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ESCOBAR - URIBE ASOCIADOS
ABOGADOS

Carrera 11A No. 94-76 Of. 305 - P.O. Box 94948, Santafé de Bogotá, Colombia, S.A.
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SUPERINDUSTRIA Y COMERCIO
Radicacion : 00058780 00020001 Folios: 45
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Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

2356/P

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. 00058780
Solicitud de Patente en nombre de
THE PROCTER & GAMBLE COMPANY

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Santafé de Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad THE PROCTER & GAMBLE COMPANY solicitante de la patente de la referencia, reasumo expresamente el poder y anexo al presente memorial el siguiente documento:

Copia certificada de la solicitud de Patente Número 60/147,132 presentada en los Estados Unidos de América el día 4 de agosto de 1999, con la debida traducción de lo pertinente, incluyendo el capítulo reivindicatorio.

Señor Superintendente,

JIMENA ESCOBAR URIBE
C.C.39.779.452 de usaquén
T.P. 68228
Cód. 5376

X es O o S;

Y es O, S o NH;

V es alquilo C_4 o heteroalquilo M_4;

a es un enlace individual, enlace *doble cis*, o enlace doble *trans*,

b es un enlace individual, enlace doble trans, o enlace triple;

cuando a es un enlace individual, W es OH o $N(R_3)(OR_4)$; en donde R_3 se selecciona de H, alquilo inferior, o heteroalquilo inferior; en donde el alquilo inferior antes mencionado es no sustituido o sustituido con 1 a 3 sustituyentes aproximadamente que se seleccionan del grupo que consiste de: hidroxilo, halo, tiol, y nitrilo; y en donde el heteroalquilo inferior antes mencionado es no sustituido o sustituido con 1 a 3 sustituyentes aproximadamente que se seleccionan del grupo que consiste de: hidroxilo, halo, tiol, y nitrilo; y R_4 es H, alquilo inferior, o heteroalquilo inferior;

cuando a es un enlace doble *cis* o enlace doble *trans*, W es $N(OR_4)$; en donde R_4 es como se define anteriormente;

Z es alquilo C_1, heteroalquilo M_1, alquilo-G' C_m, heteroalquilo-G' M_n, alquilo-G" C_p, o heteroalquilo-G" M_q; en donde 1 es un número entero de 3 a 7, aproximadamente; m es un número entero de 0 a 5 aproximadamente; n es un número entero de 2 a 5, aproximadamente; p es un número entero de 0 a 3 aproximadamente; q es 2 o 3; G' es anillo alifático carbocíclico monocíclico, anillo alifático heterocíclico monocíclico, anillo aromático monocíclico o anillo heteroaromático monocíclico; G"

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anillo alifático heterocíclico, anillo aromático, o anillo heteroaromático;

X es O o S;

Y es O, S o NH;

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cuando a es un enlace doble *cis* o enlace doble *trans*, W es $N(OR_4)$; en donde R_4 es como se define anteriormente;

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monocíclico, anillo alifático heterocíclico monocíclico, anillo aromático monocíclico o anillo heteroaromático monocíclico; G" es un anillo alifático carboxíclico bicíclico, anillo alifático heterocíclico bicíclico, anillo aromático bicíclico o anillo heteroaromático bicíclico; y

cualquier sal farmacéticamente aceptable, o amida, éster, o imida biohidrolizable de esta.

7. El método de la Reivindicación 6 en donde el trastorno óseo antes mencionado es osteoporosis.

8. El método de la Reivindicación 7 en donde el trastorno óseo antes mencionado es osteoporosis postmenopáusico.

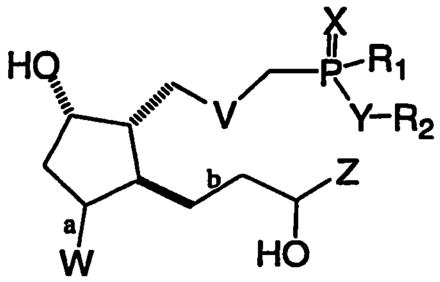
9. El método de la Reivindicación 7 en donde el trastorno óseo antes mencionado es osteoporosis inducido por cortocosteroide.

10. El método de la Reivindicación 6 en donde el trastorno óseo antes mencionado es osteopenia.

11. El método de la Reivindicación 6 en donde el trastorno óseo antes mencionado es una fractura ósea.

12. El método de la Reivindicación 6 en donde el compuesto antes mencionado se administra oralmente.

13. Un método de tratar glaucoma, el método antes mencionado comprende administrar a un humano u otro animal una cantidad segura y eficaz de un compuesto según la estructura:



monocíclico, arilo alifático heterocíclico monocíclico, arilo aromático monocíclico o arilo heteroaromático monocíclico; G" es un arilo alifático carbocíclico bicíclico, arilo alifático heterocíclico bicíclico, arilo aromático bicíclico o arilo heteroaromático bicíclico; y

cualquier sal farmacéuticamente aceptable, o amida, éster, o profármaco biohidrolizable de éstos.

7. El método de la Reivindicación 6 en donde el trastorno óseo antes mencionado es osteoporosis.

8. El método de la Reivindicación 7 en donde el trastorno óseo antes mencionado es osteoporosis postmenopáusica.

9. El método de la Reivindicación 7 en donde el trastorno óseo antes mencionado es osteoporosis inducida por corticoesteroide.

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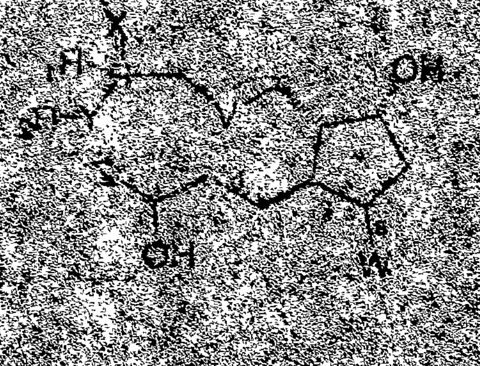

en donde

R_1 es H o alquilo inferior;

R_2 es H, alquilo, heteroalquilo, anillo alifático carbocíclico, anillo alifático heterocíclico, anillo aromático, o anillo heteroaromático;

X es O o S;

Y es O, S o NH;

V es alquilo C_4 o heteroalquilo M_4;

a es un enlace individual, enlace *doble cis*, o enlace doble *trans*,

b es un enlace individual, enlace doble trans, o enlace triple;

cuando a es un enlace individual, W es OH o $N(R_3)(OR_4)$; en donde R_3 se selecciona de H, alquilo inferior, o heteroalquilo inferior; en donde el alquilo inferior antes mencionado es no sustituido o sustituido con 1 a 3 sustituyentes aproximadamente que se seleccionan del grupo que consiste de: hidroxilo, halo, tiol, y nitrilo; y en donde el heteroalquilo inferior antes mencionado es no sustituido o sustituido con 1 a 3 sustituyentes aproximadamente que se seleccionan del grupo que consiste de: hidroxilo, halo, tiol, y nitrilo; y R_4 es H, alquilo inferior, o heteroalquilo inferior;

cuando a es un enlace doble *cis* o enlace doble *trans*, W es $N(OR_4)$; en donde R_4 es como se define anteriormente;

Z es alquilo C_1, heteroalquilo M_1, alquilo-G' C_m, heteroalquilo-G' M_n, alquilo-G" C_p, o heteroalquilo-G" M_q; en donde 1 es un número entero de 3 a 7, aproximadamente; m es un número

PA 270655

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

July 12, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/147,132***
FILING DATE: ***August 04, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. Williams
N. WILLIAMS
Certifying Officer

08/04/99

"Express Mail" mailing label number EJ302200997US

Date of Deposit August 4, 1999

I hereby certify that this paper/fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231

James C. Kellerman 43,708
Attorney mailing application Reg. No.

James C Kellerman
Signature of Attorney mailing application

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PTO/SB/16 (2-98)
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Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL PATENT APPLICATION under 37 CFR §1.53(c).

Docket Number	7702P	Type a plus sign (+) inside this box ⇒	+

JC511 U.S. PTO 60/147132 08/04/99

INVENTOR(s) / APPLICANT(s)			
FAMILY NAME OR SURNAME	GIVEN NAME (first name)	MIDDLE INITIAL (if any)	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
deLong	Mitchell	A.	West Chester, OH
Wos	John	A.	Cincinnati, OH
De	Biswanath	(NMN)	Cincinnati, OH
Ebetino	Frank	H.	Cincinnati, OH

TITLE OF THE INVENTION (280 characters max)

NOVEL 2-DECARBOXY-2-PHOSPHINICO PROSTAGLANDIN F ANALOGS

CORRESPONDENCE ADDRESS

James C. Kellerman
The Procter & Gamble Company
Health Care Research Center
8700 Mason Montgomery Road
Mason

STATE	OH	ZIP CODE	45040-8006	COUNTRY	USA

ENCLOSED APPLICATION PARTS *(check all that apply)*

x Specification Number of Pages: 33 + Abstract
_ Small Entity Statement
_ Drawing(s) Number of Sheets: _
_ Other (specify) _

METHOD OF PAYMENT *(check one)*

_ A check or money order is enclosed to cover the Provisional filing fees X The Commissioner is hereby authorized to charge filing fees specified under 37 CFR §1.19(f) and credit Deposit Account Number: 16-2480	PROVISIONAL FILING FEE AMOUNT(S)	$150.00

The invention was made by an agency of the United States Government or under a contract with an agency of United States Government.

X No
_ Yes, the name of the U. S. Government agency and the Government contract number are: ____________

Respectfully submitted,

SIGNATURE James C Kellerman Date August 4, 1999

TYPED or PRINTED NAME James C. Kellerman REGISTRATION NO. 43,708
(if appropriate)

_ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL PATENT APPLICATION FILING ONLY

Burden Hour Statement: This form is estimated to take .2 hours to complete. Time will vary depending upon the needs of the individual cases. Any comments on the amount of time you are required to complete this form should be sent to the Office of Assistance Quality and Enhancement Division, Patent and Trademark Office, Washington, DC 20231, and to the Office of Information and Regulatory Affairs, Office of Management and Budget (Project 0651-0037), Washington, DC 20503. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Patent Application; Assistant Commissioner for Patents, Washington, D.C. 20231.

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WO 99/12898; *Chem. Abstr.* 1999, *194116* "Molecular mechanisms of diverse actions of prostanoid receptors", *Biochimica et Biophysica Acta, 1259 (1995) 109-120*; U.S. Patent No. 3,776,938 issued to Bergstrom, S., and Sjovall,J., December 4, 1973; U.S. Patent No. 3,882,241 issued to Pharriss, G., May 6, 1975; G.B. Patent No. 1,456,512 (1976) issued to Pfizer Inc., Bundy, G.L.; Lincoln, F.H., "Synthesis of 17-Phenyl-18,19,20-trinor prostaglandins I. The PG1 Series", Prostaglandins Vol. 9 (1975) pp. 1-4.; CRC Handbook of Eicosanoids: Prostaglandins and Related Lipids Vol. 1, Chemical and Biochemical Aspects, Parts A & B, A.L. Willis, eds., CRC Press (1987); Liljebris, C.; et. al." Derivatives of 17-Phenyl-18,19,20-trinorprostaglandin F2α Isopropyl Ester: Potential Antiglaucoma Agents", Journal of Medicinal Chemistry Vol. 38, (1995), pp. 289-304; Collins, P.W.; Djuric, S.W. "Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs", Chemical Reviews 93 (1993), pp. 1533-1564.

All naturally occurring prostaglandins, including $PGF_{2\alpha}$, possess a carboxylic acid moiety at the C_1 position. The carboxylic acid moiety is a site for metabolic degradation by *beta* oxidation, which contributes to the rapid metabolism of the naturally occurring prostaglandins. Attempts to prevent *beta* oxidation by modifying the carboxylic acid moiety at the 1 position as an ester moiety, an amide moiety, a sulfonamide moiety, and as a tetrazole moiety are known in the art (See e.g. PCT Publication No. WO 99/12895, 1999; PCT Publication No. WO 99/12896, 1999; PCT Publication No. WO 99/12898). However, such modifications have either resulted in only modest increases in half-life (such as the esters) or resulted in compounds with diminished potency.

Prostaglandin F analogs wherein C_1 itself is replaced with a heteroatom have also been described in the art. For example, PGF analogs containing a sulfonic acid moiety at C_1 (The chemistry of prostaglandins containing the sulfo group. Iguchi, Y.; Kori, S.; Hayashi, M. *J. Org. Chem.*, 40, pp. 521-523 1975) and PGF analogs containing a phosphonic acid moiety at C_1 (The Synthesis of dimethylphosphonoprostaglandin analogs, Kluender, H. C. & Woessner, W. *Prostaglandins and Medicine*, 2: pp.441-444, 1979) have been disclosed. However, such compounds suffer from significantly diminished potency.

Further research in the area of heteroatom-containing C_1 replacements has been hampered by the lack of a general synthetic route to advanced or key intermediates that would allow for the rapid preparation of a multitude of variants to replace C_1. The Corey route to prostaglandins was specifically designed for a carboxcyclic acid moiety, and modifications which create reagents with relatively acidic protons are either incompatible with this route or cause significant

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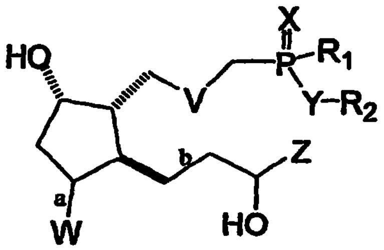
optimization of this difficult step for each new C_1 replacement. Syntheses of Prostaglandin F analogs via the Corey route are described in the following references: Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W *J. Am. Chem. Soc.*, 1969, *91*, 5675 and Corey, E. J.; Schaaf, T. K.; Huber, W; Koelliker, U.; Weinshenker, N. M.; *J. Am. Chem. Soc.*, 1970, *92*, 397.

Thus, while a few Prostaglandin F analogs wherein C_1 has been replaced with a heteroatom-containing moiety have been disclosed, there is a continuing need for suitable C_1 replacements that result in potent, selective Prostaglandin F analogs for the treatment of a variety diseases and conditions.

SUMMARY OF THE INVENTION

The invention provides novel Prostaglandin F analogs. In particular, the present invention is directed to compounds having a structure according to the following formula:



wherein R_1, R_2, X, Y, V, a, b, W, and Z are defined below.

This invention also includes optical isomers, diastereomers and enantiomers of the formula above, and pharmaceutically-acceptable salts, biohydrolyzable amides, esters, and imides thereof.

The compounds of the present invention are useful for the treatment of a variety of diseases and conditions, such as bone disorders and glaucoma. Accordingly, the invention further provides pharmaceutical compositions comprising these compounds. The invention still further provides methods of treatment for bone disorders and glaucoma using these compounds or compositions containing them.

DETAILED DESCRIPTION OF THE INVENTION

The invention is directed to novel 2-decarboxy-2-phosphinico Prostaglandin F analogs, pharmaceutical compositions comprising these compounds, and methods of treating a variety of disorders by administering these compounds.

conjunction of this difficult step for each new C_1 replacement. Syntheses of Prostaglandin F analogs via the Corey route are described in the following references: Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. J. Am. Chem. Soc. 1969, 91, 5675 and Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. J. Am. Chem. Soc. 1970, 92, 397.

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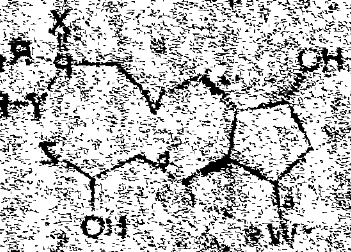

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Definitions and Usage of Terms

"Alkyl" is a saturated or unsaturated hydrocarbon chain. Unless otherwise specified (e.g. see "C_4 alkyl", "C_l alkyl", "C_m alkyl" and "C_p alkyl" below), alkyl chains have 1 to 18 carbon atoms, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4 carbon atoms. Alkyl chains may be straight or branched. Preferred branched alkyl have one or two branches, preferably one branch. Unsaturated alkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated alkyl have one or two double bonds or one triple bond, more preferably one double bond. Alkyl chains may be unsubstituted or substituted with from 1 to about 4 substituents unless otherwise specified. Preferred substituted alkyl are mono-, di-, or trisubstituted. Preferred alkyl substituents include cyano, halo, hydroxy, aryl (e.g., phenyl, tolyl, alkyloxphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, and heteroaryl.

"Aromatic ring" is an aromatic hydrocarbon ring system. Aromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic aromatic rings contain from about 5 to about 10 carbon atoms, preferably from 5 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic aromatic rings contain from 8 to 12 carbon atoms, preferably 9 or 10 carbon atoms in the ring. Aromatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred aromatic ring substituents include: halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include lower alkyl, cyano, halo and haloalkyl.

"Biohydrolyzable amide" is an amide moiety that does not interfere with the therapeutic activity of the compound, or that is readily metabolized by a human or other mammal.

"Biohydrolyzable ester" is an ester moiety that does not interfere with the therapeutic activity of the compound, or that is readily metabolized by a human or other mammal.

"Biohydrolyzable imide" is an imide moiety that does not interfere with the therapeutic activity of the compound, or that is readily metabolized by a human or other mammal.

"C_4 alkyl" is an alkyl chain having 4 carbon member atoms. C_4 alkyl may be staurated or unsaturated with one or two double bonds (*cis* or *trans*), one triple bond, or one double bond (*cis* or *trans*) and one triple bond. Preferred unsaturated C_4 alkyl have one double bond. C_4 alkyl may be unsubstituted or substituted with one or two substituents. Preferred substituents include lower alkyl, lower

heteroalkyl, cyano, halo, and haloalkyl. More preferred substituents are cyano and halo.

"C_l alkyl" is an alkyl chain having "l" carbon member atoms. C_l alkyl may be staurated or unsaturated with one *trans* double bond or one triple bond. Preferred C_l alkyl are saturated. Preferred unsaturated C_l alkyl have one *trans* double bond. C_l alkyl may be unsubstituted or substituted with from 1 to about 3 substituents. Preferred substituents include lower alkyl, lower heteroalkyl, cyano, halo, and haloalkyl.

"C_m alkyl" is an alkyl chain having "m" carbon member atoms. C_m alkyl may be staurated or unsaturated with one *trans* double bond or one triple bond. Preferred unsaturated C_m alkyl have one triple bond. C_m alkyl may be unsubstituted or substituted with one or two substituents. Preferred C_m alkyl are unsubstituted. Preferred substituents include lower alkyl, lower heteroalkyl, cyano, halo, and haloalkyl.

"C_p alkyl" is an alkyl chain having "p" carbon member atoms. C_p alkyl may be staurated or unsaturated with one *trans* double bond or one triple bond. Preferred unsaturated C_m alkyl have one triple bond. Unsaturated C_p alkyl are unsubstituted. Saturated C_p alkyl may be unsubstituted or substituted with one or two substituents. Preferred C_p alkyl are unsubstituted. Preferred substituents include lower alkyl, lower heteroalkyl, cyano, halo, and haloalkyl.

"Carbocyclic aliphatic ring" is a saturated or unsaturated hydrocarbon ring. Carbocyclic aliphatic rings are not aromatic. Carbocyclic aliphatic rings are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic carbocyclic aliphatic rings contain from about 4 to about 10 carbon atoms, preferably from 4 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic carbocyclic aliphatic rings contain from 8 to 12 carbon atoms, preferably from 9 to 10 carbon atoms in the ring. Carbocyclic aliphatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred carbocyclic aliphatic ring substituents include: halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred carbocyclic aliphatic rings include cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

"Halo" is fluoro, chloro, bromo or iodo. Preferred halo are fluoro, chloro and bromo; more preferred are chloro and fluoro.

"Haloalkyl" is a straight, branched, or cyclic hydrocarbon substituted with one or more halo substituents. Preferred haloalkyl are C_1-C_{12}; more preferred are

C_1-C_6; more preferred still are C_1-C_3. Preferred halo substituents are fluoro and chloro. The most preferred haloalkyl is trifluoromethyl.

"Heteroalkyl" is a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain from 1 to 18 member atoms (carbon and heteroatoms) in the chain, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated heteroalkyl have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to about 4 substituents unless otherwise specified. Preferred heteroalkyl are unsubstituted. Preferred heteroalkyl substituents include halo, aryl (e.g., phenyl, tolyl, alkyloxyphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, heteroaryl. For example, alkyl chains substituted with the following substituents are heteroalkyl: alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy), aryloxy (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, acyloxyphenoxy), acyloxy (e.g., propionyloxy, benzoyloxy, acetoxy), carbamoyloxy, carboxy, mercapto, alkylthio, acylthio, arylthio (e.g., phenylthio, chlorophenylthio, alkylphenylthio, alkoxyphenylthio, benzylthio, alkyloxycarbonylphenylthio), amino (e.g., amino, mono- and di- C_1-C_3 alkanylamino, methylphenylamino, methylbenzylamino, C_1-C_3 alkanylamido, carbamamido, ureido, guanidino).

"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms. As used herein, halogens are not heteroatoms.

"Heterocyclic aliphatic ring" is a saturated or unsaturated ring containing carbon and from 1 to about 4 heteroatoms in the ring, wherein no two heteroatoms are adjacent in the ring and no carbon in the ring that has a heteroatom attached to it also has a hydroxyl, amino, or thiol group attached to it. Heterocyclic aliphatic rings are not aromatic. Heterocyclic aliphatic rings are monocyclic, or are fused or bridged bicyclic ring systems. Monocyclic heterocyclic aliphatic rings contain from about 4 to about 10 member atoms (carbon and heteroatoms), preferably from 4 to 7, and most preferably from 5 to 6 member atoms in the ring. Bicyclic heterocyclic aliphatic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. Heterocyclic aliphatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred heterocyclic aliphatic ring

substituents include: halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred heterocyclic aliphatic rings include piperzyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperdyl.

"Heteroaromatic ring" is an aromatic ring system containing carbon and from 1 to about 4 heteroatoms in the ring. Heteroaromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaromatic rings contain from about 5 to about 10 member atoms (carbon and heteroatoms), preferably from 5 to 7, and most preferably from 5 to 6 in the ring. Bicyclic heteroaromatic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. Heteroaromatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred heteroaromatic ring substituents include: halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo, haloalkyl, and phenyl. Preferred heteroaromatic rings include thienyl, thiazolo, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred heteroaromatic rings include thienyl, furanyl, and pyridyl. The most preferred heteroaromatic ring is thienyl.

"Lower alkyl" is an alkyl chain comprised of 1 to 4, preferably 1 to 3 carbon member atoms, more preferably 1 or 2 carbon member atoms. Lower alkyl may be saturated or unsaturated. Preferred lower alkyl are saturated. Lower alkyl may be unsubstituted or substituted with one or about two substituents. Preferred substituents on lower alkyl include cyano, halo, triflouromethyl, and hydroxy.

"Lower heteroalkyl" is a heteroalkyl chain comprised of 1 to 4, preferably 1 to 3 member atoms, more preferably 1 to 2 member atoms. Lower heteroalkyl contain one or two heteroatom member atoms. Preferred lower heteroalkyl contain one heteroatom member atom. Lower heteroalkyl may be saturated or unsaturated. Preferred lower heteroalkyl are saturated. Lower heteroalkyl may be unsubstituted or substituted with one or about two substituents. Preferred substituents on lower heteroalkyl include cyano, halo, triflouromethyl, and hydroxy.

"M_4 heteroalkyl" is a heteroalkyl chain having 4 member atoms. M_4 heteroalkyl contain one or two heteroatom member atoms. M_4 heteroalkyl containing 1 heteroatom member atom may be saturated or unsaturated with one double bond (*cis* or *trans*) or one triple bond. Preferred M_4 heteroalkyl containing 2 heteroatom member atoms are saturated. Preferred unsaturated M_4 heteroalkyl have one double bond. M_4 heteroalkyl may be unsubstituted or substituted with one or two substituents. Preferred substituents include lower alkyl, lower heteroalkyl, cyano, halo, and haloalkyl.

substituents include halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred heterocyclic aliphatic rings include piperazyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperidyl.

"Heteroaromatic ring" is an aromatic ring system containing carbon and from 1 to about 4 heteroatoms in the ring. Heteroaromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaromatic rings contain from about 5 to about 10 member atoms (carbon and heteroatoms), preferably from 5 to 7, and most preferably from 5 to 6 in the ring. Bicyclic heteroaromatic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. Heteroaromatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred heteroaromatic ring substituents include halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo, haloalkyl, and phenyl. Preferred heteroaromatic rings include thienyl, thiazolo, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred heteroaromatic rings include thienyl, furanyl, and pyridyl. The most preferred heteroaromatic ring is thienyl.

"Lower alkyl" is an alkyl chain comprised of 1 to 4, preferably 1 to 3 carbon member atoms, more preferably 1 or 2 carbon member atoms. Lower alkyl may be saturated or unsaturated. Preferred lower alkyl are saturated. Lower alkyl may be unsubstituted or substituted with one or about two substituents. Preferred substituents on lower alkyl include cyano, halo, trifluoromethyl, and hydroxy.

"Lower heteroalkyl" is a heteroalkyl chain comprised of 1 to 4, preferably 1 to 3 member atoms, more preferably 1 to 2 member atoms. Lower heteroalkyl contain one or two heteroatom member atoms. Preferred lower heteroalkyl contain one heteroatom member atom. Lower heteroalkyl may be saturated or unsaturated. Preferred lower heteroalkyl are saturated. Lower heteroalkyl may be unsubstituted or substituted with one or about two substituents. Preferred substituents on lower heteroalkyl include cyano, halo, trifluoromethyl, and hydroxy.

"M_4 heteroalkyl" is a heteroalkyl chain having 4 member atoms. M_4 heteroalkyl contain one or two heteroatom member atoms. M_4 heteroalkyl containing 1 heteroatom member atom may be saturated or unsaturated with one double bond (cis or trans) or one triple bond. Preferred M_4 heteroalkyl containing 2 heteroatom member atoms are saturated. Preferred unsaturated M_4 heteroalkyl have one double bond. M_4 heteroalkyl may be unsubstituted or substituted with one or two substituents. Preferred substituents include lower alkyl, lower heteroalkyl, cyano, halo, and haloalkyl.

"M_l heteroalkyl" is a heteroalkyl chain having "l" member atoms. M_l heteroalkyl contain one or two heteroatom member atoms. Preferred M_l heteroalkyl have one heteroatom member atom. M_l heteroalkyl may be saturated or unsaturated with one *trans* double bond or one triple bond. Preferred M_l heteroalkyl are saturated. M_l heteroalkyl may be unsubstituted or substituted with from 1 to about 3 substituents. Preferred substituents include lower alkyl, lower heteroalkyl, and haloalkyl.

"M_n heteroalkyl" is a heteroalkyl chain having "n" member atoms. M_n heteroalkyl contain one heteroatom member atom. M_n heteroalkyl may be staurated or unsaturated with one triple bond. Preferred M_n heteroalkyl are saturated. M_n heteroalkyl may be unsubstituted or substituted with one or two substituents. Preferred substituents include lower alkyl, lower heteroalkyl, and haloalkyl.

"M_q heteroalkyl" is a heteroalkyl chain having "q" member atoms. M_q heteroalkyl contain one heteroatom member atom. M_q heteroalkyl are staurated. M_q heteroalkyl may be unsubstituted or substituted with one or two substituents. Preferred substituents include lower alkyl, lower heteroalkyl, cyano, halo, and haloalkyl.

"Member atom" refers to a polyvalent atom (C, O, N, or S atom) in a chain or ring system that continues the chain or ring system. For example, in benzene the six carbon atoms are member atoms and the six hydrogen atoms are not member atoms.

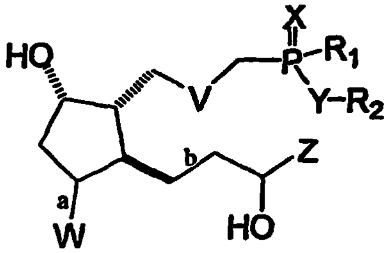
"Pharmaceutically-acceptable salt" refers to a cationic salt formed at any acidic (e.g., hydroxamic acid) group, or an anionic salt formed at any basic (e.g., amino) group. Such salts are well known in the art. See e.g: World Patent Publication 87/05297, Johnston et al., published September 11, 1987, incorporated herein by reference. Such salts are made by methods known to one of ordinary skill in the art. It is recognized that the skilled artisan may prefer one salt over another for improved solubility, stability, formulation ease, price and the like. Determination and optimization of such salts is within the purview of the skilled artisan's practice. Preferred cationic salts include the alkali metal salts (such as sodium and potassium), and alkaline earth metal salts (such as magnesium and calcium) and organic salts. Preferred anionic salts include the halides (such as chloride salts), sulfonates, carboxylates, phosphates, and the like. Clearly contemplated in such salts are addition salts that may provide an optical center where once there was none. For example, a

chiral tartrate salt may be prepared from the compounds of the invention. This definition includes such chiral salts.

"Phenyl" is a six-membered monocyclic aromatic ring which may or may not be substituted with from about 1 to about 4 substituents. The substituents may be substituted at the *ortho*, *meta* or *para* position on the phenyl ring, or any combination thereof. Preferred phenyl substituents include: halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents on the phenyl ring include halo and haloalkyl. The most preferred substituent is halo.

Compounds

The invention involves compounds having the following structure:



Formula I

In **Formula I** above, R_1 is H or lower alkyl. Preferred R_1 is lower alkyl. More preferred R_1 is methyl and ethyl. The most preferred R_1 is methyl.

In **Formula I** above, R_2 is H, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred R_2 is H and alkyl. More preferred R_2 is H and lower alkyl.

In **Formula I** above, X is O or S. Preferred X is O.

In **Formula I** above, Y is O, S or NH. Preferred Y is O and NH. The most preferred Y is O.

In **Formula I** above, V is C_4 alkyl or M_4 heteroalkyl. Preferred V is C_4 alkyl. More preferred V is unsubstituted C_4 alkyl.

In **Formula I** above, a is single bond, *cis* double bond, or *trans* double bond.

In **Formula I** above, b is single bond, *trans* double bond, or triple bond.

In **Formula I** above, when a is single bond, W is OH or $N(R_3)(OR_4)$; wherein R_3 is H, lower alkyl, or lower heteroalkyl and R_4 is H, lower alkyl, or lower heteroalkyl. Preferred R_3 is H and lower alkyl. More preferred R_3 is H and methyl.

Preferred R_4 is H and lower alkyl. More preferred R_4 is H and methyl. The most preferred R_4 is H.

In Formula I above, when a is *cis* double bond or *trans* double bond, W is $N(OR_4)$; wherein R_4, is as defined above.

In Formula I above, Z is C_l alkyl, M_l heteroalkyl, C_m alkyl-G', M_n heteroalkyl-G', C_p alkyl-G", or M_q heteroalkyl-G"; wherein l is an integer from about 3 to about 7, preferably from about 4 to about 7; m is an integer from 0 to about 5, preferably from about 1 to about 4, more preferably still about 2 or 3, most preferably 2; n is an integer from about 2 to about 5, preferably about 2 or 3; p is an integer from 0 to about 3, preferably 0 to about 2, more preferably 0 or about 1; q is 2 or 3, preferably 2; G' is monocyclic carbocyclic aliphatic ring, monocyclic heterocyclic aliphatic ring, monocyclic aromatic ring, or monocyclic heteroaromatic ring; G" is bicyclic carbocyclic aliphatic ring, bicyclic heterocyclic aliphatic ring, bicyclic aromatic ring, or bicyclic heteroaromatic ring. Preferred G' is monocyclic aromatic ring or monocyclic heteroaromatic ring. Preferred G" is bicyclic aromatic ring or bicyclic heteroaromatic ring.

The invention includes pharmaceutically-acceptable salts, or biohydrolyzable amides, esters, or imides of the above structure. The invention also includes optical isomers, diastereomers and enantiomers of the above structure. Thus, at all stereocenters where stereochemistry is not defined (e.g. C_{11} and C_{15}), both epimers are envisioned. Preferred stereochemistry at C_{11} and C_{15} mimics that of naturally occurring $PGF_{2\alpha}$.

It has been discovered that the novel PGF analogs of the subject invention are useful for treating bone disorders, especially those that require a significant increase in bone mass, bone volume, or bone strength. Surprisingly, the compounds of the subject invention have been found to provide the following advantages over known bone disorder therapies: (1) An increase trabecular number through formation of new trabeculae; (2) An increase in bone mass and bone volume while maintaining a more normal bone turnover rate; and/or (3) An increase in bone formation at the endosteal surface without increasing cortical porosity.

In order to determine and assess pharmacological activity, testing of the subject compounds in animals is carried out using various assays known to those skilled in the art. For example, the bone activity of the subject compounds can be conveniently demonstrated using an assay designed to test the ability of the subject compounds to increase bone volume, mass, or density. An example of such assays is the ovariectomized rat assay.

b. 6-(5-(2-fluorophenyl)-3-hydroxypent-1-enyl)-7-benzyloxy-2-oxabicyclo [3.3.0] octan-3-one (E1c): In a flame-dried round-bottomed flask equipped with a stirbar, **E1b** (1.0 equiv.) and cerium trichloride (1.05 equiv.) are placed in methanol. The solution is stirred at room temperature for 5 minutes. The solution is then cooled to -10°C and sodium borohydride (1.02 equiv.) in methanol is added slowly. The solution is stirred at -10°C for 3 hours. The mixture is treated with water and the pH brought between 6 and 7 with 1N hydrochloric acid. The mixture is extracted twice with ethyl acetate, and the organic layers are combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification is effected by silica gel column chromatography (3-5 % methanol in dichloromethane) to give the 15 (*R*) epimer and the 15 (*S*) epimer of 6-(5-(2-fluorophenyl)-3-hydroxypent-1-enyl)-7-benzyloxy-2-oxabicyclo [3.3.0] octan-3-one **(E1c)**.

c. 2-decarboxy-2-bromo 11-benzoyl, -15-tert-butyl dimethylsilyl 17-trinor-17-(2-fluorophenyl) $PGF_{2\alpha}$ (E1d): In a round-bottomed flask with a magnetic stir bar, a solution of **E1c** (1 equiv.) is stirred in CH_2Cl_2. To this solution, 2,6-lutidine (1.9 equiv.) is added dropwise at -78°C followed by tertbutyldimethylsilyltriflate (TBDMSOTf) (1.8 equiv.). The reaction is stirred for 30 minutes at -78°C and then warmed to 25°C overnight. The reaction is then quenched with water. The organic layer is washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to give a product which is subjected to flash chromatography on silica gel eluting with hexanes then 1% MeOH in CH_2Cl_2. The product is then washed with 0.1N HCl, water, and brine and then thoroughly dried. Separately, to a suspension of (4-bromobutyl) triphenylphosphonium bromide (2.2 equiv) in THF at 0°C under N_2, a solution of KHMDS (4.4 equiv.) is added dropwise. The resulting reaction mixture is stirred for 1 hour at 25°C. To the reaction mixture above at -78°C is added a solution of the dried silyl-protected product (1 equiv.) in THF. The reaction mixture is allowed to warm to 25°C overnight. The reaction is quenched with water at 0°C and the pH is adjusted to 3.5-4.0 with 1N HCl. The water phase is extracted with EtOAc and the combined organic phase is dried over $MgSO_4$ and concentrated *in vacuo* to give the crude alkene, which is purified *via* flash chromatography on silica gel eluting with 30% EtOAc in hexanes yielding 2-decarboxy-2-bromo 11-benzoyl, -15-*tert*-butyldimethylsilyl-17-trinor-17-(2-fluorophenyl) $PGF_{2\alpha}$ **(E1d)**.

d. 5-(3-silyloxy-5-(2-fluorophenyl)pent-1-enyl)-4-(6-(methyl (ethoxyphosphoryl))hex-2-enyl)-1-benzoyloxy-3-hydroxy-cyclopentane (E1e): A mixture of **E1d**, diethyl methylphosphonite, and toluene is stirred at 100°C for 6 hours. The solvents are evaporated and the residue is purified by dry-flash column

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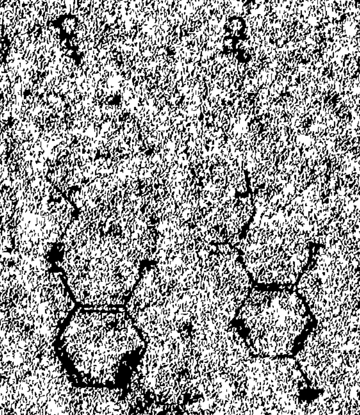
chromatography (SiO_2, 5–25% 2-propanol in 20% dichloromethane–hexane). Appropriate fractions are concentrated, diluted with water, and extracted with ether three times. The combined extracts are washed with water, dried (brine, then filtered over Na_2SO_4), and evaporated to give 5-(3-silyloxy-5-(2-fluorophenyl)pent-1-enyl)-4-(6-(methyl(ethoxyphosphoryl))hex-2-enyl) -1-benzoyloxy- 3-hydroxy-cyclopentane (E1e).

e. 5-(3-hydroxy-5-(2-fluorophenyl)pent-1-enyl)-4-(6-(methyl(hydroxyphosphoryl))hex-2-enyl)cyclopentane-1,3-diol, sodium salt (E1f): Without further purification to the crude reaction mixture of the 2-decarboxy-2-(*O*-ethyl-*P*-methylphosphinico) prostaglandin derivative E1e, 3 mL of acetonitrile and 1.1 equivalents of HF/Pyridine are added while the flask is kept at 0°C. After 3 hours at 0°C, the reaction is quenched with saturated aqueous NaCl. The aqueous layer is extracted three times with CH_2Cl_2. The organic layers are combined and washed three times with 1N HCl, brine, and dried over sodium sulfate. After column chromatography, (7:3, Hexane: ethyl acetate) the silyl-free product is obtained. To this is added 95% ethanol and 2.5 M aqueous sodium hydroxide and is stirred at reflux for 3 hours. The ethanol is evaporated and the residue is diluted with water and is washed with ethyl acetate two times. The combined washes are extracted with water, the combined aqueous phases are then acidified with 2.5M aqueous hydrochloric acid and extracted with ethyl acetate five times. The combined extracts are dried (brine, Na_2SO_4) and evaporated to give 5-(3-hydroxy-5-(2-fluorophenyl)pent-1-enyl)-4-(6-(methyl(hydroxyphosphoryl))hex-2-enyl)cyclopentane-1,3-diol, sodium salt **(E1f)**.

chromatography (SiO$_2$, 5-25% 2-propanol in 20% dichloromethane-hexane). Appropriate fractions are concentrated, diluted with water, and extracted with ether three times. The combined extracts are washed with water, dried (brine, then tumbled over Na$_2$SO$_4$), and evaporated to give 6-(tert-butoxy-(2-fluorophenyl)pent-1-enyl)-4-(6-(methylethylsulfonyl)amino)hex-2-enyl)-1-benzyloxy-3-hydroxy-cyclopentane (E10).

e. 3-[(2-hydroxy-5-(2-fluorophenyl)pent-1-enyl]-4-(6-(methyl)ethylsulfonylamino)hex-2-enyl)cyclopentane-1,3-diol, sodium salt (E11).

Without further purification to the crude reaction mixture of the 2-decarboxy-2-(O-allyl-P-methylphosphono) prostaglandin derivative E10, 3 mL of acetonitrile and 1.1 equivalents of HF/Pyridine are added while the flask is kept at 0°C. After 3 hours at 0°C, the reaction is quenched with saturated aqueous NaCl. The aqueous layer is extracted three times with CH$_2$Cl$_2$. The organic layers are combined and washed three times with 1N HCl, brine, and dried over sodium sulfate. After column chromatography (SiO$_2$, Hexane: ethyl acetate) the silyl-free product is obtained. To this is added 95% ethanol and 2.5 M aqueous sodium hydroxide and is stirred at 15°C for 6 hours. The ethanol is evaporated and the residue is diluted with water and is washed with ethyl acetate two times. The combined washes are extracted with water, the combined aqueous phases are then acidified with 2.5M aqueous hydrochloric acid and extracted with ethyl acetate five times. The combined extracts are dried (brine, Na$_2$SO$_4$) and evaporated to give 6-(3-hydroxy-5-(2-fluorophenyl)pent-1-enyl)-4-(methyl(hydroxy)phosphoryl)hex-2-enyl)cyclopentane-3,5-diol, sodium salt (E11).



1 M aqueous hydrochloric acid and is then extracted with ethyl acetate five times. The combined extracts are dried (brine, Na_2SO_4) and evaporated to give 16-phenoxy-16-tetranor-PGF$_{2\alpha}$ triacetate (**E10b**).

b. 2-decarboxy-2-iodo-16-phenoxy-16-tetranor-PGF$_{2\alpha}$ triacetate (E10c): Oxalyl chloride is added to a solution of 16-phenoxy-16-tetranor-PGF$_{2\alpha}$ triacetate (**E10b**) and dimethylformamide in dichloromethane. The mixture is allowed to stand at room temperature for 30 minutes and is then concentrated. The residue is taken up in dichloromethane. Separately, a mixture of the sodium salt of *N*-hydroxypyridine-2-thione, DMAP, and dichloromethane under argon is brought to reflux by irradiation with a 250 Watt General Electric floodlamp. To this mixture is added 1,1,1-trifluoro-2-iodoethane, followed by the solution of acid chloride which is added over 15 minutes. Irradiation is continued for 45 minutes and then the mixture is concentrated and purified by dry-flash column chromatography (SiO_2, 5–45% ethyl acetate–hexane) to give 2-decarboxy-2-iodo-16-phenoxy-16-tetranor-PG$_{2\alpha}$ triacetate (**E10c**).

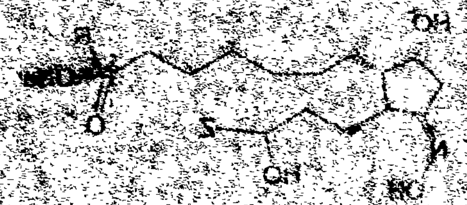
c. 2-decarboxy-2-(*O*-ethyl-*P*-methylphosphinico)-16- phenoxy-16-tetranor-PGF$_{2\alpha}$ (E10d): A mixture of **E10c**, diethyl methylphosphonite, and toluene is stirred at 100°C for 7 hours. The solvents are evaporated and the residue is purified by SiO_2 column chromatography (5-25% 2-propanol in 20% dichloromethane-hexane). Appropriate fractions are concentrated, diluted with water and extracted with ethyl acetate three times. The combined extracts are washed with water, dried (brine, Na_2SO_4), and evaporated to give 2-decarboxy-2-(*O*-ethyl-*P*-methylphosphinico)-16-phenoxy-16-tetranor-PGF$_{2\alpha}$ triacetate (**E10d**).

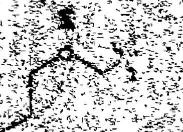
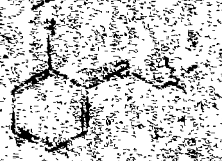
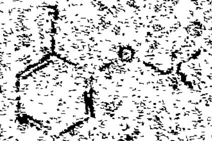
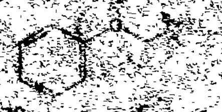
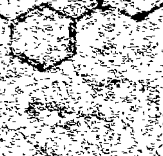
d. 5-(3-hydroxy-4-phenoxybut-1-enyl)-4-(6-(methyl(hydroxyphosphoryl))hex-2-enyl)cyclopentane-1,3-diol, sodium salt (E10e): A mixture of **E10d**, 95% ethanol, and 2.5M aqueous sodium hydroxide is stirred at reflux for 3 hours. The mixture is diluted with water and is washed with ethyl acetate two times. The combined washes are extracted with water. The combined aqueous phases are acidified with 1M aqueous hydrochloric acid and extracted with ethyl acetate four times. The combined extracts are dried (brine, Na_2SO_4) and are evaporated. The residue is taken up in methanol and stirred with Amberlite CG-50 (Na^+ form) for 15 minutes. The resin is removed by filtration and the filtrate is concentrated to give 5-(3-hydroxy-4-phenoxybut-1-enyl)-4-(6-(methyl(hydroxyphosphoryl))hex-2-enyl)cyclopentane-1,3-diol, sodium salt (**E10e**).

reaction is cooled to room temperature and the solvent removed. The organic extracts are combined and chromatographed and the crude product is stirred overnight with hydroxylamine and sodium acetate (1:8) in 1:1:3 p-dioxane: water: methanol. The residue is taken up in methanol and stirred with Amberlite CG-50 (H+ form) for 16 min. The resin is removed by filtration and the filtrate is concentrated to give 3-hydroxy-4-(hexoxybutyl)-4-(6-(methylhydroxycarbonyl)hexyl)-1-oximyl-cyclopentane sodium salt (32).

Examples 33-37

Examples 33-37 are prepared using substantially the same procedure as that described in Example 32, substituting the appropriate starting materials. The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan may use protecting groups to block side reactions or increase yields as appropriate. All such modifications can readily be carried out by the skilled artisan in the art of organic chemistry, and thus are within the scope of the invention.



Example	R_1	R_2
33	CH_3	
34	CH_3	
35	CH_3	
36	CH_2CH_3	
37	CH_2CH_3	

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acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

In addition to the compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a subject. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the subject being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as cornstarch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, cellulose acetate; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid, magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the Tweens®; wetting agents such as sodium lauryl sulfate; coloring agents; flavoring agents, excipients; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

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The choice of a pharmaceutically-acceptable carrier to be used in conjunction with a compound is basically determined by the way the compound is to be administered. The compounds of the present invention may be administered systemically. Routes of administration include transdermal; oral; parenterally, including subcutaneous or intravenous injection; topical; and/or intranasal.

The appropriate amount of the compound to be used may be determined by routine experimentation with animal models. Such models include, but are not limited to the intact and ovariectomized rat models, the ferret, canine, and non human primate models as well as disuse models.

Preferred unit dosage forms for injection include sterile solutions of water, physiological saline, or mixtures thereof. The pH of said solutions should be adjusted to about 7.4. Suitable carriers for injection or surgical implants include

hydrogels, controlled- or sustained release devises, polylactic acid, and collagen matrices.

Suitable pharmaceutically-acceptable carriers for topical application include those suited for use in lotions, creams, gels and the like. If the compound is to be administered perorally, the preferred unit dosage form is tablets, capsules and the like. The pharmaceutically-acceptable carriers suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Their selection will depend on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be made without difficulty by those skilled in the art.

Methods of Use

The compounds of the present invention are useful in treating many medical disorders, including for example, bone disorders and ocular disorders.

It is believed that the compounds of the present invention are useful in increasing bone volume and trabecular number through formation of new trabeculae, increasing bone mass while maintaining a normalized bone turnover rate, and formation of bone at the endosteal surface without removing bone from the existing cortex. Thus, it is further believed that these compounds are useful in the treatment and prevention of bone disorders.

The preferred routes of administration for treating bone disorders are oral, transdermal, and intranasal. Other preferred routes of administration include rectal, and sublingual.

The dosage range of the compound for systemic administration is from about 0.01 to about 1000 μg/kg body weight, preferably from about 0.1 to about 100 μg/kg per body weight, most preferably from about 1 to about 50 μg/kg body weight per day. The transdermal dosages will be designed to attain similar serum or plasma levels, based upon techniques known to those skilled in the art of pharmacokinetics and transdermal formulations. Plasma levels for systemic administration are expected to be in the range of 0.01 to 100 nanograms/ml, more preferably from 0.05 to 50 ng/ml, and most preferably from 0.1 to 10 ng/ml. While these dosages are based upon a daily administration rate, weekly or monthly accumulated dosages may also be used to calculate the clinical requirements.

Dosages may be varied based on the patient being treated, the condition being treated, the severity of the condition being treated, the route of administration, etc. to achieve the desired effect.