

ESCOBAR - URIBE ASOCIADOS

A B O G A D O S

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SUPERINDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E.

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D.

Re: Expediente No. 00016009

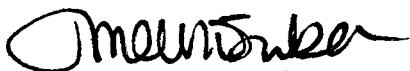
Solicitud de Patente en nombre de

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, anexo al presente memorial el siguiente documento:

Copia certificada de la solicitud de Patente Número 60/123,063 presentada en los Estados Unidos de América el día 5 de marzo 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

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ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE LLEGUE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

Febrero 14, 2000

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 60/123,063

Fecha de Presentación: Marzo 05, 1999

Por la autoridad del
Comisionado de Patentes y Marcas

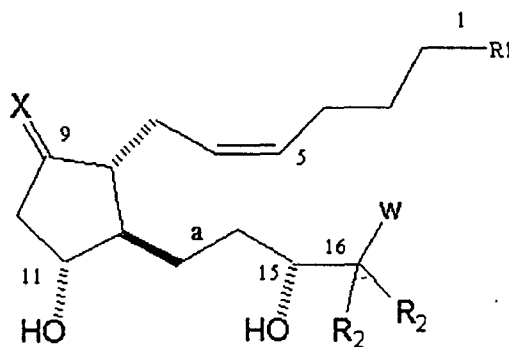
(fdo) H. L. JACKSON
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América.

REIVINDICACIONES

1. Un método de aumentar el volumen óseo, que comprende administrar a un sujeto una cantidad eficaz de un agonista EP_1 selectivo que no ocurre naturalmente.
2. El método de la Reivindicación 1 en donde el agonista EP_1 que no ocurre naturalmente es selectivo para el receptor EP_1 sobre otros receptores de prostaglandina excitatorios en una relación de por lo menos 1:10.
3. El método de la Reivindicación 2 en donde el agonista EP_1 que no ocurre naturalmente es adicionalmente selectivo sobre todos los otros receptores prostanoideos en una relación de por lo menos 1:10.
4. El método de la Reivindicación 3 en donde el agonista EP_1 que no ocurre naturalmente es selectivo para el receptores EP_1 sobre otros receptores de prostaglandina excitatorios en una relación de por lo menos 1:20.
5. El método de la Reivindicación 4 en donde el agonista EP_1 que no ocurre naturalmente es adicionalmente selectivo sobre todos los otros receptores prostanoideos en una relación de por lo menos 1:20.
6. El método de la Reivindicación 5 en donde el agonista EP_1 que no ocurre naturalmente es selectivo para todos los otros receptores de prostaglandina excitatorios en una relación de por lo menos 1:50.
7. El método de la Reivindicación 6 en donde el agonista EP_1 que no ocurre naturalmente es adicionalmente selectivo para todos los otros receptores prostanoideos en una relación de por lo menos 1:50.
8. El método de la Reivindicación 7 en donde el agonista EP_1 que no

ocurre naturalmente es un análogo de prostaglandina.

9. El método de la Reivindicación 8 en donde el agonista EP₁ que no ocurre naturalmente se administra transdérmicamente.
10. El método de la Reivindicación 8 en donde el análogo de prostaglandina tiene la fórmula general:



en donde:

R₁ es CO₂H, C(O)NHOH, CO₂R₃, CH₂OH, S(O)₂R₃, o C(O)NHR₃; que se caracteriza en que R₃ independientemente es alquilo, heteroalquilo, anillo alifático carbocíclico, anillo alifático heterocíclico, anillo aromático, o anillo heteroaromático;

X es CH₂, O, o N-OH₄; en donde R₄ es hidrógeno o alquilo inferior;

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

cada R₂ independientemente es hidrógeno o alquilo inferior.

W es:

- (a) [C(R₅)(R₅)]_m-Y-[C(R₅)(R₅)]_n-Z; en donde cada R₅ independientemente es hidrógeno, alquilo inferior, alcoxi, o halo; m es un número entero de 0 a 1 aproximadamente, n es un número entero de 0 a 1 aproximadamente; Y es C(R₅)(R₅), o, NH, S o un enlace covalente; y Z es fenilo, tienilo, o furanilo, el fenilo, tienilo, o furanilo antes mencionado están sustituidos o sustituidos con 1 o

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2 halógenos;

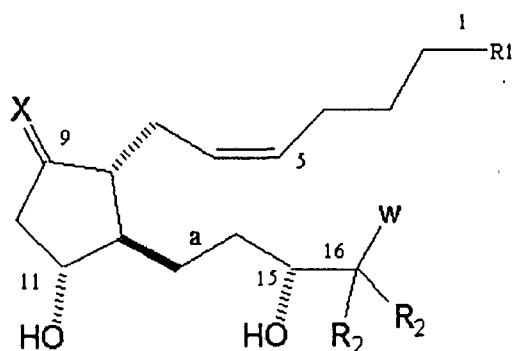
o (b) $[C(R_5)(R_5)]_p-U-[C(R_5)(R_5)]_q$; en donde cada R_5 es como se define anteriormente; p es un número entero de 0 a 3 aproximadamente, q es un número entero de 1 a 3 aproximadamente, y p + q es de 1 a 4, aproximadamente; y U es $C(R_5)(R_5)$, o, NH, o S; y

cualquier isómeros ópticos, diastereómeros, enantiómeros de la estructura anterior o una farmacéuticamente aceptable, o una amida biohidrolizable, éster, o imida de estos.

11. El método de la Reivindicación 8 en donde el análogo de prostaglandina se selecciona del grupo que consiste de 17-fenil-17-trinor PGE_2 , 9-metilen-9-deoxi PEG_2 , y 9-metilen-9-deoxi-16,16-dimetilo PGE_2 .
12. El método de la Reivindicación 8 en donde el análogo de prostaglandina es 17-fenil trinor PGE_2 .
13. El método de la Reivindicación 12 en donde el 17-fenil trinor PGE_2 se administra transdérmicamente.
14. Un método de aumentar el número trabecular, que comprende administrar a un sujeto una cantidad terapéuticamente eficaz de un agonista EP_1 que no ocurre naturalmente.
15. El método de Reivindicación 14 en donde el agonista EP_1 que no ocurre naturalmente es selectivo para el receptor EP_1 sobre otros receptores de prostaglandina excitatorios en una relación de por lo menos 1:10.
16. El método de Reivindicación 15 en donde el agonista EP_1 que no ocurre naturalmente es adicionalmente selectivo sobre todos los otros

receptores prostanoïdes en una relación de por lo menos 1:10.

17. El método de Reivindicación 16 en donde el agonista EP_1 que no ocurre naturalmente es selectivo para el receptor EP_1 sobre otros receptores de prostaglandina excitatorios en una relación de por lo menos 1:20.
18. El método de Reivindicación 17 en donde el agonista EP_1 que no ocurre naturalmente es adicionalmente selectivo sobre todos los otros receptores prostanoïdes en una relación de por lo menos 1:20.
19. El método de Reivindicación 18 en donde el agonista EP_1 que no ocurre naturalmente es selectivo para el receptor EP_1 sobre otros receptores de prostaglandina excitatorios en una relación de por lo menos 1:50.
20. El método de Reivindicación 19 en donde el agonista EP_1 que no ocurre naturalmente es adicionalmente selectivo sobre todos los otros receptores prostanoïdes en una relación de por lo menos 1:50.
21. El método de Reivindicación 20 en donde el agonista EP_1 que no ocurre naturalmente es un análogo de prostaglandina.
22. El método de Reivindicación 21 en donde el agonista EP_1 que no ocurre naturalmente se administra transdérmicamente.
23. El método de la Reivindicación 21 en donde el análogo de prostaglandina tiene la fórmula general:



en donde:

R_1 es CO_2H , $C(O)NHOH$, CO_2R_3 , CH_2OH , $S(O)_2R_3$, o $C(O)NHR_3$; que se caracteriza en que R_3 independientemente es alquilo, heteroalquilo, anillo alifático carbocíclico, anillo alifático heterocíclico, anillo aromático, o anillo heteroaromático;

X es CH_2 , O , o $N-OH_4$; en donde R_4 es hidrógeno o alquilo inferior;

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

cada R_2 independientemente es hidrógeno o alquilo inferior.

W es:

(a) $[C(R_5)(R_5)]_m-Y-[C(R_5)(R_5)]_n-Z$; en donde cada R_5 independientemente es hidrógeno, alquilo inferior, alcoxi, o halo; m es un número entero de 0 a 1 aproximadamente, n es un número entero de 0 a 1 aproximadamente; Y es $C(R_5)(R_5)$, o, NH , S o un enlace covalente; y Z es fenilo, tienilo, o furanilo, el fenilo, tienilo, o furanilo antes mencionado están sustituidos o sustituidos con 1 o 2 halógenos;

o (b) $[C(R_5)(R_5)]_p-U-[C(R_5)(R_5)]_q$; en donde cada R_5 es como se define anteriormente; p es un número entero de 0 a 3 aproximadamente, q es un número entero de 1 a 3 aproximadamente, y $p + q$ es de 1 a 4, aproximadamente; y U es $C(R_5)(R_5)$,

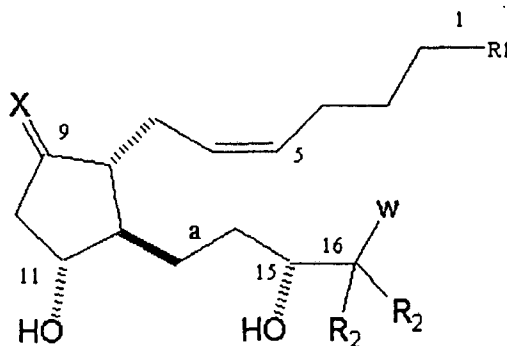
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o, NH, o S; y

cualquier isómeros ópticos, diastereómeros, enantiómeros de la estructura anterior o una farmacéuticamente aceptable, o una amida biohidrolizable, éster, o imida de estos.

24. El método de la Reivindicación 21 en donde el análogo de prostaglandina se selecciona del grupo que consiste de 17-fenil-17-trinor PGE_2 , 9-metilen-9-deoxi PGE_2 , y 9-metilen-9-deoxi-16,16-dimetilo PGE_2 .
25. El método de la Reivindicación 21 en donde el análogo de prostaglandina es 17-fenil trinor PGE_2 .
26. El método de la Reivindicación 25 en donde el 17-fenil trinor PGE_2 se administra transdérmicamente.
27. Un método de tratar un trastorno óseo, que comprende administrar a un sujeto una cantidad terapéuticamente eficaz de un agonista EP_1 que no ocurre naturalmente
28. El método de la Reivindicación 27 en donde el agonista EP_1 que no ocurre naturalmente es selectivo para el receptor EP_1 sobre otros receptores de prostaglandina excitatorios en una relación de por lo menos 1:10.
29. El método de la Reivindicación 28 en donde el agonista EP_1 que no ocurre naturalmente es adicionalmente selectivo sobre todos los otros receptores prostanoides en una relación de por lo menos 1:10.
30. El método de la Reivindicación 29 en donde el agonista EP_1 que no ocurre naturalmente es selectivo para el receptores EP_1 sobre otros receptores de prostaglandina excitatorios en una relación de por lo menos 1:20.

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31. El método de la Reivindicación 30 en donde el agonista EP₁ que no ocurre naturalmente es adicionalmente selectivo sobre todos los otros receptores prostanoideos en una relación de por lo menos 1:20.
 32. El método de la Reivindicación 31 en donde el agonista EP₁ que no ocurre naturalmente es selectivo para el receptor EP₁ sobre otros receptores de prostaglandina excitatorios en una relación de por lo menos 1:50.
 33. El método de la Reivindicación 32 en donde el agonista EP₁ que no ocurre naturalmente es adicionalmente selectivo para todos los otros receptores prostanoideos en una relación de por lo menos 1:50.
 34. El método de la Reivindicación 33 en donde el agonista EP₁ que no ocurre naturalmente es un análogo de prostaglandina.
 35. El método de la Reivindicación 34 en donde el agonista EP₁ que no ocurre naturalmente se administra transdérmicamente.
 36. El método de la Reivindicación 34 en donde el análogo de prostaglandina tiene la fórmula general:



en donde:

R₁ es CO₂H, C(O)NHOH, CO₂R₃, CH₂OH, S(O)₂R₃, o C(O)NHR₃; que se caracteriza en que R₃ independientemente es alquilo, heteroalquilo, anillo alifático carbocíclico, anillo alifático

heterocíclico, anillo aromático, o anillo heteroaromático;

X es CH₂, O, o N-OH₄; en donde R₄ es hidrógeno o alquilo inferior;

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

cada R₂ independientemente es hidrógeno o alquilo inferior.

W es:

(a) [C(R₅)(R₅)]_m-Y-[C(R₅)(R₅)]_n-Z; en donde cada R₅ independientemente es hidrógeno, alquilo inferior, alcoxi, o halo; m es un número entero de 0 a 1 aproximadamente, n es un número entero de 0 a 1 aproximadamente; Y es C(R₅)(R₅), o, NH, S o un enlace covalente; y Z es fenilo, tienilo, o furanilo, el fenilo, tienilo, o furanilo antes mencionado están sustituidos o sustituidos con 1 o 2 halógenos;

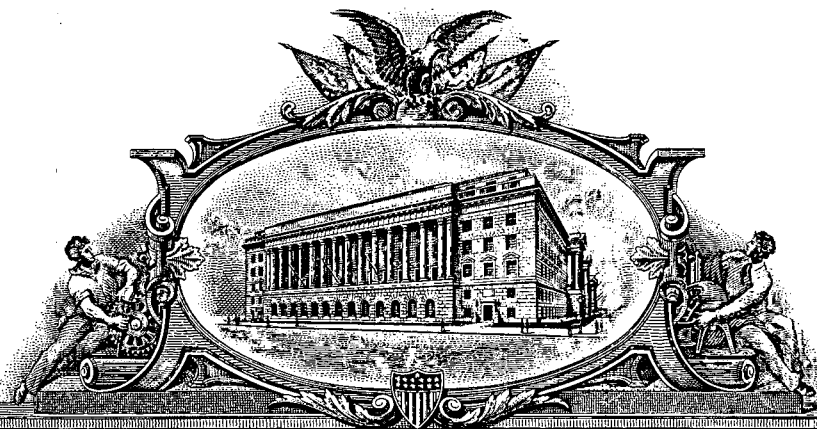
o (b) [C(R₅)(R₅)]_p-U-[C(R₅)(R₅)]_q; en donde cada R₅ es como se define anteriormente; p es un número entero de 0 a 3 aproximadamente, q es un número entero de 1 a 3 aproximadamente, y p + q es de 1 a 4, aproximadamente; y U es C(R₅)(R₅), o, NH, o S; y

cualquier isómeros ópticos, diastereómeros, enantiómeros de la estructura anterior o una farmacéuticamente aceptable, o una amida biohidrolizable, éster, o imida de estos.

37. El método de la Reivindicación 34 en donde el análogo de prostaglandina se selecciona del grupo que consiste de 17-fenil-17-trinor PGE₂, 9-metilen-9-deoxi PGE₂, y 9-metilen-9-deoxi-16,16-dimetilo PGE₂.

38. El método de la Reivindicación 34 en donde el análogo de prostaglandina es 17-fenil trinor PGE₂.

39. El método de la Reivindicación 38 en donde el 17-fenil trinor PGE_2 se administra transdérmicamente.
40. El método de la Reivindicación 38 en donde el trastorno óseo es osteoporosis.
41. El método de la Reivindicación 40 en donde la osteoporosis es osteoporosis posmenopáusica.
42. El método de la Reivindicación 27 en donde el trastorno óseo se selecciona del grupo que consiste de osteoporosis, osteoartritis, enfermedad de Paget, osteomalacia, y fractura ósea.
43. El método de la Reivindicación 27 en donde el trastorno óseo es osteoporosis.



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME;

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 14, 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: 60/123,063

FILING DATE: March 05, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

**H. L. JACKSON
Certifying Officer**

"Express Mail" mailing label number EJ30220089-SUS
Date of Deposit March 5, 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 P43,708
Attorney mailing application Reg. No.
Signature of Attorney mailing application

PTO/SB/16 (6-95)
Approved for use through 04/11/98, OMB 0651-0037
Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

PROVISIONAL PATENT APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL PATENT APPLICATION under 37 CFR §1.53(b)(2).

Docket Number		7466P		Type a plus sign (+) inside this box ⇒	+
INVENTOR(s) / APPLICANT(s)					
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)		
Hartke	James	R.	West Chester, Ohio		
Lundy	Mark	W.	Cincinnati, Ohio		
deLong	Mitchell	A.	West Chester, Ohio		
TITLE OF THE INVENTION (280 characters max)					
Method of Increasing Bone Volume Using Non-Naturally-Occurring EP ₁ Selective Agonists					
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)					
☒ Specification	Number of Pages: 20	+ 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				PROVISIONAL FILING FEE AMOUNT(S)	\$150.00
☒ The Commissioner is hereby authorized to charge filing fees specified under 37 CFR §1.19(f) and credit Deposit Account Number: 16-2480					

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

☒ No

☐ Yes, the name of the U. S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE

Date _____

TYPED or PRINTED NAME James C. Kellerman REGISTRATION NO. P43,708
(if appropriate)

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

PROVISIONAL PATENT APPLICATION FILING ONLY

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METHOD OF INCREASING BONE VOLUME USING
NON-NATURALLY-OCCURRING EP₁ SELECTIVE AGONISTS

James Richard Hartke
Mark Walden Lundy
Mitchell Anthony deLong

TECHNICAL FIELD

The present invention relates to novel methods of increasing bone volume comprising the administration of a non-naturally-occurring selective EP₁ agonist to a subject in need of such treatment. This invention further relates to a method of treating or preventing bone disorders comprising the administration of a non-naturally-occurring selective EP₁ agonist to a subject in need of such treatment.

BACKGROUND OF THE INVENTION

In osteoporotics an imbalance in the bone remodeling process develops in which bone is resorbed at a rate faster than it is being made. Although this imbalance occurs to some extent in most individuals, both male and female, as they age, it is much more severe in osteoporotics, particularly those who develop the post menopausal form of the condition. Accelerated bone loss may also result from drug administration, such as corticosteroids; prolonged bedrest; disuse of a limb; and microgravity. A consequence of this loss of bone is the complete removal of trabeculae and a deterioration of bone architecture such that the remaining bone is disproportionately decreased in strength.

It is thought that to completely return the bone to normal strength, new trabeculae should be formed to restore architecture and increase bone mass. It is further thought that when the restoration of normal architecture is associated not only with an increase in the strength, but also a return to normal stiffness and shock absorbing capability, the bone is less likely to fracture. Subjects suffering from other bone disorders such as rheumatoid arthritis, periodontal disease, and fractures may also benefit from treatments that restore bone mass and normal architecture to bone.

There have been many attempts to treat bone disorders with a variety of pharmacologic agents with the goal being to either slow further bone loss or to produce a net gain in bone mass. There are antiresorptive agents, such as bisphosphonates, which slow further bone loss, and there are anabolic agents, such as PTH, fluoride, and prostaglandins, which build bone. But, none of these

agents build bone that is substantially similar, i.e. structurally or architecturally, to the type of bone lost.

PTH and prostaglandins, especially non-selective prostaglandins of the E series (e.g. PGE₂), are known to be potent stimulators of bone resorption and formation. The acceleration in turnover seen with these known bone anabolic agents may be detrimental to an already osteoporotic skeleton since the increased resorption may cause perforation and loss of trabeculae, or may weaken the existing trabecular structure. In addition, increased resorption may occur in cortical bone. These effects may in turn lead to increased fracture incidence at some sites.

Prostaglandins, in addition, have several drawbacks which limit their desirability for systemic administration. For example, although prostaglandins are characterized by their activity at a particular prostaglandin receptor, they often bind to and stimulate other prostaglandin receptors. Thus, systemic administration of prostaglandins is known to cause side effects such as inflammation, as well as smooth muscle contraction, bronchoconstriction, and vasoconstriction. Systemic administration of non-selective prostaglandin analogs can likewise cause side effects.

Thus, there is a continuing need to develop methods of replacing bone that result in bone that is substantially similar, structurally and architecturally, to the type of bone lost with a bone-specific agent.

SUMMARY OF THE INVENTION

It has been surprisingly found that the systemic administration of non-naturally-occurring selective EP₁ agonists results in a bone anabolic effect. It has been further surprisingly found that the quality of bone formed by the administration of non-naturally-occurring selective EP₁ agonists is superior to that formed by the administration of other prostaglandins of the E series. Accordingly, the present invention is directed to methods of increasing bone volume by administering to a subject a safe and effective amount of a non-naturally-occurring selective EP₁ agonist. Particularly preferred non-naturally-occurring EP₁ agonists are selective for the EP₁ receptor over other excitatory prostaglandin receptors in a ratio of at least about 1:10, more preferably at least about 1:20, and most preferably at least about 1:50. Still more preferred non-naturally-occurring EP₁ agonists are selective for EP₁ receptors over all other prostanoid receptors in a ratio of at least about 1:10, more preferably at least about 1:20, and most preferably at least about 1:50.

It has been further found that non-naturally-occurring selective EP₁ agonists increase trabecular number increase bone volume and mass while maintaining a

more normal bone turnover rate, and increase formation at the endosteal surface without removing bone from the existing cortex. Accordingly, the present invention is directed to methods of increasing trabecular number by administering to a subject a safe and effective amount of a non-naturally-occurring selective EP₁ agonist.

It has similarly been found that non-naturally-occurring selective EP₁ agonists are useful in treating bone disorders. Accordingly, the present invention is directed to methods of treating bone disorders by administering to a subject a safe and effective amount of a non-naturally-occurring selective EP₁ agonist.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to methods of increasing bone volume, methods of increasing trabecular number, and methods of treating bone disorders by administering to a subject a safe and effective amount of a non-naturally-occurring selective EP₁ agonist.

Definitions and Usage of Terms

"Alkyl" is a saturated or unsaturated hydrocarbon chain having 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. Preferred alkyl are saturated. 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 4 substituents. Preferred substituted alkyl are mono-, di-, or trisubstituted. The substituents may be lower alkyl, halo, hydroxy, aryloxy (e.g., phenoxy), acyloxy (e.g., acetoxy), carboxy, monocyclic aromatic ring (e.g., phenyl), monocyclic heteroaromatic ring, monocyclic carbocyclic aliphatic ring, monocyclic heterocyclic aliphatic ring, and amino.

"Lower alkyl" is an alkyl chain comprised of 1 to 6, preferably 1 to 3 carbon atoms.

"Aromatic ring" is an aromatic hydrocarbon ring. 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 system. Bicyclic aromatic rings include ring systems wherein one ring in the system is

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aromatic. Preferred bicyclic aromatic rings are ring systems wherein both rings in the system are aromatic. Aromatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. The substituents may be halo, cyano, lower alkyl, heteroalkyl, haloalkyl, or any combination thereof. Preferred substituents include halo and haloalkyl. Preferred aromatic rings include naphthyl and phenyl. The most preferred aromatic ring is phenyl.

"Bone disorder" means the need for bone repair or replacement. Conditions in which the need for bone repair or replacement may arise include: osteoporosis (including post menopausal osteoporosis, male and female senile osteoporosis and corticosteroid induced osteoporosis), rheumatoid arthritis, osteomalacia, multiple myeloma and other forms of cancer, prolonged bed rest, chronic disuse of a limb, anorexia, microgravity, exogenous and endogenous gonadal insufficiency, bone fracture, non-union, defect, prosthesis implantation and the like.

"Bone turnover rate" is the amount of bone resorption and formation per unit time measured or estimated using incorporation of fluorescent labels into bone, fluorescent and bright field microscopy, and histomorphometric techniques or by measurement of bone metabolism markers. For example, a subject may resorb and replace (turn over) approximately 3% of its skeleton over a 3 month period. A further description of histomorphometric techniques can be found in Bone Histomorphometry, 1994, by Eriksen et al., Raven Press.

"Bone volume" is the percentage of the bone occupied by a mineralized matrix. Measurement or estimation of the mineralized matrix volume can be accomplished using histomorphometry, computed tomography, or magnetic resonance imaging. Two dimensional measurements may be used to estimate the three dimensional volume. A further description of histomorphometric techniques can be found in Bone Histomorphometry, 1994, by Eriksen et al., Raven Press.

"Carbocyclic aliphatic ring" is a saturated or unsaturated hydrocarbon ring. Carbocyclic aliphatic rings are not aromatic. Carbocyclic aliphatic rings are 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. Carbocyclic aliphatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. The substituents may be halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof.

"Excitatory prostaglandin receptor" means prostanoid receptors which cause contraction of smooth muscle or release of internal calcium stores. Such receptors include but are not limited to EP₁, EP₃, FP, TP₁ and TP₂.

"EP" is an abbreviation for E prostanoid. "EP₁" is an abbreviation for E prostanoid subtype 1.

"EP₁ agonist" is a compound with affinity for the EP₁ receptor that results in measurable biological activity (including but not limited to an elevation in intracellular calcium or the contraction of smooth muscle) in cells, tissues, or organisms which contain the EP₁ receptor. Whole cell, tissue, and organism assays which demonstrate EP₁ activity of compounds are well known in the art. One particularly useful assay is a modified R-SAT™ Assay. The R-SAT™ Assay is described by Brann, et al. in J. Biomole. Screen, Vol. 1, Number 1, 1996. The R-SAT™ Assay may be modified by transfecting the cDNA sequence for the human EP₁ receptor (described in WO 94/28125) as the appropriate nucleic acid sequence. Further modifications to the R-SAT™ Assay may be made to optimize the repeatability of the assay results. All such modifications can readily be carried out by one of ordinary skill in the art.

"EP₁ receptor" refers to known human EP₁ receptors, their splice variants, and undescribed receptors that preferentially bind PGE₁. A human EP₁ receptor is disclosed in PCT Publication WO 94/28125.

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

"Haloalkyl" is a straight, branched, or cyclic hydrocarbon substituted with one or more halo substituents. Preferred haloalkyl are C₁-C₁₂; more preferred are C₁-C₆; more preferred still are C₁-C₃. 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 4 substituents. Preferred substituted heteroalkyl are mono-, di-, or trisubstituted. The substituents may be lower alkyl, halo, hydroxy, aryloxy (e.g., phenoxy), acyloxy (e.g., acetoxy), carboxy, monocyclic aromatic ring (e.g., phenyl), monocyclic heteroaromatic ring, monocyclic carbocyclic aliphatic ring, monocyclic heterocyclic aliphatic ring, and amino.

"Lower heteroalkyl" is a heteroalkyl chain comprised of 1 to 6, preferably 1 to 3 member atoms.

"Heteroaromatic ring" is an aromatic ring 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 include ring systems wherein only one ring in the system is aromatic. Preferred bicyclic heteroaromatic rings are ring systems wherein both rings in the system are aromatic. Bicyclic heteroaromatic rings contain from 8 to 12 member atoms, preferably 9 or 10 in the ring. Heteroaromatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. The substituents may be halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. Preferred substituents include halo, haloalkyl, and phenyl.

"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different 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. Heterocyclic aliphatic rings contain from about 4 to about 10 member atoms (carbon and heteroatoms), preferably from 4 to 7 member atoms, and most preferably from 5 to 6 member atoms in the ring. Heterocyclic aliphatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. The substituents may be halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. Preferred substituents include halo and haloalkyl.

"Measurable" means the biologic effect is both reproducible and significantly different from the baseline variability of the assay.

"Non-naturally-occurring" means an agent that is not biologically derived in mammals.

"Prostaglandin analog" is a non-naturally-occurring compound which is structurally similar to a prostaglandin.

"Prostaglandin receptor" or "prostanoid receptor" is a naturally-occurring protein that binds prostaglandins, which when bound alters the function of a cell. Prostaglandin receptors may be characterized as either excitatory or relaxant. Such receptors include but are not limited to EP₁, EP₂, EP₃,

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EP₄, DP, FP, IP, TP₁ and TP₂. These receptors are further discussed by Coleman et al., in Pharmacological Reviews, 1994, Volume 6, No. 2, pages 205 - 229.

"Selective" means having an activation preference for a specific receptor over other receptors which can be quantified based upon whole cell, tissue, or organism assays which demonstrate receptor activity, such as the modified R-SAT™ Assay disclosed above. A compound's selectivity is determined from a comparison of its EC₅₀ (or ED₅₀ if using an organism assay) at the relevant receptors. For example, a compound having an EC₅₀ of 8nM at the EP₁ receptor and an EC₅₀ of 80 nM at the EP₂ receptor has a selectivity ratio for the EP₁ receptor over the EP₂ receptor of 1:10.

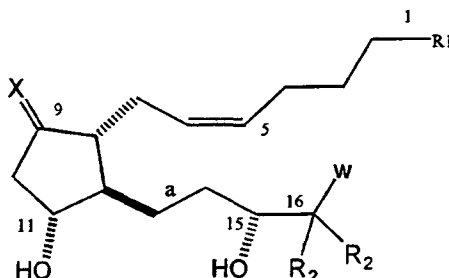
"Subject" is a living vertebrate animal such as a mammal (especially human) in need of treatment.

"Trabecular number" is to the number of individual trabeculae of bone per unit volume of cancellous bone measured or estimated from a two dimensional representation or a three dimensional specimen using histomorphometry, computed tomography, or magnetic resonance imaging.

Compounds

Compounds useful in the present invention are non-naturally-occurring selective EP₁ agonists. Particularly preferred non-naturally-occurring EP₁ agonists are selective for the EP₁ receptor over other excitatory prostaglandin receptors in a ratio of at least about 1:10, more preferably at least about 1:20, and most preferably at least about 1:50. Still more preferred non-naturally-occurring EP₁ agonists are selective for EP₁ receptors over all other prostanoid receptors in a ratio of at least about 1:10, more preferably at least about 1:20, and most preferably at least about 1:50.

Particularly useful non-naturally-occurring selective EP₁ agonists are prostaglandin analogs. Examples of such compounds are prostaglandin analogs having the following general structure:



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In the above structure, R_1 is CO_2H , $\text{C}(\text{O})\text{NHOH}$, CO_2R_3 , CH_2OH , $\text{S}(\text{O})_2\text{R}_3$, or $\text{C}(\text{O})\text{NHR}_3$; characterized in that each R_3 is independently alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred R_1 is CO_2H .

In the above structure, X is CH_2 , O , or N-OR_4 ; wherein R_4 is hydrogen or lower alkyl. Preferred X is CH_2 and N-OR_4 . Most preferred X is CH_2 .

In the above structure, a is single bond, trans double bond, or triple bond. Preferred a is a trans double bond.

In the above structure, each R_2 is independently hydrogen or lower alkyl. Preferred R_2 is lower alkyl. Most preferred R_2 is methyl.

In the above structure, W is: (a) $[\text{C}(\text{R}_5)(\text{R}_5)]_m\text{-Y-}[\text{C}(\text{R}_5)(\text{R}_5)]_n\text{-Z}$; wherein each R_5 is independently hydrogen, lower alkyl, alkoxy, or halo; m is an integer from 0 to about 1, n is an integer from 0 to about 1; Y is, $\text{C}(\text{R}_5)(\text{R}_5)$, O , NH , S or a covalent bond; and Z is phenyl, thienyl, or furanyl, said phenyl, thienyl, or furanyl being unsubstituted or substituted with 1 or 2 halogens; or (b) $[\text{C}(\text{R}_5)(\text{R}_5)]_p\text{-U-}[\text{C}(\text{R}_5)(\text{R}_5)]_q$; wherein R_5 is as defined above; p is an integer from 0 to about 3, q is an integer from about 1 to about 3, and $p + q$ is from about 1 to about 4; and U is $\text{C}(\text{R}_5)(\text{R}_5)$, O , NH , or S . Preferred Z is unsubstituted. Preferred substituted Z is substituted with fluoro.

The above structure includes optical isomers, diastereomers, enantiomers of the above structure or pharmaceutically-acceptable salts, or bio-hydrolyzable amides, esters, or imides thereof. Preferred stereochemistry mimics that of naturally occurring PGE_2 .

Prostaglandin analogs of the above structure include: 17-phenyl-17-trinor PGE_2 , 9-methylene-9-deoxy PGE_2 , and 9-methylene-9deoxy-16,16-dimethyl PGE_2 .

Methods of Use

The compounds described above are useful in increasing bone volume, increasing trabecular number through formation of new trabeculae, increasing bone mass without increasing the bone turnover rate, and/or increasing formation at the endosteal surface without removing bone from the existing cortex. Additionally, the quality of bone formed by the administration of these compounds is superior to that formed by the administration of other prostaglandins of the E series. Bone quality refers to the combination of bone matrix (inorganic and organic), bone mass or volume, and bone architecture which impart overall strength and fracture

resistance to bone. Accordingly, these compounds are further useful in the treatment and prevention of a variety of bone disorders.

The preferred routes of administration for increasing bone volume and treating bone disorders are transdermal and subcutaneous, e.g. injection or pellet. Other preferred routes of administration include oral, sublingual, and intranasal.

The dosage range for systemic administration of the non-naturally-occurring EP₁ agonists of the present invention is from about 0.1 µg/kg to about 10 mg/kg body weight per day, preferably from about 0.5 µg/kg to about 1 mg/kg per body weight per day, most preferably from about 1 to about 500 µg/kg body weight per day. Plasma levels are expected to be in the range of about 0.01 to about 500 ng/ml, more preferably from about 0.05 to 100 ng/ml, and most preferably from about 0.1 to 50 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. The non-naturally-occurring EP₁ agonists of the present invention may be administered, based on a weekly dosage, more frequently than once daily. The non-naturally-occurring EP₁ agonists of the present invention may also be administered, based on a weekly dosage, less frequently than once daily. Hence, the weekly dosage may be divided into 3, 4, 5, 6, or 7 daily dosages, preferably 5, 6, or 7 daily dosages.

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

It is expected that prolonged delivery (also referred to as "prolonged administration") of the non-naturally-occurring EP₁ agonist results in improved dose separation between side effects and the desired bone effect. As used herein, "prolonged delivery" or "prolonged administration" means that the total daily dosage is delivered into the subject's circulation over a period of at least about 6 hours and up to 24 hours. Preferred prolonged delivery periods are for at least about 12 hours and up to 24 hours. Examples of prolonged delivery include administration of the non-naturally-occurring EP₁ agonist via a transdermal patch or a subcutaneous pump that delivers the total daily dosage over a twenty-four hour period.

It is believed that the flattening of the plasma concentration curve resulting from prolonged delivery mitigates side effects while maintaining bone efficacy. It is further believed that the administration of non-naturally-occurring EP₁ agonists with extended half-lives will likewise result in a flattening of the plasma concentration curve without prolonging the administration.

The following non-limiting examples serve to further illustrate the use of the agents of the present invention.

Example I

The EP₁ agonist, 17-phenyl-17-trinor PGE₂, is administered to a 65 year old woman who has decreased bone mass and has been diagnosed with osteoporosis by her physician. She is treated daily with a subcutaneous injection that delivers 10 µg/kg 17-phenyl-17-trinor-PGE₂ over a 24 hour period. This treatment is continued for 12 months, at which time, vertebral bone mass is substantially increased compared to her vertebral bone mass at the onset of therapy as measured by dual energy X-ray absorptiometry (DXA).

Example II

The EP₁ agonist, 17-phenyl-17-trinor PGE₂, is administered to a 65 year old woman who has decreased bone mass and has been diagnosed with osteoporosis by her physician. She is treated daily with a transdermal patch that delivers 10 µg/kg 17-phenyl-17-trinor PGE₂ over a 24 hour period. This treatment is continued for 24 months, at which time, vertebral bone mass is substantially increased compared to her vertebral bone mass at the onset of therapy as measured by dual energy X-ray absorptiometry (DXA).

Example III

The EP₁ agonist, 17-phenyl-17-trinor PGE₂, is administered to a 63 year old woman who has decreased bone mass and has been diagnosed with osteoporosis by her physician. She is treated with an implantable subcutaneous pump that delivers 10 µg/kg 17-phenyl-17-trinor PGE₂ over a 24 hour period. This treatment is continued for 12 months, at which time, vertebral bone mass is substantially increased compared to her vertebral bone mass at the onset of therapy as measured by dual energy X-ray absorptiometry (DXA).

Pharmaceutical Formulations

Pharmaceutical formulations of the present invention comprise a safe and effective amount of the non-naturally-occurring EP₁ agonist and a pharmaceutically acceptable carrier.

The phrase "safe and effective amount", as used herein means an amount of a compound or composition high enough to significantly positively modify the symptoms and/or condition to be treated, but low enough to avoid serious side

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models. Such a model includes, but is not limited to, the intact and ovariectomized rat models of osteoporosis, the ferret, canine, and non human primate models of osteoporosis, as well as disuse models of osteoporosis.

A preferred method of administering non-naturally-occurring EP₁ agonists is via transdermal delivery. Preferred transdermal dosage forms include transdermal patches, creams, ointments, gels and the like. Another preferred method of administering non-naturally-occurring EP₁ agonists is via subcutaneous injection in a unit dosage form. 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. Yet another preferred method of administering non-naturally-occurring EP₁ agonists is via subcutaneous implant or other subcutaneous slow release dosage forms.

Other preferred dose forms include nasal, rectal, sublingual, and oral. Suitable carriers for injection or surgical implants include hydrogels, controlled- or sustained-release devices, polylactic acid, and collagen matrices. Implant devices may be coated with the non-naturally-occurring EP₁ agonist. The non-naturally-occurring prostaglandin EP₁ agonist may be dissolved in a buffer and may be mixed with a collagen gel which is then coated onto the porous end of the implant device.

Preferred oral forms include, for example liposomes, lipid emulsions, proteinaceous cages and pharmaceutically-acceptable excipients.

The term "pharmaceutically-acceptable excipients" as used herein includes any physiologically inert, pharmacologically inactive material known to one skilled in the art, which is compatible with the physical and chemical characteristics of the particular active ingredient selected for use. Pharmaceutically-acceptable excipients include, but are not limited to, polymers, resins, plasticizers, fillers, lubricants, binders, disintegrants, solvents, co-solvents, buffer systems, surfactants, preservatives, sweetening agents, flavoring agents, pharmaceutical grade dyes and pigments.

The following non-limiting examples illustrate formulations of the subject invention.

Example IV

Pharmaceutical formulations (compositions) in the form of tablets are prepared by conventional methods, such as mixing and direct compaction, formulated as follows

<u>Ingredient</u>	<u>Quantity (mg per tablet)</u>
17-phenyl-17-trinor PGE ₂	5

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Microcrystalline Cellulose	100
Sodium Starch Glycollate	30
Magnesium Stearate	3

The above tablet administered orally once daily for six months substantially increases bone volume of a patient afflicted with Osteoporosis.

Example V

A pharmaceutical composition in liquid form is prepared by conventional methods, formulated as follows:

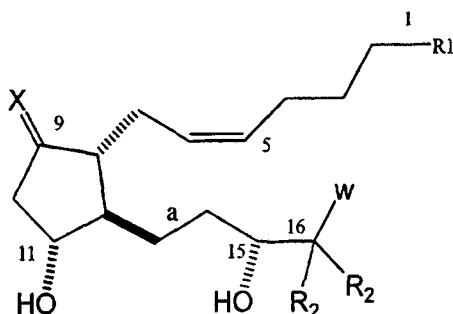
<u>Ingredient</u>	<u>Quantity</u>
17-phenyl-17-trinor PGE ₂	5mg
Phosphate buffered physiologic saline	10 ml
Methyl paraben	0.05 ml

1.0 ml of the above composition administered subcutaneously once daily for six months substantially increases bone volume of a patient afflicted with osteoporosis.

While particular embodiments of the subject invention have been described, it would be obvious to those skilled in the art that various changes and modifications to the compositions disclosed herein can be made without departing from the spirit and scope of the invention.

What is claimed is:

1. A method of increasing bone volume, comprising administering to a subject a therapeutically effective amount of a non-naturally-occurring selective EP₁ agonist.
2. The method of claim 1 wherein the non-naturally-occurring EP₁ agonist is selective for the EP₁ receptor over other excitatory prostaglandin receptors in a ratio of at least 1:10.
3. The method of claim 2 wherein the non-naturally-occurring EP₁ agonist is further selective over all other prostanoid receptors in a ratio of at least 1:10.
4. The method of Claim 3 wherein the non-naturally-occurring EP₁ agonist is selective for the EP₁ receptor over other excitatory prostaglandin receptors in a ratio of at least 1:20.
5. The method of Claim 4 wherein the non-naturally-occurring EP₁ agonist is further selective over all other prostanoid receptors in a ratio of at least 1:20.
6. The method of Claim 5 wherein the non-naturally-occurring EP₁ agonist is selective for the EP₁ receptor over other excitatory prostaglandin receptors in a ratio of at least 1:50.
7. The method of Claim 6 wherein the non-naturally-occurring EP₁ agonist is further selective over all other prostanoid receptors in a ratio of at least 1:50.
8. The method of Claim 7 wherein the non-naturally-occurring EP₁ agonist is a prostaglandin analog.
9. The method of Claim 8 wherein the non-naturally-occurring EP₁ agonist is administered transdermally.
10. The method of Claim 8 wherein the prostaglandin analog has the general formula:

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wherein:

R_1 is CO_2H , C(O)NHOH , CO_2R_3 , CH_2OH , $\text{S(O)}_2\text{R}_3$, or C(O)NHR_3 ; characterized in that each R_3 is independently alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

X is CH_2 , O , or N-OR_4 ; wherein R_4 is hydrogen or lower alkyl;

a is single bond, trans double bond, or triple bond;

each R_2 is independently hydrogen or lower alkyl;

W is:

(a) $[\text{C}(\text{R}_5)(\text{R}_5)]_m\text{-Y-}[\text{C}(\text{R}_5)(\text{R}_5)]_n\text{-Z}$; wherein each R_5 is independently hydrogen, lower alkyl, alkoxy, or halo; m is an integer from 0 to about 1, n is an integer from 0 to about 1; Y is, $\text{C}(\text{R}_5)(\text{R}_5)$, O , NH , S or a covalent bond; and Z is phenyl, thienyl, or furanyl, said phenyl, thienyl, or furanyl being unsubstituted or substituted with 1 or 2 halogens; or

(b) $[\text{C}(\text{R}_5)(\text{R}_5)]_p\text{-U-}[\text{C}(\text{R}_5)(\text{R}_5)]_q$; wherein R_5 is as defined above; p is an integer from 0 to about 3, q is an integer from about 1 to about 3, and $p + q$ is from about 1 to about 4; and U is $\text{C}(\text{R}_5)(\text{R}_5)$, O , NH , or S ; and

any optical isomer, diastereomer, enantiomer of the above structure or a pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or imide thereof.

11. The method of Claim 8 wherein the prostaglandin analog is selected from the group consisting of 17-phenyl-17-trinor PGE_2 , 9-methylene-9-deoxy PGE_2 , and 9-methylene-9-deoxy-16,16-dimethyl PGE_2 .

12. The method of Claim 8 wherein the prostaglandin analog is 17-phenyl trinor PGE_2 .

13. The method of Claim 12 wherein the 17-phenyl trinor PGE₂ is administered transdermally.

14. A method of increasing trabecular number, comprising administering to a subject a therapeutically effective amount of a non-naturally-occurring EP₁ agonist.

15. The method of claim 14 wherein the non-naturally-occurring EP₁ agonist is selective for the EP₁ receptor over other excitatory prostaglandin receptors in a ratio of at least 1:10.

16. The method of claim 15 wherein the non-naturally-occurring EP₁ agonist is further selective over all other prostanoid receptors in a ratio of at least 1:10.

17. The method of Claim 16 wherein the non-naturally-occurring EP₁ agonist is selective for the EP₁ receptor over other excitatory prostaglandin receptors in a ratio of at least 1:20.

18. The method of Claim 17 wherein the non-naturally-occurring EP₁ agonist is further selective over all other prostanoid receptors in a ratio of at least 1:20.

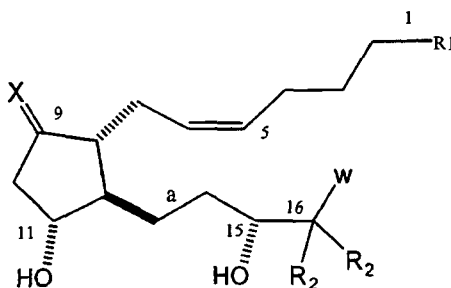
19. The method of Claim 18 wherein the non-naturally-occurring EP₁ agonist is selective for the EP₁ receptor over other excitatory prostaglandin receptors in a ratio of at least 1:50.

20. The method of Claim 19 wherein the non-naturally-occurring EP₁ agonist is further selective over all other prostanoid receptors in a ratio of at least 1:50.

21. The method of Claim 20 wherein the non-naturally-occurring EP₁ agonist is a prostaglandin analog.

22. The method of Claim 21 wherein the non-naturally-occurring EP₁ agonist is administered transdermally.

23. The method of Claim 21 wherein the prostaglandin analog has the general formula:



wherein:

R_1 is CO_2H , $\text{C}(\text{O})\text{NHOH}$, CO_2R_3 , CH_2OH , $\text{S}(\text{O})_2\text{R}_3$, or $\text{C}(\text{O})\text{NHR}_3$; characterized in that each R_3 is independently alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

X is CH_2 , O , or N-OR_4 ; wherein R_4 is hydrogen or lower alkyl;

a is single bond, trans double bond, or triple bond;

each R_2 is independently hydrogen or lower alkyl;

W is:

(a) $[\text{C}(\text{R}_5)(\text{R}_5)]_m\text{-Y-}[\text{C}(\text{R}_5)(\text{R}_5)]_n\text{-Z}$; wherein each R_5 is independently hydrogen, lower alkyl, alkoxy, or halo; m is an integer from 0 to about 1, n is an integer from 0 to about 1; Y is, $\text{C}(\text{R}_5)(\text{R}_5)$, O , NH , S or a covalent bond; and Z is phenyl, thienyl, or furanyl, said phenyl, thienyl, or furanyl being unsubstituted or substituted with 1 or 2 halogens; or

(b) $[\text{C}(\text{R}_5)(\text{R}_5)]_p\text{-U-}[\text{C}(\text{R}_5)(\text{R}_5)]_q$; wherein R_5 is as defined above; p is an integer from 0 to about 3, q is an integer from about 1 to about 3, and $p + q$ is from about 1 to about 4; and U is $\text{C}(\text{R}_5)(\text{R}_5)$, O , NH , or S ; and

any optical isomer, diastereomer, enantiomer of the above structure or a pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or imide thereof.

24. The method of Claim 21 wherein the prostaglandin analog is selected from the group consisting of 17-phenyl-17-trinor PGE_2 , 9-methylene-9-deoxy PGE_2 , and 9-methylene-9-deoxy-16,16-dimethyl PGE_2 .

25. The method of Claim 21 wherein the prostaglandin analog is 17-phenyl trinor PGE_2 .

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26. The method of Claim 25 wherein the 17-phenyl trinor PGE₂ is administered transdermally.

27. A method of treating a bone disorder, comprising administering to a subject a therapeutically effective amount of a non-naturally-occurring EP₁ agonist.

28. The method of claim 27 wherein the non-naturally-occurring EP₁ agonist is selective for the EP₁ receptor over other excitatory prostaglandin receptors in a ratio of at least 1:10.

29. The method of claim 28 wherein the non-naturally-occurring EP₁ agonist is further selective over all other prostanoid receptors in a ratio of at least 1:10.

30. The method of Claim 29 wherein the non-naturally-occurring EP₁ agonist is selective for the EP₁ receptor over other excitatory prostaglandin receptors in a ratio of at least 1:20.

31. The method of Claim 30 wherein the non-naturally-occurring EP₁ agonist is further selective over all other prostanoid receptors in a ratio of at least 1:20.

32. The method of Claim 31 wherein the non-naturally-occurring EP₁ agonist is selective for the EP₁ receptor over other excitatory prostaglandin receptors in a ratio of at least 1:50.

33. The method of Claim 32 wherein the non-naturally-occurring EP₁ agonist is further selective over all other prostanoid receptors in a ratio of at least 1:50.

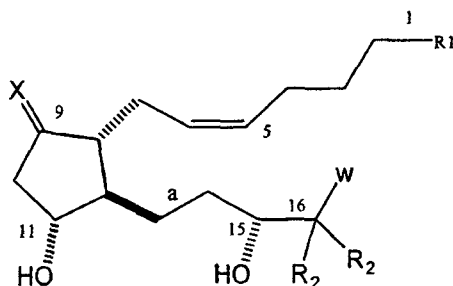
34. The method of Claim 33 wherein the non-naturally-occurring EP₁ agonist is a prostaglandin analog.

35. The method of Claim 34 wherein the non-naturally-occurring EP₁ agonist is administered transdermally.

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36. The method of Claim 34 wherein the prostaglandin analog has the general formula:



wherein:

R_1 is CO_2H , C(O)NHOH , CO_2R_3 , CH_2OH , $\text{S(O)}_2\text{R}_3$, or C(O)NHR_3 ; characterized in that each R_3 is independently alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

X is CH_2 , O , or N-OR_4 ; wherein R_4 is hydrogen or lower alkyl;

a is single bond, trans double bond, or triple bond;

each R_2 is independently hydrogen or lower alkyl;

W is:

(a) $[\text{C}(\text{R}_5)(\text{R}_5)]_m\text{-Y-}[\text{C}(\text{R}_5)(\text{R}_5)]_n\text{-Z}$; wherein each R_5 is independently hydrogen, lower alkyl, alkoxy, or halo; m is an integer from 0 to about 1, n is an integer from 0 to about 1; Y is, $\text{C}(\text{R}_5)(\text{R}_5)$, O , NH , S or a covalent bond; and Z is phenyl, thienyl, or furanyl, said phenyl, thienyl, or furanyl being unsubstituted or substituted with 1 or 2 halogens; or

(b) $[\text{C}(\text{R}_5)(\text{R}_5)]_p\text{-U-}[\text{C}(\text{R}_5)(\text{R}_5)]_q$; wherein R_5 is as defined above; p is an integer from 0 to about 3, q is an integer from about 1 to about 3, and $p + q$ is from about 1 to about 4; and U is $\text{C}(\text{R}_5)(\text{R}_5)$, O , NH , or S ; and

any optical isomer, diastereomer, enantiomer of the above structure or a pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or imide thereof.

37. The method of Claim 34 wherein the prostaglandin analog is selected from the group consisting of 17-phenyl-17-trinor PGE_2 , 9-methylene-9-deoxy PGE_2 , and 9-methylene-9deoxy-16,16-dimethyl PGE_2 .

38. The method of Claim 34 wherein the prostaglandin analog is 17-phenyl trinor PGE_2 .

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39. The method of Claim 38 wherein the 17-phenyl trinor PGE₂ is administered transdermally.
40. The method of Claim 38 wherein the bone disorder is osteoporosis.
41. The method of Claim 40 wherein the osteoporosis is post-menopausal osteoporosis.
42. The method of Claim 27 wherein the bone disorder is selected from the group consisting of: osteoporosis, osteoarthritis, Paget's disease, osteomalacia, and bone fracture.
43. The method of Claim 27 wherein the bone disorder is osteoporosis.

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METHOD OF INCREASING BONE VOLUME USING
NON-NATURALLY-OCCURRING EP₁ AGONISTS

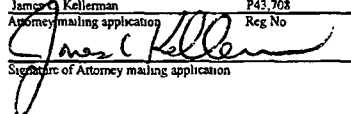
ABSTRACT OF THE INVENTION

The present invention relates to novel methods of increasing bone volume comprising the administration of a non-naturally-occurring selective EP₁ agonist to a subject in need of such treatment. This invention further relates to a method of treating or preventing bone disorders comprising the administration of a non-naturally-occurring selective EP₁ agonist to a subject in need of such treatment.

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