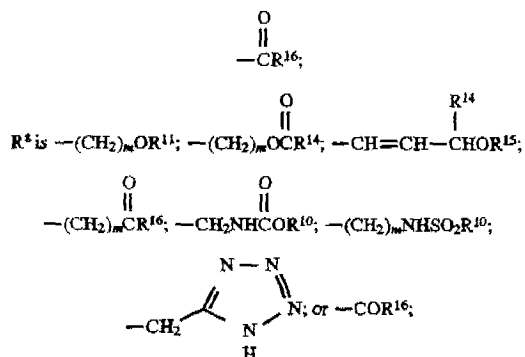
More preferred for the treatment of atherosclerosis, anticholesterolemia and hypertension are compounds of the preferred scope wherein:

13

R² is H, alkyl of 1 to 4 carbon atoms, halogen, or alkoxy of 1 to 4 carbon atoms;

R⁶ is alkyl, alkenyl or alkynyl of 3 to 7 carbon atoms;

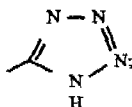
R⁷ is H, Cl, Br, C_vF_{2v+1}, where v=1-3, or



R¹⁰ is CF₃, alkyl of 1 to 6 carbon atoms or phenyl;

R¹¹ is H, or alkyl of 1 to 4 carbon atoms;

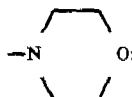
R¹³ is CO₂H; CO₂CH₂OCOC(CH₃)₃; NHSO₂CF₃; and



R¹⁴ is H, or alkyl of 1 to 4 carbon atoms;

R¹⁵ is H, alkyl of 1 to 4 carbon atoms, or acyl of 1 to 4 carbon atoms;

R¹⁶ is H, alkyl of 1 to 5 carbon atoms; OR¹⁷; or



m is 1 to 5;

X is single bond, —O—; —CO—; —NHCO—; or —OCH₂—; and pharmaceutically acceptable salts.

Specifically preferred for their activity in the treatment of atherosclerosis, high cholesterol and hypertension are:

2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole.

2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]-5-hydroxymethyl imidazole.

2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]-5-(methoxycarbonyl) aminomethylimidazole.

2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]-5-(propoxycarbonyl) aminomethylimidazole.

2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.

2-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-imidazole-5-carboxaldehyde.

2-(1E-Butenyl)-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole.

2-(1E-Butenyl)-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.

2-Propyl-4-chloro-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole.

2-Propyl-4-chloro-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.

2-Butyl-4-chloro-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.

14

2-(1E-Butenyl)-4-chloro-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-hydroxymethyl imidazole.

2-(1E-Butenyl)-4-chloro-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.

5 2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.

2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.

2-Propyl-4-trifluoromethyl-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.

10 2-Propyl-4-trifluoromethyl-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-hydroxymethylimidazole.

2-Butyl-4-trifluoromethyl-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.

15 2-Propyl-4-trifluoromethyl-1-[(2'-carboxybiphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.

2-Propyl-4-pentafluoroethyl-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-hydroxymethylimidazole.

2-Propyl-1-[(2-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-4,5-dicarboxylic acid.

20 2-Propyl-4-pentafluoroethyl-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.

2-Propyl-4-pentafluoroethyl-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde, or a pharmaceutically acceptable salt thereof.

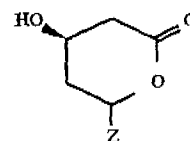
25 The most preferred angiotensin II receptor antagonist compounds for the treatment of atherosclerosis and/or high cholesterol alone or in conjunction with hypertension are:

2-Butyl-4-chloro-1-[(2'-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-hydroxymethyl imidazole; and

30 2-Butyl-4-chloro-1-[(2'-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof.

Note that throughout the text when an alkyl substituent is mentioned, the normal alkyl structure is meant (i.e., butyl is n-butyl) unless otherwise specified.

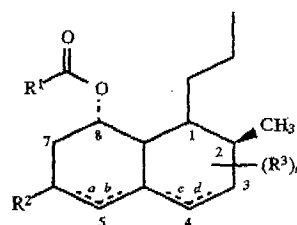
35 The angiotensin II antagonist compounds of the present invention can be administered in combination with an HMG-Co A reductase inhibitor for the treatment of atherosclerosis and/or to lower cholesterol. The HMG-Co A reductase inhibitors which are used in this combination therapy, include the compounds represented by the following structural formula (II):



II

wherein:

Z is selected from:



(a)

wherein

R¹ is C₁₋₁₀alkyl,

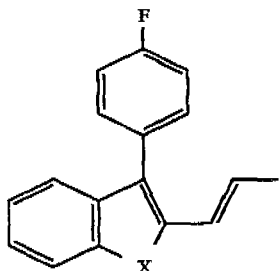
R² is selected from the group consisting of: hydrogen, C₁₋₃ alkyl, hydroxy, and C₁₋₃ alkyl substituted with hydroxy;

R³ is selected from the group consisting of: C₁₋₃ alkyl, hydroxy, oxo, and C₁₋₃ alkyl substituted with hydroxy;

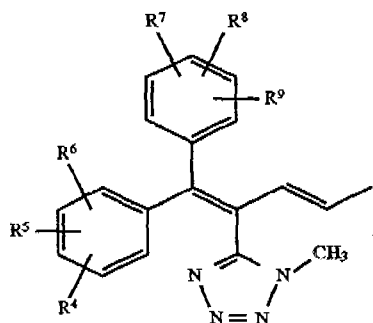
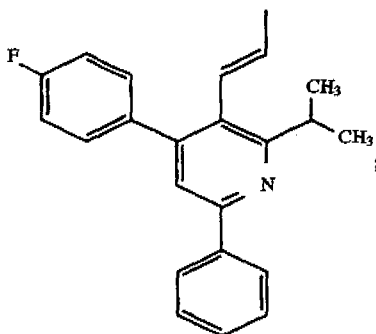
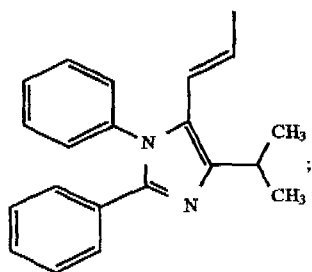
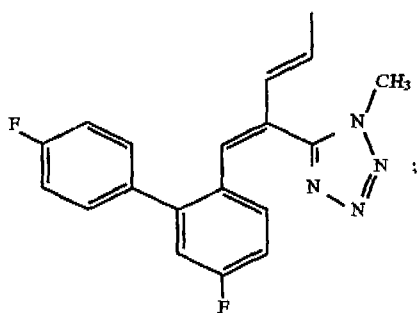
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n is 0, 1, or 2;

a, b, c and d are all single bonds or a and c are double bonds or b and d are double bonds or one of a, b, c or d is a double bond;



wherein X is $\text{NCH}(\text{CH}_3)_2$ or $\text{C}(\text{CH}_2)_4$;



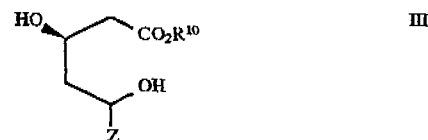
wherein:

16

R^4 and R^9 are each independently selected from hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy and trifluoromethyl, and

R^5 , R^6 , R^7 , and R^8 are each independently selected from hydrogen, halogen, C_{1-4} alkyl, and C_{1-4} alkoxy;

and corresponding open-ring dihydroxy acid forms of formula III:



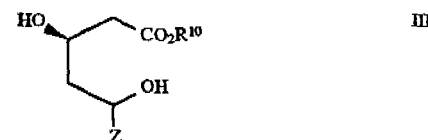
wherein:

(c) R^{10} is selected from the group consisting of: hydrogen, C_{1-5} alkyl, substituted C_{1-5} alkyl in which the substituent is selected from the group consisting of: phenyl, dimethylamino, acetylamino, and 2,3-dihydroxypropyl and pharmaceutically acceptable salts;

and pharmaceutically acceptable salts and esters thereof; provided that when R^1 is 1-methylpropyl or 1,1-dimethylpropyl, R^3 is hydrogen and b and d represent double bonds and R^2 is not methyl.

(d) The terms "halo" and "halogen" each refer to $-\text{F}$, $-\text{Cl}$, $-\text{Br}$ and $-\text{I}$.

The term "open-ring dihydroxy acid form and pharmaceutically acceptable salts, and esters" of the compound of formula II refers to the corresponding compound of formula III below:



wherein

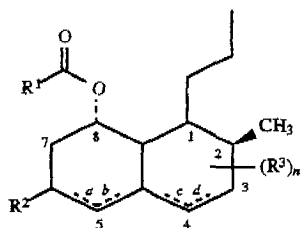
R^{10} is selected from the group consisting of: hydrogen, C_{1-5} alkyl, substituted C_{1-5} alkyl in which the substituent is selected from the group consisting of: phenyl, dimethylamino, acetylamino, and 2,3-dihydroxypropyl;

and pharmaceutically acceptable salts thereof.

(f) The pharmaceutically acceptable salts of the compounds of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris (hydroxymethyl)aminomethane, and tetramethyl ammonium hydroxide. These salts are prepared by standard procedures.

One class of HMG-Co A reductase inhibitor compounds are those wherein Z is:

17



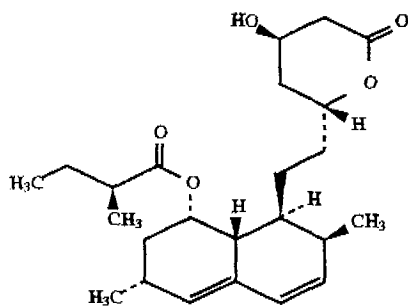
and n is 1.

One subclass of these compounds is where R^3 is 5-OH, and a, b, c, and d are each single bonds.

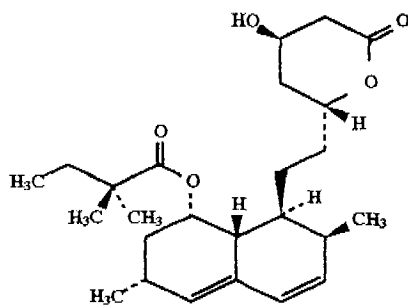
Another subclass of compounds is characterized by R^3 being 3-oxo and either a and c are double bonds and b and d are single bonds, or c is a double bond and a, b, and d are single bonds.

Yet a third subclass of these compounds is where R^3 is 7-(1-hydroxyethyl), h and d are double bonds; provided that when R^2 is OH, either b and d are double bonds and a, and c are single bonds, or c is a double bond and a, b, and d are single bonds, or a, b, c, and d are single bonds.

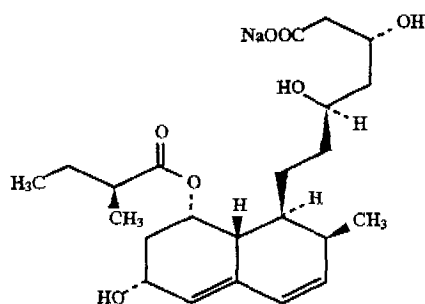
Representative compounds of this class are: lovastatin, simvastatin and pravastatin:



LOVASTATIN



SIMVASTATIN

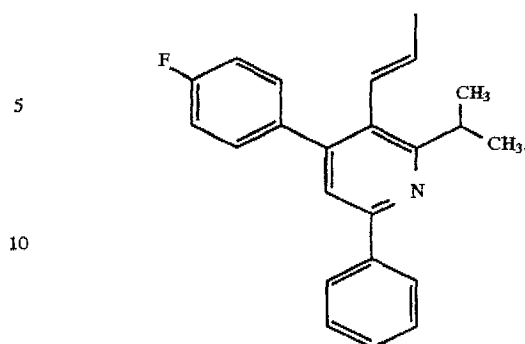


PRAVASTATIN

Another class of HMG-Co A reductase inhibitor compounds are those wherein Z is:

18

(a)



A method of treatment for atherosclerosis and/or to lower cholesterol administering a combination of an angiotensin II antagonist compound, an HMG-Co A reductase inhibitor and an angiotensin converting enzyme inhibitor. An embodiment of the ACE inhibitors useful in this method of treatment are enalapril and lisinopril.

Pharmaceutically suitable salts include both the metallic (inorganic) salts and organic salts; a list of which is given in *Remington's Pharmaceutical Sciences*, 17th Edition, pg. 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hygroscopicity and solubility. Preferred salts of this invention for the reasons cited above include potassium, sodium, calcium and ammonium salts.

Also within the scope of this invention is a method of treatment of atherosclerosis, high cholesterol and hypertension using pharmaceutical compositions comprising a suitable pharmaceutical carrier and a compound of Formula (I). The pharmaceutical compositions which contain one or more other therapeutic agents, such as a diuretic or a non-steroidal anti-inflammatory drug.

It should be noted in the foregoing structural formula, when a radical can be a substituent more than one previously defined radical, that first radical can be selected independently in each previously defined radical. For example, R^1 , R^2 and R^3 can each be CONHOR¹². R^{12} need not be the same substituent in each of R^1 , R^2 and R^3 but can be selected independently for each of them.

SYNTHESIS

The novel compounds of Formula (I) may be prepared using the reactions and techniques described in U.S. Pat. No. 5,138,069 and WO 93/10106 or one of its three U.S. counterparts, U.S. Pat. No. 5,130,439 issued Jul. 14, 1992, U.S. Pat. No. 5,206,374 issued Apr. 27, 1993, and U.S. Ser. No. 07/911,813 filed Jul. 10, 1992.

EXAMPLE 1

2-n-butyl-4-chloro-5-hydroxymethyl-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole [DuP-753]

Step A: Preparation of 4'-methylbiphenyl-2-carboxylic acid

Methyl 4'-methylbiphenyl-2-carboxylate (10.0 g, 44.2 mmol, 1 eq), 0.5N KOH in methanol (265.5 mL, 133 mmol, 3 eq), and water (50 mL) were mixed and refluxed under N_2 . After 5 hours, the solvent was removed in vacuo and water (200 mL) and ethyl acetate (200 mL) added. The aqueous layer was acidified with concentrated hydrochloric acid to a pH of 3 and the layers were separated. The aqueous phase was extracted with ethyl acetate (2x200 mL), the organic

layers collected, dried (MgSO_4) and the solvent removed in vacuo to yield 8.71 g of a white solid; m.p. $140.0^\circ\text{--}145.0^\circ$. NMR (200 MHz, $\text{DMSO}-d_6$) δ 7.72 (d, 1H, $J=7$ Hz); 7.56 (t, 1H, $J=7$ Hz); 7.45 (d, 1H, $J=7$ Hz); 7.40 (t, 1H, $J=7$ Hz); 7.25 (s, 4H); 2.36 (s, 3H). Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_2$; C, 79.23; H, 5.70. Found: C, 79.22; H, 5.47.

Step B: Preparation of 4'-Methyl-2-cyanobiphenyl

4'-Methylbiphenyl-2-carboxylic acid (8.71 g, 41 mmol, 1 eq) and thionyl chloride (30.0 mL, 411 mmol, 10 eq) were mixed and refluxed for 2 hours. The excess thionyl chloride was removed in vacuo and the residue was taken up in toluene. The toluene was removed by rotary evaporation and this toluene evaporation procedure was repeated to ensure that all of the thionyl chloride was removed. The crude acid chloride was then added slowly to cold (0°C .) concentrated NH_4OH (50 mL) so that the temperature was kept below 15° . After 15 minutes of stirring, water (100 mL) was added and solids precipitated. These were collected, washed well with water and dried under high vacuum over P_2O_5 in a dessicator overnight to yield 7.45 g of white solid; m.p. $126.0^\circ\text{--}128.5^\circ$. NMR (200 MHz, $\text{DMSO}-d_6$) δ 7.65–7.14 (m, 10H), 2.32 (s, 3H). Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}$; C, 79.59; H, 6.20; N, 6.63. Found C, 79.29; H, 6.09; N, 6.52.

The above product amide (7.45 g, 35 mmol, 1 eq) and thionyl chloride (25.7 mL, 353 mmol, 10 eq) were mixed and refluxed for 3 hours. The thionyl chloride was removed using the same procedure as described above. The residue was washed with a little hexane which partly solubilized the product, but removed the impurity as well to yield 6.64 g of white solid; m.p. $44.0^\circ\text{--}47.0^\circ$. NMR (200 MHz, $\text{DMSO}-d_6$) δ 7.95 (d, 1H, $J=8$ Hz); 7.78 (t, 1H, $J=7$ Hz); 7.69–7.32 (m, 6H); 2.39 (s, 3H). Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{N}$; C, 87.01; H, 5.74. Found C, 86.44; H, 5.88.

Step C: Preparation of 4'-bromomethyl-2-cyanobiphenyl

A solution of 5.59 g of 4'-methyl-2-cyanobiphenyl, 29 mmol of N-bromosuccinimide, 0.9 mmol of benzoylperoxide and 500 mL of carbon tetrachloride was refluxed for 3 hours. After cooling to room temperature, the resulting suspension was filtered and then concentrated in vacuo to provide the crude 4'-bromomethyl-2-cyanobiphenyl. The product was recrystallized from ether to yield 4.7 g of product; m.p. $114.5^\circ\text{--}120.0^\circ$. NMR (200 MHz, CDCl_3) δ 7.82–7.37 (m, 8H); 4.50 (s, 2H). Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{BrN}$; C, 61.79; H, 3.70; N, 5.15. Found: C, 62.15; H, 3.45; N, 4.98.

Step D: Preparation of 2-n-butyl-4-chloro-1-[(2'-cyanobiphenyl-4-yl)methyl]-5-hydroxymethyl-imidazole

To a suspension of 1.43 g of sodium methoxide in 20 mL of dimethylformamide at 25° was added a solution of 15.3 mmol of 2-butyl-4(5)-chloro-5(4)-hydroxymethyl imidazole (prepared as described in U.S. Pat. No. 4,355,040) in 15 mL of DMF. The resulting mixture was stirred at 25° for 0.25 hours, and then to this mixture 4.6 g, 16.9 mmol of 4'-bromomethyl-2-cyanobiphenyl in 15 mL of DMF. Finally, the reaction mixture was stirred at 40° for 4 hours. After cooling to 25° , the solvent was removed in vacuo. The residue was dissolved in 1:1 hexane/ethyl acetate, and this solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product contains two regioisomers, the faster moving one by TLC being the more potent isomer. Flash chromatography in 1:1 hexane/ethyl acetate over silica gel to separate the regioisomeric products yielded 2.53 g of the faster eluting isomer. Recrystallization from acetonitrile yielded 1.57 g of analytically pure product; m.p. $153.5^\circ\text{--}155.5^\circ$. NMR (200 MHz, CDCl_3) δ 7.82–7.43 (m, 6); 7.12 (d, 2, $J=8$ Hz); 5.32 (s, 2); 4.52 (s, 2); 2.62 (t, 2, $J=7$

Hz); 1.70 (t of t, 2, $J=7.7$ Hz); 1.39 (t of q, 2, $J=7.7$ Hz); 0.90 (t, 3, $J=7$ Hz). Anal. Calcd. for $\text{C}_{22}\text{H}_{22}\text{ClN}_3\text{O}$; C, 69.56; H, 5.84; N, 11.06. Found: C, 69.45; H, 5.89; N, 10.79.

Step E: Preparation of 2-n-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole

2-n-Butyl-4-chloro-1-[(2'-cyanobiphenyl-4-yl)methyl]-5-(hydroxymethyl) imidazole (11.93 g, 1.0 eq), sodium azide (3 eq), and ammonium chloride (3 eq) were mixed and stirred in DMF (150 mL) in a round bottom connected to a reflux condenser under N_2 . An oil bath with a temperature controller was then used to heat the reaction at 100°C . for 2 days, after which the temperature was raised to 120°C ., for 6 days. The reaction was cooled and 3 more equivalents of ammonium chloride and sodium azide were added. The reaction was again heated for 5 more days at 120°C . The reaction was cooled, the inorganic salts filtered, and the filtrate solvent removed in vacuo. Water (200 mL) and ethyl acetate (200 mL) were added to the residue and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 $\times$ 200 mL), the organic layers were collected, dried (MgSO_4) and the solvent removed in vacuo, to yield a dark yellow oil. The product was purified by flash chromatography in 100% ethyl acetate to 100% ethanol over silica gel to yield 5.60 g of a light yellow solid. Recrystallization from acetonitrile yielded 4.36 g of light yellow crystals which still melted broadly. The crystals were taken up in 100 mL of hot acetonitrile. The solid that did not dissolve was filtered off to yield 1.04 g of product as a light yellow solid; m.p. $183.5^\circ\text{--}184.5^\circ$. Upon cooling, the mother liquor yielded an additional 1.03 g of product as a light yellow solid; m.p. $179.0^\circ\text{--}180.0^\circ$. NMR (200 MHz, $\text{DMSO}-d_6$) δ 7.75–7.48 (m, 4H); 7.07 (d, 2H, $J=9$ Hz); 7.04 (d, 2H, $J=9$ Hz); 5.24 (s, 2H); 5.24 (bs, 1H); 4.34 (s, 2H); 2.48 (t, 2H, $J=7$ Hz); 1.48 (t of t, 2H, $J=7.7$ Hz); 1.27 (t of q, 2H, $J=7.7$ Hz); 0.81 (t, 3H, $J=7$ Hz). Anal. Calcd. for $\text{C}_{22}\text{H}_{22}\text{ClN}_6\text{O}$; C, 62.48; H, 5.48; Cl, 8.38. Found for the solids which did not dissolve in 100 mL of acetonitrile: C, 62.73; H, 5.50; Cl, 8.26. Found for the solids obtained from the mother liquor: C, 62.40; H, 5.23; Cl, 8.35.

EXAMPLE 2

2-butyl-1-[(2'-1H-tetrazol-5-yl)-biphenyl-4-yl)methyl]-4-chloroimidazole-5-Carboxylic acid (EXP-3174)

A mixture of 2-butyl-5-hydroxymethyl-4-chloro-1-[(2'-triphenylmethyltetrazol-5-yl)-biphenyl-4-yl)methyl] imidazole and activated manganese dioxide in 50 mL of methylene chloride was stirred at 25°C . At 24 hours into the reaction 2.00 g of manganese dioxide was added. After a total of 100 hours the reaction mixture was filtered with methylene chloride. The solids then were washed with methanol, and the methanol filtrate concentrated. The residue was dissolved in water. The resulting aqueous solution was adjusted to pH 3 using 10% hydrochloric acid and then extracted with 4:1 chloroform/i-propanol. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution(95:5:0.5 chloroform/methanol/acetic acid) furnished 2-butyl-1-[(2'-1H-tetrazol-5-yl)-biphenyl-4-yl)methyl]-4-chloroimidazole-5-carboxylic acid as an amorphous solid. NMR (200 MHz, $\text{DMSO}-d_6$) δ 7.46–7.63 (m, 4H), 7.05 (d, 2H, $J=8$ Hz), 6.93 (d, 2H, $J=8$ Hz), 5.56 (s, 2H), 4.10 (s, 12H), 2.55 (t, 2H, $J=7.5$ Hz), 1.44–1.52 (m, 2H), 1.17–1.28 (m, 2H), 0.78 (t, 3H, $J=7$ Hz).

EXAMPLE 3

2-n-Butyl-4-chloro-1-[(2'-2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl]-1H-imidazole-5-methanol

Step A: 2-(2'-Triphenylmethyl-2'H-tetrazol-5'-yl) phenylboronic acid

Alternative 1

To a 22 L flask under nitrogen purge was charged 8.25 L acetone, followed by 1.1 kg 5-phenyltetrazole. Triethylamine (800 g) was added in such a rate that the temperature was maintained below 35° C. with some cooling. Solid trityl chloride was charged to this light suspension in five 440 g portions. The temperature was maintained below 35° C. An additional 1.38 L acetone was added to the reaction which was then maintained at 25° to 30° C. with stirring for 2 hours. Water (2.2 L) was added and the mixture was chilled to 15° to 20° C. The solid was collected by filtration; the filter cake was rinsed with 1.65 L 50% acetone-water followed by excess amount of water. The wet cake was re-slurried in 8 L acetone and 8 L of water was added slowly. The suspension was stirred for 1 hour then filtered. The filter cake was rinsed with 3 to 5 L of water. The white solid was dried in a vacuum oven at 40°–45° C. to a constant weight of 3.0 kg, mp 158°–160° C.

To a dry 12 L flask under nitrogen purge was charged 3.19 L of dry tetrahydrofuran (THF). With agitation, 398 g of 5-phenyl-2-trityl-tetrazole prepared above was charged. The system was evacuated and released to nitrogen three times and then cooled to –20° C. A solution of butyl lithium in heptane (1.6M, 477 g) was then added to the reaction mixture while maintaining the temperature at –15° C. to –20° C. The resultant deep red solution was stirred at –15° C. for 1 hour during which time the lithium salt crystallized out. The solid suspension was cooled to –25° C. again 333 g triisopropylborate was charged at a temperature range of –20° to –25° C. After the addition, the mixture was allowed to warm to 20° C. without heating. About 2.5 L of solvent was removed by vacuum distillation. The pot temperature was kept below 40° C. To the mixture was then added 2.66 L of 3% acetic acid in water and the resultant suspension was stirred for 1 hour. The white solid was collected by filtration. The solid cake was rinsed with 1.5 L of 20% tetrahydrofuran in water, followed by 3 L of water. The solid was dried under vacuum at room temperature to a constant weight of 502.3 g, mp 142°–146° C. (dec.).

Alternative 2

A preferred alternative procedure for preparing the title compound of this Example 1 is by means of the following procedure.

5-Phenyltetrazole (14.6 g, 100 mmol) was suspended in dry THF (120 ml) under nitrogen and triethylamine (14.8 ml, 105 mmol) was added while maintaining the temperature at 15° to 20° C. Triphenylchloromethane (29.3 g, 105 mmol) in dry THF (60 ml) was then added slowly to the mixture at ≤25° C. After the addition was complete the mixture was warmed to 35° C. for 1 hour and then cooled at 0° C. for 1 hour. The precipitated triethylammonium chloride was filtered and the filtrate was degassed via vacuum/nitrogen purges (3×). The degassed solution was cooled to –20° C. and butyllithium (1.6M in hexanes) was added until a pink color persisted for 2 minutes. The pink color indicated that the solution was completely dry. More butyllithium (65.6 ml, 105 mmol) was charged at ≤–15° C. The deep red heterogeneous mixture was aged at –20° to –15° C. for 1 hour and triisopropylborate (30.6 ml, 130 mmol) was added while maintaining the temperature at ≤–15° C.

The deep red solution was aged at –15° C. for 30 minutes and then warmed to 10° C. over 1 hour. The mixture volume was reduced by ~200 ml in vacuo at ≤15° C. at which time <5% of hexanes (vs THF) remained. The residue was diluted with THF to a total volume of 160 ml and isopropanol (60 ml) was added. The solution was cooled to 0° C. and

saturated aqueous ammonium chloride (40 ml, 200 mmol) was charged within 15 minutes. The mixture was aged at 20° to 25° C. for 30 minutes and water (100 ml) was added over 30 to 45 minutes. After aging the mixture for 1 hour, the crystallized product was collected by filtration and washed with cold 80% aqueous isopropanol. The filter cake was air dried on the filter to give 69.7 g (86% yield, corrected for 82% purity) of product as the THF mono-solvate.

Step B: 2-n-butyl-4-chloro-5-hydroxymethyl-1-p-bromobenzyl-1H-imidazole

A suspension of 2-n-butyl-4-chloro-1H-imidazole-5-carboxyaldehyde (146.9 g, 0.78 tool) and p-bromobenzyl bromide (195 g, 0.78 mol) in dimethylacetamide (1.0 L) was cooled to 0° C. and potassium carbonate (1.38 g, 1.0 tool) was added. The mixture was aged for three hours at 0° C. and then at 20° to 25° C. or two to four hours. The mixture was diluted with dimethylacetamide (0.15 L) and then filtered. The filter cake was washed with dimethylacetamide (50 ml). The combined filtrates were diluted with methanol (0.66 L) and cooled to 0° C. Sodium borohydride (37.8 g, 1.0 mol) was added as a solid and the mixture was aged with stirring at 20° to 25° C. for two hours. Water (1.56 L) was added slowly to crystallize the product. The filter cake was washed carefully with water (1.56 L) and dried in vacuo at 60° C. The yield was 255 g (91%, corrected for 99.5% purity).

Step C: 2-n-butyl-4-chloro-1-[(2'-2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl]-1H-imidazole-5-methanol

All operations described for this example were performed under an atmosphere of nitrogen.

Catalyst Preparation

To a mixture of palladium chloride (10.6 mg) and triphenylphosphine (31.5 mg) was added anhydrous toluene (4 ml). The heterogeneous solution was degassed by vacuum/nitrogen purges (3×) and then heated to 60° C. for 30 minutes. Triisopropylphosphite (30.0 microliters) was added and the mixture was further heated at 60° C. until a homogeneous solution was obtained (1 to 2 hours).

Coupling

2-(2'-triphenylmethyl-2H-tetrazol-5'-yl)phenylboronic acid of Example 3, Step A (1.3 g) was suspended in toluene (4 ml) and water (100 microliters) was added. The heterogeneous mixture was stirred at room temperature for 30 minutes and potassium carbonate (0.7 g) was then charged followed by the titled product of Example 3, Step B (0.7 g). The mixture was degassed via vacuum/nitrogen purges (3×) and the above catalyst solution was added. The temperature of the mixture was raised 80° to 85° C. and kept at this temperature for 2 hours. After the mixture was cooled to 40° C., water (5 ml) was added. The aqueous layer was removed and the organic phase was concentrated in vacuo at ≤30° C. to a volume of ~3 ml. Methyl i-butyl ketone (MIBK) (8 ml) was added and the mixture was again reduced to ~3 ml. The mixture was diluted with MIBK (4 ml) and water (36 microliters), heated to 60° C. and then cooled and aged first at 0° C. for 30 minutes followed by aging at –10° C. with stirring for 2 hours. The crystallized product was collected by filtration as a mono-MIBK solvate (1.44 g, 94% yield). The crude product was dissolved in MIBK (2.1 ml) at 80° C., the solution was filtered hot at 80° C. and water (33.8 microliters) was added. The solution was cooled slowly to 0° C. over 1 hour and aged at 0° C. for 30 minutes followed by aging at –10° C. with stirring for 2 hours. After filtration 1.38 g of the mono-MIBK solvated product was recovered (90% yield).

EXAMPLE 4

2-n-Butyl-4-chloro-1-[(2'-2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-methyl]-1H-imidazole-5-methanol

All operations described for this example were performed under an atmosphere of nitrogen.

Step A: Catalyst Preparation

The following two procedures can be used with similar results.

Alternative Procedure 1

To a mixture of palladium chloride (354 mg) and triphenylphosphine (2.1 g) was added anhydrous tetrahydrofuran (THF) (75 ml). The heterogeneous solution was degassed by vacuum/nitrogen purges (3×) and then refluxed for 4 hours.

Most of the palladium chloride changed over to bis(triphenylphosphine) palladium chloride during the reflux. Some insoluble black solids were still observed at this point.

The heterogeneous THF solution containing the phosphinated palladium chloride was cooled to room temperature and diethylzinc (4.0 ml, 1M in hexanes) was added. Except for a small amount of black solids, the solution essentially became homogeneous after stirring for 30 minutes. This activated catalyst solution was used in the coupling step described below.

Alternative Procedure 2

To a mixture of palladium chloride (354 mg) and triphenylphosphine (2.1 g) was added anhydrous THF (75 ml). The heterogeneous solution was degassed by vacuum/nitrogen purges (3×) and then triisopropylphosphite (0.99 ml) was added. The mixture was maintained at room temperature until all the palladium chloride was dissolved and a homogeneous solution was obtained (0.5 to 1 hour).

Step B: Benzyltrimethylammonium Carbonate Preparation

To a benzyltrimethylammonium hydroxide solution (42 g) was added ammonium carbonate (5.0 g) and the reaction was aged with stirring until all of the ammonium carbonate dissolved (~30 minutes). The methanol solvent was removed in vacuo and further displaced with THF (3×10 ml). The residual carbonate was dissolved in THF (90 ml).

Step C: Coupling Step

To the carbonate solution prepared in Example 4, Step B was charged the titled product of Example 3 (24.0 g) and the titled product of Example 3, Step B (14.2 g). The mixture was degassed by vacuum/nitrogen purges (5×), followed by the addition of the catalyst solution prepared as recited in Example 4, Step A (procedure 1 or 2). The reaction mixture was heated to reflux, aged until completion (8 to 10 hours), cooled to room temperature and filtered through a pad Celite. The Celite was further washed with THF (3×10 ml). The yield was 89 wt %.

EXAMPLE 5

2-n-Butyl-4-chloro -1-[(2'-(tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl]-1H-imidazole-5-methanol potassium salt

2-n-butyl-4-chloro -1-[(2'-2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl]-1H-imidazole-5-methanol, obtained from Example 3 or 4, (5.0 g, 6.54 mmol) was dissolved in THF (60 ml). 4N Sulfuric acid (38 ml, 152 mmol) was added with stirring at 25° to 30° C. The solution was aged overnight at 20° to 25° C. and isopropyl acetate (60 ml) was then added. The layers were separated and the organic phase was back-extracted with 4N sulfuric acid (19 ml). The aqueous layers were combined and the organic solvents (THF and isopropyl acetate) were removed in vacuo. The remaining aqueous solution was diluted with THF (10% of THF by volume) and passed through a pad of Ecosorb S 402 (5.0 g). The pad was rinsed with 10% THF in 4 N sulfuric acid. The filtrate was then passed through a column of SP-207 (60 ml) and the column was washed with water (180 ml) followed with 1M K₂HPO₄ (180 ml). The pH of the eluent was monitored to ensure complete potassium

salt formation. Further washing with water (180 ml) removed the surf ate and excess phosphate. The potassium salt product was eluted with 20% aqueous THF. Concentration of the aqueous solution and dilution with isopropanol gave crystalline product. Attentively, the product was isolated by spray drying. The yield was 2.56 g (85%).

EXAMPLE 6

1-Bromo-4-2'-n-butyl-4'-chloro-5'-hydroxymethylimidazole-1'H-1'-yl) methylbenzene

Step A: Alkylation

To 200 mL of dimethyl acetamide under a nitrogen atmosphere in a 1-liter 3-necked flask fitted with a mechanical stirrer and thermocouple is charged 30.8 g (0.163 mol) of 2-n-butyl-4-chloro-5-formyl-1H-imidazole and 43.7 g (0.16 mol) of 4-bromobenzyl bromide. The solution is cooled to -5° C. followed by portionwise addition of 27.1 g (0.19 mol) of powdered potassium carbonate over 10 min with rapid stirring while keeping the reaction temperature between -5°-0° C. The slurry is stirred at -5° C. for 2 h and room temperature for 2 h or until the alkylation is complete.

Step B: Filtration

The slurry is filtered and the cake is washed with an anhydrous mixture of dimethyl acetamide (30 mL) and methanol (130 mL). The filtrate is used directly in the next step.

Step C: Reduction

Under a nitrogen atmosphere, 1.85 g (48 mmol) of powdered sodium borohydride is added portionwise over 0.5 h to the filtrate at -15° C. in a 5-liter 3-necked flask with a mechanical stirrer and a thermocouple, keeping the reaction temperature between -15° to -5° C. The mixture is warmed to room temperature and aged for 1 h or until the reduction is complete.

Step D: Crystallization

Acetic acid (2.74 mL) is added dropwise over 10 min with rapid stirring while keeping the temperature of the mixture at 20°-25° C. This mixture is aged at room temperature for 0.5 h, followed by the addition of water (160 mL) dropwise over 1 h. The solution is seeded with imidazole 4 and followed by the addition of water (166 mL) dropwise over 1 h. The product precipitated within 0.5 h. The slurry is aged at room temperature for 2 h, cooled to 10° C., aged for 0.5 h and the solid is filtered. The cake is washed with 320 mL of water, suction dried under nitrogen at room temperature for 2 h and oven dried under house vacuum (-24 psi) at ≤60° C. for 12 h to afford 54.3 g of 1-bromo-4-(2'-n-butyl-4'-chloro -5'-hydroxymethylimidazole -1'H-1'-yl) methylbenzene as a white solid (HPLC assay: 98.8 A%, 97.2 W%, overall yield: 92.4%, 0.5 W% of the regioisomer).

EXAMPLE 7

2-n-Butyl-4-chloro-1-[(2'-(2-triphenylmethyl -2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl]-1H-imidazole-5-methanol

Step A: Catalyst Preparation

Triphenylphosphine (262 mg, 1.0 mmol) is dissolved in THF (20 mL) and the solution is degassed by vacuum/nitrogen purges (3×). Palladium acetate (56 mg, 0.25 mmol) is added and the solution is degassed again (3×). The resulting solution is warmed to 60° C. for 30 min. and then cooled to 25° C.

Step B: Coupling

Note: All solvent must be degassed.

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2-(2'-triphenylmethyl-2'H-tetrazol-5'-yl)phenylboronic acid (15.4 g, 26.7 mmol, 75 wt % pure) is suspended in diethoxymethane (DEM) (80 mL, KF $\leq$ 500 mg/mL). Water (0.55 mL, 31 mmol) is added and the slurry is aged at ambient temperature for 30 min. After the age, another charge of water (0.55 mL, 31 mmol) is added to the boronic acid suspension under agitation. The slurry is then treated with powdered potassium carbonate (8.6 g, 62 mmol) and alkylated imidazole, the titled product of Example 6 (8.97 g, 25 mmol). The mixture is aged at 20°–25° C. for 30 min then degassed well (3 $\times$). (Note: in the pilot plant, degassing takes much longer and can be started immediately after the imidazole and carbonate are added). The catalyst solution is then charged and the mixture is heated to reflux (76°–79° C.). The reaction is complete in 2–6 hours. When the imidazole has been consumed, water (30 mL) and THF (25 mL) are added and the mixture is stirred at 55°–60° C. The water layer is separated and the organic layer is washed with water (30 mL). The organic layer is concentrated in vacuo to a volume of 50 mL to remove most of the THF. More DEM (50 mL) is added and removed by distillation to further reduce THF to $<$ 5 vol%. The residual organic solution is diluted with warm (60° C.) DEM (to a final volume of 75 mL) and water (0.5 mL, 28 mmol). The mixture is then cooled slowly to –12° C. over 2 hours. After aging at –12° C. for 1 hour, the product is collected by filtration. The cake is washed with cold DEM (25 mL). Vacuum drying at 40° C. gave 15.5 g (93%) of the titled product (non-solvated). [Pd=600 to 1000 ppm].

EXAMPLE 8

2-n-Butyl-4-chloro-1-[(2'-2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl]-1H-imidazole-5-methanol

Step A: Catalyst preparation

Triphenylphosphine (262 mg, 1.0 mmol) is dissolved in THF (20 mL) and the solution is degassed by vacuum/nitrogen purges (3 $\times$). Palladium acetate (56 mg, 0.25 mmol) is added and the solution is degassed again (3 $\times$). The resulting solution is warmed to 60° C. for 30 min. and then cooled to 25° C.

Step B: Coupling

Note: All solvents must be degassed.

2'-2-Triphenylmethyl-2'H-tetrazol-5'-yl)phenylboronic acid (15.4 g, 26.7 mmol, 75 wt % pure) is suspended in diethoxy-methane (DEM) (80 mL, KF $\leq$ 500 mg/mL). Water (0.55 mL, 31 mmol) is added and the slurry is aged at ambient temperature for 30 min. After the age, another charge of water (0.55 mL, 31 mmol) is added to the boronic acid suspension under agitation. The slurry is then treated with powdered potassium carbonate (8.6 g, 62 mmol) and the titled product of Example 22, the alkylated imidazole (8.97 g, 25 mmol). The mixture is aged at 20°–25° C. for 30 min then degassed well (3 $\times$). (Note: in the pilot plant, degassing takes much longer and can be started immediately after the imidazole and carbonate are added). The catalyst solution is then charged and the mixture is heated to reflux (76°–79° C.). The reaction is complete in 2–6 hours. When the imidazole has been consumed, water (30 mL) and THF (25 mL) are added and the mixture is stirred at 55°–60° C. The water layer is separated and the organic layer is washed with water (30 mL). Tributylphosphine (0.62 mL, 10 mol %) is added and the organic layer is concentrated in vacuo to a volume of 50 mL to remove most of the THF. More DEM (50 mL) is added and removed by distillation to further reduce THF to $\leq$ 5 vol %. The residual organic solution is diluted

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with warm (60° C.) DEM (to a final volume of 75 mL) and water (0.5 mL, 28 mmol). The mixture is then cooled slowly to –12° C. over 2 hours. After aging at –12° C. for 1 hour, the product is collected by filtration. The cake is washed with cold DEM (25 mL). Vacuum drying at 40° C. gave 15.5 g (93%) of the titled product (non-solvated). [Pd $\leq$ 10 ppm].

EXAMPLE 9

2-n-Butyl-4-chloro-1-[(2'-2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl(methyl)-1H-imidazole-5-methanol as the methyl isobutyl ketone solvate

A suspension of the titled product of Example 7 (5 g) in methyl isobutyl ketone (MIBK) (40 mL) is degassed (3 $\times$) and tributylphosphine (0.12 g, 8 mol %) is added. The mixture is heated to 85° C. at which time a homogeneous solution was obtained. Degassed water (0.135 g, 100 mol %) is then added and the solution is cooled to –10° C. over 2 hours. The heterogeneous solution is aged at –10° C. for 2 hours, the crystallized product is collected by filtration and washed with cold MIBK (–10° C., 15 mL). The recovery was 5.40 g of the rifled product (93.9%, as the MIBK solvate).

EXAMPLE 10

2-n-butyl-4-chloro-1-[(2'-tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-1H-imidazole-5-methanol potassium salt

Step A: Deprotection

Dissolve 2.50 g of the titled product of Example 8, the methyl isobutyl ketone solvate, by adding 10 mL of 0.75M H₂SO₄ in 50:50 MeCN:water. Age 2 hours 25 min, 23°–25° C. Add 15 mL of water in 2 min (can be added in 30 min to an hour in larger scales), and age 1.75 hours, 23°–25° C. Filter and wash with 5 mL of 20:80 MeCN:water. There was almost no starting material left in the trityl alcohol filter cake ($\leq$ 0.05 area%).

Step B: Free Acid Formation

Dilute the above filtrate with 13 mL of MeCN. The pH of the solution is 1.50. The temperature of the solution following neutralization and crystallization was 22°–24° C. After adding 1.5 mL of 3N NaOH (pH 1.75–1.65), the reaction is seeded with 20 mg of the free acid. Age 15 min. Slowly add the next 1 mL of 3M NaOH to allow for good crystal growth (on this scale, the addition time was 5–10 min). Age 30 min. Add the remaining 3M NaOH (pH 3.60–3.50). Age 1 hour. The white slurry is filtered and washed with 5 mL of 20:80 MeCN:water then 10 mL of water. A thorough water wash of the free acid filter cake is necessary to remove all the salts. The wash can be checked for SO₄²⁻. The filter cake is dried in a vacuum oven at 35° C. for 18 hours with nitrogen purge. The yield of the free acid was 1.28 g (92.5%) and there was 54 mg (4%) of the free acid in the mother liquors.

Step C: Salt Formation

To 4.0 g (9.46 mmoles) of the free acid is added 10.9 mL of 0.842N KOH solution all in one portion. The slurry is aged at room temperature for 30 minutes, during which time most of the solid dissolves. The cloudy solution is filtered and the solids collected on a sintered glass funnel. The pH of the filtrate is measured at 9.05. The aqueous solution is added slowly to a refluxing azeotropic mixture of cyclohexane/isopropanol (69° C.) whereupon the ternary azeotrope cyclohexane/isopropanol/water (64° C.) begins to distill. When the solution is dry the temperature of the overhead rises to 69° and the potassium salt crystallizes.

When the water content of the pot is $\leq 0.05\%$ the distillation is halted and the white slurry is cooled to room temperature. The white crystalline solid is collected on a sintered glass funnel and washed with 10–15 ml of cyclohexane/isopropanol 67/33 and dried in a vacuum oven. (wt 3.8 g yield 95%).

Synthetic routes for the preparation of lovastatin, pravastatin, simvastatin, enalapril and lisinopril can be found in the following U.S. Pat. Nos. 4,231,938, 4,346,227, and 4,444,784, 4,374,829 and 4,555,502, respectively. For a review of syntheses for mevastatin see T. Rosen, C. H. Heathcock *Tetrahedron* 42, 4909–4951 (1986).

Utility

The hormone angiotensin II (AII) produces numerous biological responses (e.g. vasoconstriction) through stimulation of its receptors on cell membranes. For the purpose of identifying compounds such as AII antagonists which are capable of interacting with the AII receptor, a ligand-receptor binding assay was utilized for the initial screen. The assay was carried out according to the method described by [Glossmann, et al., *J. Biol. Chem.*, 249, 825 (1974)], but with some modifications. The reaction mixture contained rat adrenal cortical microsomes (source of AII receptor) in Tris buffer and 2 nM of ^3H -AII with or without potential AII antagonist. This mixture was incubated for 1 hour at room temperature and the reaction was subsequently terminated by rapid filtration and rinsing through glass micro-fibre filter. Receptor-bound ^3H -AII trapped in filter was quantitated by scintillation counting. The inhibitory concentration (IC_{50}) of potential AII antagonist which gives 50% displacement of the total specifically bound ^3H -AII is presented as a measure of the affinity of such compound for the AII receptor (See Tables 1 and 2).

The potential antihypertensive effects of the compounds of this invention may be demonstrated by administering the compounds to awake rats made hypertensive by ligation of the left renal artery [Cangiano, et al., *J. Pharmacol. Exp. Ther.*, 208, 310 (1979)]. This procedure increases blood pressure by increasing renin production with consequent elevation of AII levels. Compounds are administered orally at 100 mg/kg and/or intravenously via a cannula in the jugular vein at 10 mg/kg. Arterial blood pressure is continuously measured directly through a carotid artery cannula and recorded using a pressure transducer and a polygraph. Blood pressure levels after treatment are compared to pretreatment levels to determine the antihypertensive effects of the compounds (See Table 1).

TABLE 1

Antihypertensive activity of 2-n-butyl-4-chloro-1-[(2'-(tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-1H-imidazole-5-methanol potassium salt (Losartan)			
	Angiotensin II Receptor Binding- IC_{50} (μ molar)	Antihypertensive Effects in Renal Hypertensives Rats	
Losartan	0.039	Intravenous Activity ¹	+
		Oral Activity ²	+

¹Significant decrease in blood pressure at 10 mg/kg or less

²Significant decrease in blood pressure at 100 mg/kg or less

Compound listed in Table 2 was tested in the same manner as described for Table 1, except that in the test for antihypertensive effects in renal hypertensive rats, the compounds were administered orally at 30 mg/kg and intravenously at 3 mg/kg.

TABLE 2

Antihypertensive activity of 2-n-butyl-4-chloro-1-[(2'-(tetrazol-5-yl)-1,1'-biphenyl-4-yl)-methyl]-1H-imidazole-5-carboxylic acid (Compound 2)			
	Angiotensin II Receptor Binding- IC_{50} (μ molar)	Antihypertensive Effects in Renal Hypertensives Rats	
Compound 2	0.011	Intravenous Activity ¹	+
		Oral Activity ²	+

¹Significant decrease in blood pressure at 3.0 mg/kg or less

²Significant decrease in blood pressure at 30 mg/kg or less

The hypotensive effects of 2-butyl-4-chloro-1-[(2'-1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-hydroxymethylimidazole sodium salt were compared before and after furosemide administration to conscious dogs. Cumulative intravenous injections of imidazole at 0.3 to 3 mg/kg did not lower blood pressure in normotensive conscious Dogs (n=4) but they were effective in inhibiting the pressor response to AII (0.1 $\mu\text{g/kg}$ iv) determined at 10 min post dose. Plasma renin activity (PRA) in these animals was 1.5 ± 0.5 ng AI/ml/hr. Four days later, furosemide was given to three of these dogs at 10 mg/kg im at 18 and 2 hours before the experiment and increased PRA to 19.9 ± 7.2 ng AI/ml/hr. Imidazole was then given cumulatively iv at the same doses and caused a significant decrease in blood pressure in a dose-dependent manner. It also inhibited the pressor response to AII at the two higher doses. A similar hypotensive enhancement by furosemide was also observed with captopril at 0.3 mg/kg iv. These results indicate that diuretics enhance the hypotensive efficacy of imidazole AII blockers. Thus a combined therapy of these two classes of drugs will be likely to increase the response rate to therapy among hypertensive patients.

Angiotensin II (AII) is a powerful arterial vasoconstrictor, and it exerts its action by interacting with specific receptors present on cell membranes. In order to identify AII antagonists and determine their efficacy in vitro, the following two ligand-receptor binding assays were established.

Receptor Binding Assay Using Rabbit Aortae Membrane Preparation:

Three frozen rabbit aortae (obtained from Pel-Freeze Biologicals) are suspended in 5 mM Tris-0.25M Sucrose, pH 7.4 buffer (50 ml) homogenized, and then centrifuged. The mixture is filtered through a cheesecloth and the supernatant is centrifuged for 30 minutes at 20,000 rpm at 4° C. The pellet thus obtained is resuspended in 30 ml of 50 mM Tris-5 mM MgCl_2 buffer containing 0.2% Bovine Serum Albumin and 0.2 mg/ml Bacitracin and the suspension is used for 100 assay tubes. Samples tested for screening are done in duplicate. To the membrane preparation (0.25 ml) there is added ^{125}I -Sar¹Ile⁸-angiotensin II [obtained from New England Nuclear] (10 μl ; 20,000 cpm) with or without the test sample and the mixture is incubated at 37° C. for 90 minutes. The mixture is then diluted with ice-cold 50 mM Tris-0.9% NaCl, pH 7.4 (4 ml) and filtered through a glass fiber filter (GF/B Whatman 2.4" diameter). The filter is soaked in scintillation cocktail (10 ml) and counted for radioactivity using Packard 2660 Tricarb liquid scintillation counter. The inhibitory concentration (IC_{50}) of a potential AII antagonist which gives 50% displacement of the total specifically

bound ^{125}I -Sar ^{1} Ile ^{8} -angiotensin II is presented as a measure of the efficacy of such compounds as AII antagonists.

Receptor Assay Using Bovine Adrenal Cortex Preparation

Bovine adrenal cortex is selected as the source of AII receptor. Weighed tissue (0.1 g is needed for 100 assay tubes) is suspended in Tris.HCl (50 mM), pH 7.7 buffer and homogenized. The homogenate is centrifuged at 20,000 rpm for 15 minutes. Supernatant is discarded and pellets resuspended in buffer [Na_2HPO_4 (10 mM)-NaCl (120 mM)-disodium EDTA (5 mM) containing phenylmethane sulfonyl fluoride (PMSF)(0.1 mM)]. (For screening of compounds, generally duplicates of tubes are used). To the membrane preparation (0.5 ml) there is added 3H-angiotensin II (50 mM) (10 μl) with or without the test sample and the mixture is incubated at 37° C. for 1 hour. The mixture is then diluted with Tris buffer (4 ml) and filtered through a glass fiber filter (GF/B Whatman 2.4" diameter). The filter is soaked in scintillation cocktail (10 ml) and counted for radioactivity using Packard 2660 Tricarb liquid scintillation counter. The inhibitory concentration (IC_{50}) of a potential AII antagonist which gives 50% displacement of the total specifically bound ^3H -angiotensin II is presented as a measure of the efficacy of such compounds as AII antagonists.

Receptor Assay Using Rat Brain Membrane Preparation

Membranes from rat brain (thalamus, hypothalamus and midbrain) are prepared by homogenization in 50 mM Tris HCl(pH 7.4), and centrifuged at 50,000 $\times$ g. The resulting pellets are washed twice in 100 mM NaCl, 5 mM Na_2EDTA , 10 mM Na_2HPO_4 (pH 7.4) and 0.1 mM PMSF by resuspension and centrifugation. For binding assays, the pellets are resuspended in 160 volumes of binding assay buffer (100 mM NaCl, 10 mM Na_2HPO_4 , 5 mM Na_2EDTA , pH 7.4, 0.1 mM PMSF, 0.2 mg/ml soybean trypsin inhibitor, 0.018 mg/ml α -phenanthroline, 77 mg/ml dithiothreitol and 0.14 mg/ml bacitracin. For ^{125}I -Ile ^{8} -angiotensin II binding assays, 10 μl of solvent (for total binding), Sar ^{1} Ile ^{8} -angiotensin II (1 μM) (for nonspecific binding) or test compounds (for displacement) and 10 μl of [^{125}I]Sar ^{1} Ile ^{8} -angiotensin II (23–46 pM) are added to duplicate tubes. The receptor membrane preparation (500 μl) is added to each tube to initiate the binding reaction. The reaction mixtures are incubated at 37° C. for 90 minutes. The reaction is then terminated by filtration under reduced pressure through glass-fiber GF/B filters and washed immediately 4 times with 4 ml of 5 mM ice-cold Tris HCl(pH 7.6) containing 0.15M NaCl. The radioactivity trapped on the filters is counted using a gamma counter.

Using the methodology described above, representative compounds of this invention could be evaluated and an $\text{IC}_{50}<50$ μM determined, thereby demonstrating and confirming the utility of the compounds of the invention as effective A II antagonists.

The antihypertensive effects of the compounds described in the present invention may be evaluated using the methodology described below:

Male Charles River Sprague-Dawley rats (300–375 gm) are anesthetized with methohexital (Brevital; 50 mg/kg i.p.) and the trachea is cannulated with PE 205 tubing. A stainless steel pithing rod (1.5 mm thick, 150 mm long) is inserted into the orbit of the right eye and down the spinal column. The rats are immediately placed on a Harvard Rodent Ventilator (rate—60 strokes per minute, volume—1.1 cc per

100 grams body weight). The right carotid artery is ligated, both left and right vagal nerves are cut, and the left carotid artery is cannulated with PE 50 tubing for drug administration, and body temperature is maintained at 37° C. by a thermostatically controlled heating pad which received input from a rectal temperature probe. Atropine (1 mg/kg i.v.) is then administered, and 15 minutes later propranolol (1 mg/kg i.v.). Thirty minutes later antagonists of formula I are administered intravenously or orally. Angiotensin II is then typically given at 5, 10, 15, 30, 45 and 60 minute intervals and every half-hour thereafter for as long as the test compound showed activity. The change in the mean arterial blood pressure is recorded for each angiotensin II challenge and the percent inhibition of the angiotensin II response is calculated.

The effects of 2-butyl-4-chloro-1-[2'-1H-tetrazol-5-yl]biphenyl-4-yl)methyl]-5-hydroxymethylimidazole potassium salt (Losartan) were studied in a multicenter, double-blind, randomized, placebo-controlled clinical study. Losartan was administered in a 50 mg oral dose administered once daily to patients with mild to moderate hypertension (patients with a sitting diastolic blood pressure of 95–115 mmHg of a median age of 54), but with no other active medical problem that could, of itself or its treatment, affect blood pressure. After six weeks the non-responders were titrated to a 100 mg oral dose administered once daily.

The total, HDL, LDL and VLDL cholesterol levels were measured using the procedures described below:

High Density Lipoprotein Cholesterol

The high density lipoprotein (HDL) cholesterol was measured by analyzing a 2.0 mL volume of non-hemolyzed serum or EDTA plasma (heparinized plasma is not recommended), which has been separated from the cells within 30 minutes of collection. A fasting specimen of at least 12 hours is required for accurate interpretation. In most persons, the plasma cholesterol level is affected very little by a recent meal. However, in some persons an increase of up to 100 mg/dL may be induced by a recent meal. The level of cholesterol in plasma is slightly lower than serum (approximately 3%) due to the fact that the liquid EDTA dilutes the plasma slightly and it somotically draws water out of the erythrocytes.

The method used for in this procedure utilizes the precipitating properties of phosphotungstate. Addition of the HDL precipitating reagent lowers the pH of the sample to the isoelectric point for the LDL and VLDL. LDL and VLDL molecules at pH 5.7 have overall electrical neutrality.

Phosphotungstate then selectively forms insoluble ligand complexes with LDL and VLDL. Differences in ionic strength forcefully precipitate these complexes. Centrifugation removes them, leaving the HDL fraction in the supernatant. The resulting supernatant cholesterol (HDL) is then assayed for cholesterol. Cholesterol esters in the sample are hydrolyzed by cholesterol esterase to cholesterol and free fatty acids. The cholesterol produced in the reaction plus the free cholesterol present in the sample, are oxidized by cholesterol oxidase to form cholesten-3-one and hydrogen peroxide. Peroxidase catalyzes the hydrogen peroxide oxidation and 4-aminoantipyrine (4-AAP) and phenol with subsequent coupling to 3,4-dichlorophenol.

The end product is a quinoneimine dye which is read at a primary wavelength of 520 nm. The color formation is