

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 September 2010 (23.09.2010)

PCT

(10) International Publication Number
WO 2010/108012 A1

(51) International Patent Classification:
A01N 29/04 (2006.01)

(21) International Application Number:
PCT/US2010/027831

(22) International Filing Date:
18 March 2010 (18.03.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/161,246 18 March 2009 (18.03.2009) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: COMPOSITIONS AND METHODS FOR PROMOTING NASAL PATENCY AND TREATING NEUROGENIC BLADDER USING PROSTAGLANDINS

(57) Abstract: The invention provides methods for maintaining or promoting patency (e.g., nasal patency) comprising administering to a subject in need thereof an effective amount of at least one prostaglandin F analog (PGF) as described herein, methods for relieving nasal congestion comprising administering to a subject in need thereof an effective amount of at least one PGF as described herein, methods of treating neurogenic bladder comprising administering to a subject in need thereof an effective amount of at least one PGF as described herein, methods of treating, relieving, or reducing the symptoms of neurogenic bladder comprising administering to a subject in need thereof an effective amount of at least one PGF as described herein, and methods of treating or relieving a respiratory disorder comprising administering to a subject in need thereof an effective amount of at least one PGF as described herein. The invention further provides compositions comprising at least one PGF as described herein.



WO 2010/108012 A1

COMPOSITIONS AND METHODS FOR PROMOTING NASAL PATENCY AND TREATING NEUROGENIC BLADDER USING PROSTAGLANDINS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 61/161,246, which was filed March 18, 2009, and is incorporated herein by reference in its entirety.

BACKGROUND

Nasal congestion is a fairly common affliction, which has many causes and can be an annoyance or a life-threatening condition. For example, nasal congestion can be particularly serious for newborns who can only breathe through the nasal passage. Accordingly, nasal congestion in newborns can cause respiratory distress and can interfere with breastfeeding. Nasal congestion in children, adolescents and adults is generally an annoyance. It can, however, be more serious and interfere with speech development and hearing. Additionally, nasal congestion can cause snoring and sleep apnea, both interfering with normal sleep cycles. Furthermore, nasal congestion in conjunction with enlarged adenoids may cause chronic sleep apnea, and ultimately hypoxia and right-sided heart failure.

Current topical decongestants (e.g., Afrin, oxymetazoline) have limited value because after three successive days of patient use, rebound congestion in the form of rhinitis medicamentosa is likely. As a result, there is an ongoing need for a replacement nasal spray or oral drug to treat nasal congestion.

Neurogenic bladder is a malfunctioning bladder caused by neurological disorder. The causes of neurogenic bladder are many and varied. Causes may include disease or disorder of the central and/or peripheral nervous system involved in the control of urination. More specifically, neurogenic bladder may be caused by disorders such as supraspinal lesions, spinal cord lesions, and peripheral nerve lesions. As such, neurogenic bladder may be associated with spinal cord diseases, injuries, and neural tube defects including spina bifida, tumors such as brain tumors, diseases of the brain, pelvic surgery, and peripheral nerve diseases. Neurogenic bladder may also be associated with diabetes, infection, and heavy metal poisoning.

Neurogenic bladder involves the malfunction of the nerves that work with the muscles of the bladder to hold urine and release urine from the bladder at the appropriate time. Neurogenic bladder may cause difficulty or full inability to pass urine,

leading to urinary incontinence, and can lead to infection and hospitalization. Symptoms of neurogenic bladder may include urinary tract infections, kidney stones, urinary frequency and urgency, loss of sensation of bladder fullness, increased voiding intervals, urinary retention, increased residual urine, and incontinence such as stress, urge, mixed, functional, and overflow incontinence. Treatments of neurogenic bladder are currently limited. As a result, new treatments for neurogenic bladder (e.g., post-surgical neurogenic bladder) and urinary incontinence are currently being sought.

SUMMARY

In one aspect, the invention may provide a method for maintaining or promoting patency (e.g., nasal patency) comprising administering to a subject in need thereof an *effective amount of at least one prostaglandin F analog (PGF) as described herein*.

In another aspect, the invention may provide a method for relieving nasal congestion comprising administering to a subject in need thereof an effective amount of at least one PGF as described herein.

In yet another aspect, the invention may provide a method of treating neurogenic bladder comprising administering to a subject in need thereof an effective amount of at least one PGF as described herein.

In a further aspect, the invention may provide a method of treating, relieving, or reducing the symptoms of neurogenic bladder comprising administering to a subject in need thereof an effective amount of at least one PGF as described herein.

In another aspect, the invention may provide a method of treating or relieving a respiratory disorder comprising administering to a subject in need thereof an effective amount of at least one PGF as described herein.

In another aspect, the invention may provide a composition for maintaining or promoting patency (e.g., nasal patency), the composition comprising at least one prostaglandin F analog (PGF) as described herein.

In another aspect, the invention may provide a composition for relieving nasal congestion, the composition comprising at least one prostaglandin F analog (PGF) as described herein.

In another aspect, the invention may provide a composition for treating neurogenic bladder, the composition comprising at least one prostaglandin F analog (PGF) as described herein.

In another aspect, the invention may provide a composition for treating, relieving, or reducing the symptoms of neurogenic bladder, the composition comprising at least one prostaglandin F analog (PGF) as described herein.

In another aspect, the invention may provide a composition for treating or relieving a respiratory disorder, the composition comprising at least one prostaglandin F analog (PGF) as described herein.

DETAILED DESCRIPTION

The invention relates to compositions and methods for using PGFs for maintaining or promoting nasal patency; relieving nasal congestion; treating neurogenic bladder; treating, relieving or reducing symptoms of neurogenic bladder; and/or treating or relieving respiratory disorders.

The invention also relates to publications and patents are referred to throughout this disclosure. All U.S. patents and publications cited herein are hereby incorporated by reference.

All percentages, ratios, and proportions used herein are by weight unless otherwise specified.

Definition and Usage of Terms

The following is a list of definitions for terms, as used herein:

"Activate" means binding and signal transduction of a receptor.

"Acyl group" means a monovalent group suitable for acylating a nitrogen atom to form an amide or carbamate, an alcohol to form a carbonate, or an oxygen atom to form an ester group. Preferred acyl groups include benzoyl, acetyl, tert-butyl acetyl, para-phenyl benzoyl, and trifluoroacetyl. More preferred acyl groups include acetyl and benzoyl. The most preferred acyl group is acetyl.

"Aromatic group" means a monovalent group having a monocyclic ring structure or fused bicyclic ring structure. Monocyclic aromatic groups contain 5 to 10 carbon atoms, preferably 5 to 7 carbon atoms, and more preferably 5 to 6 carbon atoms in the ring. Bicyclic aromatic groups contain 8 to 12 carbon atoms, preferably 9 or 10 carbon atoms in the ring. Aromatic groups are unsubstituted. The most preferred aromatic group is phenyl. Bicyclic aromatic groups include ring systems wherein one ring in the system is aromatic. Preferred bicyclic aromatic groups are ring systems wherein both

rings in the system are aromatic. Preferred aromatic rings include naphthyl and phenyl. The most preferred aromatic ring is phenyl.

“Carbocyclic group” means a monovalent saturated or unsaturated hydrocarbon ring. Carbocyclic groups are monocyclic. Carbocyclic groups contain 4 to 10 carbon atoms, preferably 4 to 7 carbon atoms, and more preferably 5 to 6 carbon atoms in the ring. Carbocyclic groups are unsubstituted. Preferred carbocyclic groups include cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. More preferred carbocyclic groups include cyclohexyl, cycloheptyl, and cyclooctyl. The most preferred carbocyclic group is cycloheptyl. Carbocyclic groups are not aromatic.

“FP agonist” means a compound that activates the FP receptor.

“FP receptor” means known human FP receptors, their splice variants, and undescribed receptors that have similar binding and activation profiles as the known human FP receptors. “FP” means the receptor is of the class which has the highest affinity for PGF_{2α} of all the naturally occurring prostaglandins. FP refers to a known protein.

“Halogen atom” means F, Cl, Br, or I. Preferably, the halogen atom is F, Cl, or Br; more preferably Cl or F; and most preferably F.

“Halogenated heterogenous group” means a substituted heterogenous group or a substituted heterocyclic group, wherein at least one substituent is a halogen atom. Halogenated heterogenous groups can have a straight, branched, or cyclic structure. Preferred halogenated heterogenous groups have 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms, and most preferably 1 to 3 carbon atoms. Preferred halogen atom substituents are Cl and F.

“Halogenated hydrocarbon group” means a substituted monovalent hydrocarbon group or a substituted carbocyclic group, wherein at least one substituent is a halogen atom. Halogenated hydrocarbon groups can have a straight, branched, or cyclic structure. Preferred halogenated hydrocarbon groups have 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms, and most preferably 1 to 3 carbon atoms. Preferred halogen atom substituents are Cl and F. The most preferred halogenated hydrocarbon group is trifluoromethyl.

“Heteroaromatic group” means an aromatic ring containing carbon and 1 to 4 heteroatoms in the ring. Heteroaromatic groups are monocyclic or fused bicyclic rings. Monocyclic heteroaromatic groups contain 5 to 10 member atoms (i.e., carbon and heteroatoms), preferably 5 to 7, and more preferably 5 to 6 in the ring. Bicyclic

heteroaromatic rings contain 8 to 12 member atoms, preferably 9 or 10 in the ring. Heteroaromatic groups are unsubstituted. Bicyclic heteroaromatic groups include ring systems in which only one ring is aromatic. Preferred bicyclic heteroaromatic groups are ring systems in which both rings are aromatic. Preferred monocyclic heteroaromatic groups include thienyl, thiazolyl, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred monocyclic heteroaromatic groups include thienyl, furanyl, and pyridyl. The most preferred monocyclic heteroaromatic group is thienyl. Preferred bicyclic heteroaromatic rings include benzothiazolyl, benzothiophenyl, quinolinyl, quinoxalinyl, benzofuranyl, benzimidazolyl, benzoxazolyl, indolyl, and anthranilyl. More preferred bicyclic heteroaromatic rings include benzothiazolyl, benzothiophenyl, and benzoxazolyl.

"Heteroatom" means an atom other than carbon in the ring of a heterocyclic group or the chain of a heterogeneous group. Preferably, heteroatoms are selected from the group consisting of nitrogen, sulfur, and oxygen atoms. Groups containing more than one heteroatom may contain different heteroatoms.

"Heterocyclic group" means a saturated or unsaturated ring structure containing carbon and 1 to 4 heteroatoms in the ring. No two heteroatoms are adjacent in the ring, and no carbon in the ring that has a heteroatom bonded to it also has a hydroxyl, amino, or thiol group bonded to it. Heterocyclic groups are not aromatic. Heterocyclic groups are monocyclic. Heterocyclic groups contain 4 to 10 member atoms (i.e., including both carbon atoms and at least 1 heteroatom), preferably 4 to 7, and more preferably 5 to 6 in the ring. Heterocyclic groups are unsubstituted. Preferred heterocyclic groups include piperzyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, and piperdyl.

"Heterogeneous group" means a saturated or unsaturated chain containing 1 to 18 member atoms (i.e., including both carbon and at least one heteroatom). No two heteroatoms are adjacent. Preferably, the chain contains 1 to 12 member atoms, more preferably 1 to 6. "Lower heterogeneous" means a heterogeneous group having 1 to 6, preferably 1 to 3, member atoms. The chain may be straight or branched. Preferred branched heterogeneous groups have one or two branches, preferably one branch. Preferred heterogeneous groups are saturated. Unsaturated heterogeneous groups have one or more double bonds, one or more triple bonds, or both. Preferred unsaturated heterogeneous groups have one or two double bonds or one triple bond. More preferably, the unsaturated heterogeneous group has one double bond. Heterogeneous groups are unsubstituted.

"Nasal congestion" means at least a partial to complete blockage of a nasal

passage. Nasal congestion may be caused by the membranes of the nose lining becoming swollen from inflamed blood vessels.

"Monovalent hydrocarbon group" means a chain of 1 to 18, preferably 1 to 12, carbon atoms. "Lower monovalent hydrocarbon group" means a monovalent hydrocarbon group having 1 to 6, preferably 1 to 3, carbon atoms. Monovalent hydrocarbon groups may have a straight chain or branched chain structure. Preferred monovalent hydrocarbon groups have one or two branches, preferably 1 branch. Preferred monovalent hydrocarbon groups are saturated. Unsaturated monovalent hydrocarbon groups have one or more double bonds, one or more triple bonds, or combinations thereof. Preferred unsaturated monovalent hydrocarbon groups have one or two double bonds or one triple bond; more preferred unsaturated monovalent hydrocarbon groups have one double bond.

"Patency" means opening of a passage and/or tract, such as a nasal passage or respiratory tract, which may facilitate airflow and breathing.

"Pharmaceutically acceptable" means suitable for use in a human or other mammal.

"Prostaglandin" means a fatty acid derivative which has a variety of potent biological activities of a hormonal or regulatory nature.

"PGF" means a prostaglandin or prostaglandin analogue of the 'F' series, that is one that has a hydroxy group attached to C-9 and a hydroxy group attached to C-11 (using the standard prostaglandin numbering system)

"Protecting group" means a group that replaces the active hydrogen of a hydroxyl moiety thus preventing undesired side reaction at the hydroxyl moiety. Use of protecting groups in organic synthesis is well known in the art. Examples of protecting groups are found in Chapter 2 Protecting Groups in Organic Synthesis by Greene, T. W. and Wuts, P. G. M., 2nd ed., Wiley & Sons, Inc., 1991. Preferred protecting groups include silyl ethers, alkoxymethyl ethers, tetrahydropyranyl, tetrahydrofuranyl, esters, and substituted or unsubstituted benzyl ethers.

"Respiratory disorders" include, but are not limited to, nasal congestion and rhinitis.

"Safe and effective amount" means a quantity of a prostaglandin high enough to provide a significant positive modification of the subject's condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio).

"Selective" means having a binding or activation preference for a specific receptor over other receptors which can be quantitated based upon receptor binding or activation assays.

"Subject" means a living, vertebrate, animal such as a mammal (preferably human) in need of treatment.

"Substituted aromatic group" means an aromatic group wherein 1 to 4 of the hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. Preferred substituents include: halogen atoms, cyano groups, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, heterogeneous groups, substituted heterogeneous groups, aromatic groups, substituted aromatic groups, or any combination thereof. More preferred substituents include halogen atoms, halogenated monovalent hydrocarbon groups, phenyl groups, and phenoxy groups. Preferred substituted aromatic groups include naphthyl. The substituents may be substituted at the ortho, meta, or para position on the ring, or any combination thereof. The preferred substitution pattern on the ring is ortho or meta. The most preferred substitution pattern is ortho.

"Substituted carbocyclic group" means a carbocyclic group wherein 1 to 4 hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. Preferred substituents include: halogen atoms, cyano groups, monovalent hydrocarbon groups, monovalent heterogeneous groups, substituted monovalent hydrocarbon groups, substituted heterogeneous groups, aromatic groups, substituted aromatic groups, or any combination thereof. More preferred substituents include halogen atoms, halogenated monovalent hydrocarbon groups, phenyl groups, and phenoxy groups.

"Substituted heteroaromatic group" means a heteroaromatic group wherein 1 to 4 hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. The substituents include halogen atoms, acyl groups, cyano groups, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, heterogeneous groups, substituted heterogeneous groups, aromatic groups, substituted aromatic groups, heteroaromatic groups, substituted heteroaromatic groups, and any combination thereof. Preferred substituents include halogen atoms, cyano groups, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, heterogeneous groups, substituted heterogeneous groups, phenyl groups, phenoxy groups, or any combination thereof. More preferred substituents include halogen atoms,

halogenated hydrocarbon groups, monovalent hydrocarbon groups, halogenated heterogenous groups, and phenyl groups.

“Substituted heterocyclic group” means a heterocyclic group wherein 1 to 4 hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. Preferred substituents include: halogen atoms, cyano groups, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, heterogeneous groups, substituted heterogeneous groups, aromatic groups, substituted aromatic groups, or any combination thereof. More preferred substituents include halogen atoms, halogenated hydrocarbon groups, phenyl groups, phenoxy groups, or any combination thereof. Substituted heterocyclic groups are not aromatic.

“Substituted heterogeneous group” means a heterogeneous group, wherein 1 to 4 of the hydrogen atoms bonded to carbon atoms in the chain have been replaced with other substituents. Preferably substituted heterogeneous groups are mono, di, or trisubstituted. Preferred substituents include halogen atoms, hydroxy groups, carboxy groups, aryloxy groups (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, and acyloxyphenoxy), acyloxy groups (e.g., propionyloxy, benzoyloxy, and acetoxy), aromatic groups (e.g., phenyl and tolyl), substituted aromatic groups (e.g., alkoxyphenyl, alkoxy carbonylphenyl, and halophenyl), heterocyclic groups, heteroaromatic groups, substituted heterocyclic groups, and amino groups (e.g., amino, mono- and di- alkylamino having 1 to 3 carbon atoms, methylphenylamino, methylbenzylamino, alkanylamido groups of 1 to 3 carbon atoms, carbamamido, ureido, and guanidino).

“Substituted monovalent hydrocarbon group” means a monovalent hydrocarbon group wherein 1 to 4 of the hydrogen atoms bonded to carbon atoms in the chain have been replaced with other substituents. Preferred substituted monovalent hydrocarbon groups are mono, di, or trisubstituted. Preferred substituents include halogen atoms; lower monovalent hydrocarbon groups; hydroxy groups; aryloxy groups (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, and acyloxyphenoxy); acyloxy groups (e.g., propionyloxy, benzoyloxy, and acetoxy); carboxy groups; monocyclic aromatic groups; monocyclic heteroaromatic groups; monocyclic carbocyclic groups, monocyclic heterocyclic groups, and amino groups (e.g., amino, mono- and di- alkanylamino groups of 1 to 3 carbon atoms, methylphenylamino, methylbenzylamino, alkanylamido groups of 1 to 3 carbon atoms, carbamamido, ureido, and guanidino).

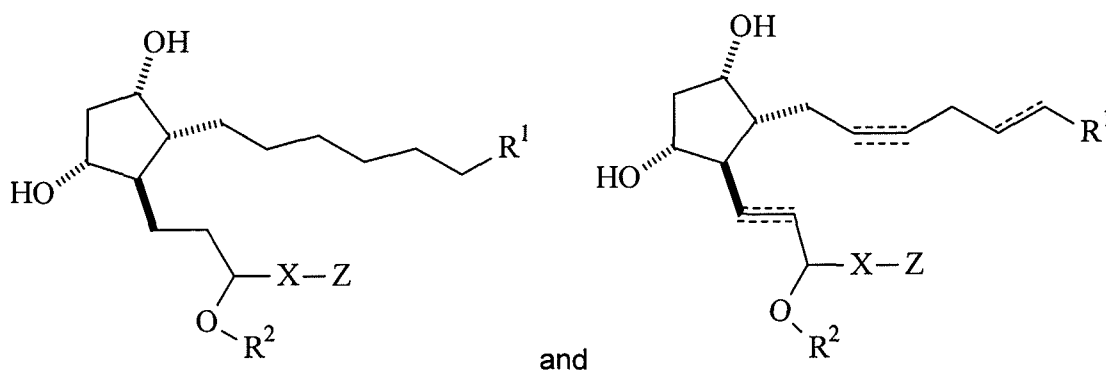
Prostaglandins Used in the Invention

Generally speaking, prostaglandins are a large group of fatty-acid derived second messengers. All are synthesized in vivo from arachidonic acid and show extraordinarily potent biological activities, often in nanomolar range. The prostaglandin receptors are a family of seven-transmembrane G-protein-coupled receptors. Nine prostaglandin receptors, differentiated by their native prostanoid ligand, are found in humans, including DP 1 and 2, EP 1 through 4, FP, IP and DP. A wide variety of synthetic ligands are known for the FP receptor, many of which are used as human drugs, including the synthetic prostanoids used for the treatment of glaucoma (Xalatan/Latanoprost, Travatan/Travaprost, Rescula/Unoprostone). The endogenous ligand for the FP prostaglandin receptor is PGF_{2α} which affects smooth muscle contraction, and human prostaglandins are active in uterine contraction, bronchoconstriction, and gastrointestinal sphincters.

The compounds of the invention have a unique structure that make them specific, rather than selective or non-selective, agonists of the human prostaglandin receptor (hFP receptor). Thus, they may have a uniquely innocuous side-effect profile that will enable them to be used topically without causing headaches or irritation (due to the older compounds activating non-target receptors such as the EP1 receptor).

Suitable PGF's for use in the methods described herein may be found, among other places, in U.S. Patent No. 5,977,173, U.S. Patent No. 6,107,338, U.S. Patent U.S. Patent No. 6,048,895, U.S. Patent No. 6,410,780, U.S. Patent No. 6,444,840, U.S. Patent No. 6,451,859, U.S. Patent Application No. 09/774,555, U.S. Patent No. 7,407,987, U.S. Patent Application No. 12/138,733, U.S. Patent Application No. 09/774,558, U.S. Patent Application No. 11/476,246, U.S. Patent Application No. 09/774,557, U.S. Patent No. 7,388,029, U.S. Patent Application No. 11/967,423, U.S. Patent Application No. 09/774,556, U.S. Patent Application No. 11/334,689, U.S. Patent Application No. 11/412,207, U.S. Patent No. 6,586,463, U.S. Patent Application No. 11/174,420, and U.S. Patent No. 6,372,730, each of which is fully incorporated herein by reference in its entirety.

For example, suitable PGF's can have a structure selected from the group consisting of:



The PGF can also be selected from the group consisting of pharmaceutically acceptable salts and hydrates of the structures above; biohydrolyzable amides, esters, and imides of the structures above; and optical isomers, diastereomers, and enantiomers of the structures above. Thus, at all stereocenters where stereochemistry is not defined (C_{11} , C_{12} , and C_{15}), both epimers are envisioned. Preferred stereochemistry at all such stereocenters of the compounds of the invention mimic that of naturally occurring $\text{PGF}_{2\alpha}$. A combination of two or more PGF's can also be used.

R^1 is selected from the group consisting of C(O)OH , C(O)NHOH , C(O)OR^3 , CH_2OH , $\text{S(O)}_2\text{R}^3$, C(O)NHR^3 , $\text{C(O)NHS(O)}_2\text{R}^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms. Preferably, R^1 is selected from the group consisting of CO_2H , C(O)NHOH , CO_2R^3 , $\text{C(O)NHS(O)}_2\text{R}^4$, and tetrazole. More preferably, R^1 is selected from the group consisting of CO_2H and CO_2R^3 .

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogenous group, and lower monovalent hydrocarbon groups. Preferably, R^2 is a hydrogen atom.

R^3 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group.

R^4 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group,

a substituted aromatic group, and a substituted heteroaromatic group. Preferably, R^4 is a phenyl group.

X is divalent. X is selected from the group consisting of $-C\equiv C-$, $-C\equiv C-CH_2-$, a covalent bond, $-CH=C=CH-$, $-CH=CH-$, $-CH=N-$, $-C(O)-$, $-C(O)Y-$, $-(CH_2)_n-$, wherein n is 2 to 4, $-CH_2NH-$, $-CH_2S-$, and $-CH_2O-$.

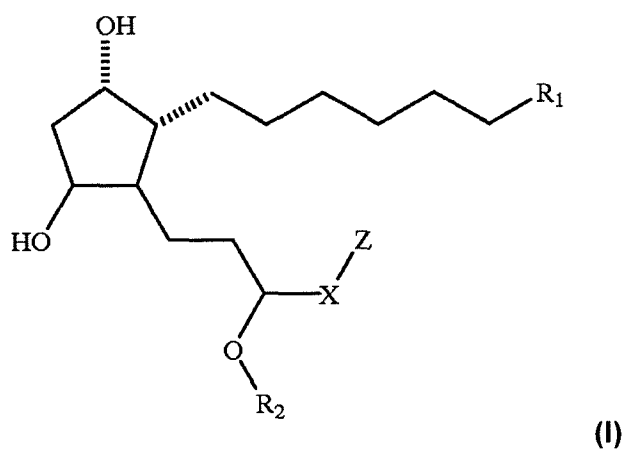
Y is selected from the group consisting of O, S, and NH.

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group.

Preferably, when X is a covalent bond, Z is selected from the group consisting of an aromatic group, a heteroaromatic group, a substituted aromatic group, and a substituted heteroaromatic group. More preferably, when X is a covalent bond, Z is a bicyclic heteroaromatic group.

Preferably, when X is $-C\equiv C-$, Z is a monocyclic aromatic group. More preferably, when X is $-C\equiv C-$, Z is selected from the group consisting of furanyl, thienyl, and phenyl.

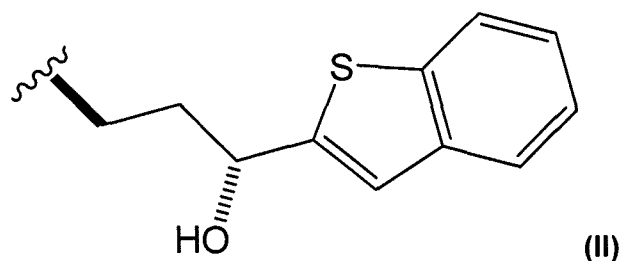
Preferred PGFs according to the invention include the following according to Formula I:



wherein R_1 is CO_2H , CO_2R_3 , $S(O)_2R_3$, or $C(O)NHR_3$; R_3 is unsubstituted or substituted lower alkyl, lower heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic aromatic ring, or monocyclic heteroaromatic ring, wherein the alkyl or the heteroalkyl can be saturated or unsaturated; R_2 is H; X is a covalent bond; and Z is benzo(β)thiazolyl, benzo(β)thiophenyl, thianaphthyl, or benzoxazolyl. The invention

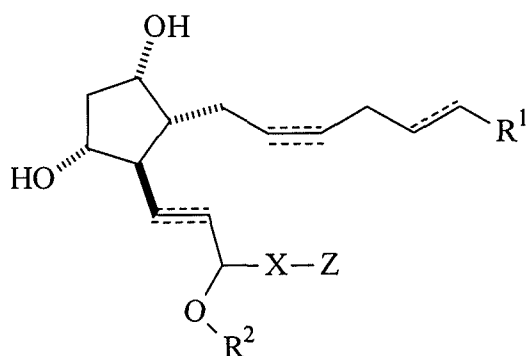
further provides any optical isomer, diastereomer, enantiomer of the compound or a pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or imide thereof.

Suitably, the invention provides a compound according to Formula I as described above, wherein Z is benzo(β)thiophenyl. More suitably, the invention provides a compound according to Formula I wherein the omega chain is according to Formula II:



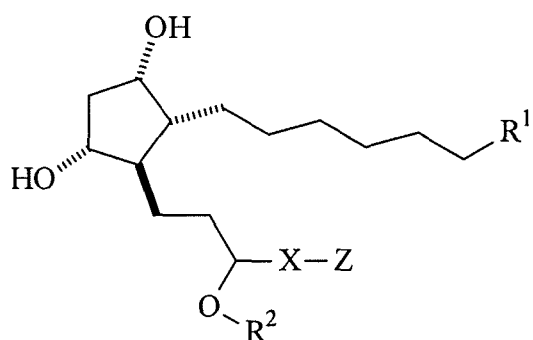
Suitably, the invention provides compounds according to Formula I as described above, wherein R_3 is unsubstituted or substituted monocyclic aromatic ring, monocyclic heteroaromatic ring, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, or phenyl. In one embodiment, the invention provides compounds according to Formula I as described above, wherein R_1 is CO_2R_3 and R_3 is a substituted lower alkyl. More suitably, the invention provides compounds according to Formula I, wherein R_3 is a lower alkyl substituted with from 1 to 4 OH groups.

Bonds shown as dashed lines in the second structure above indicate that those bonds may optionally be double or triple bonds. For example, when R^1 is $\text{C}(\text{O})\text{OH}$ in the structure:



The bond at the C2-C3 position may be a single bond or a double bond. The bond at the C5-C6 position may be a single, double, or triple bond. The bond at the C13-C14 position may be a single, double, or triple bond.

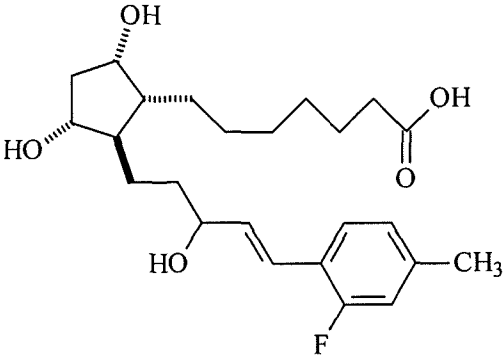
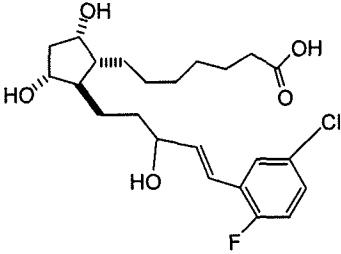
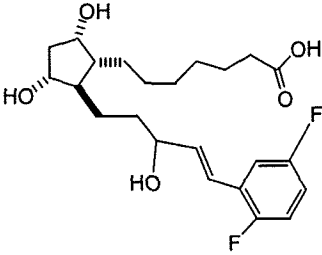
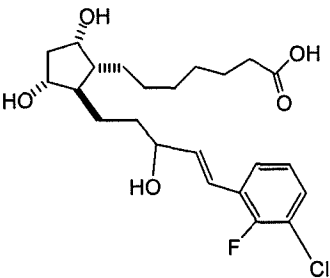
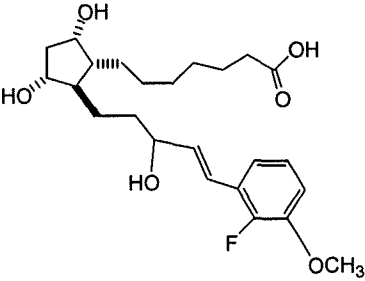
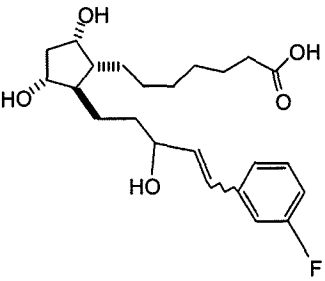
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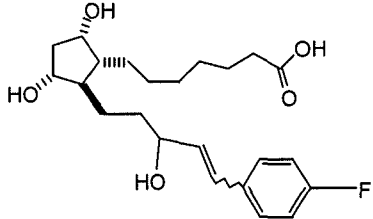
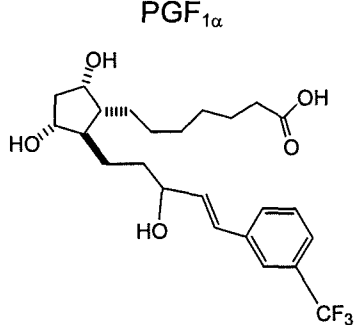
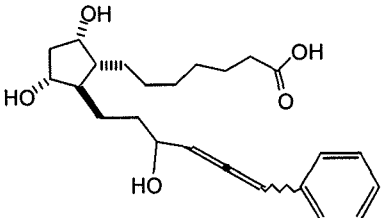
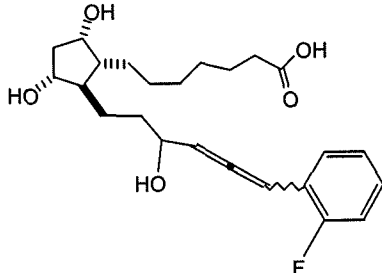
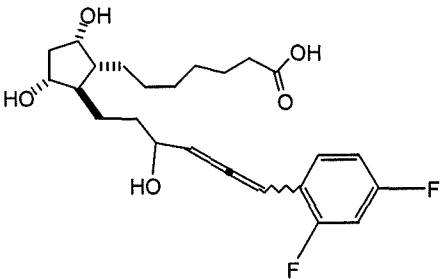
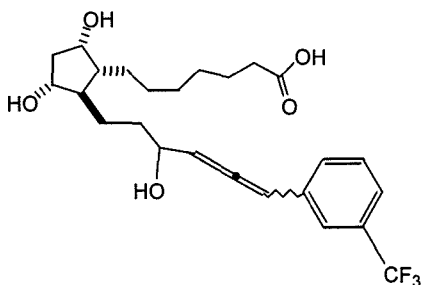


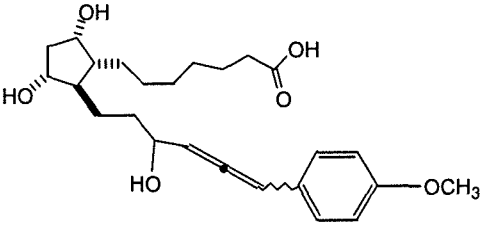
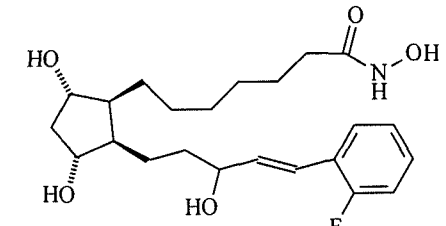
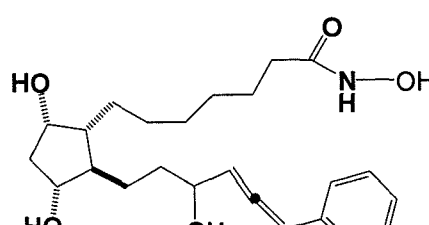
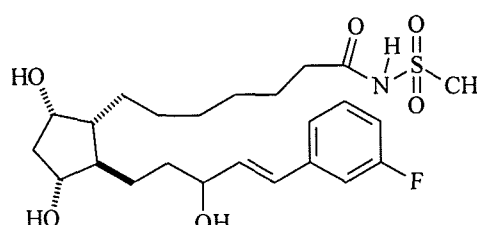
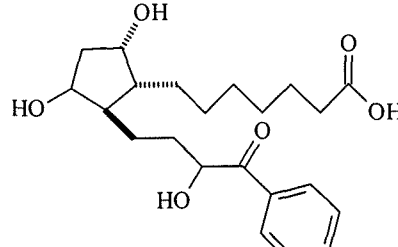
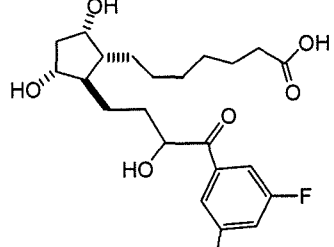
which are suitable for component A) are shown below in Tables 1 and 2 and 3.

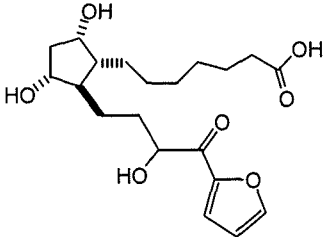
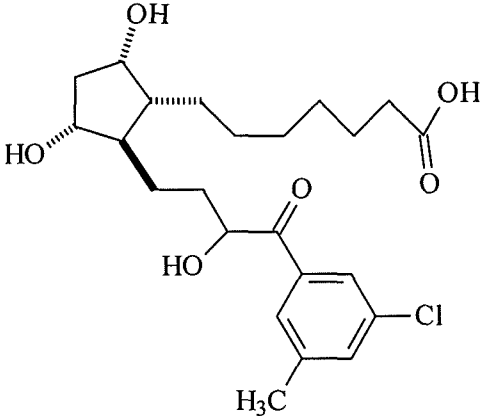
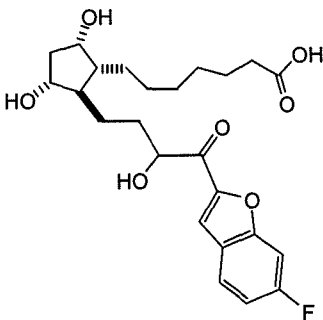
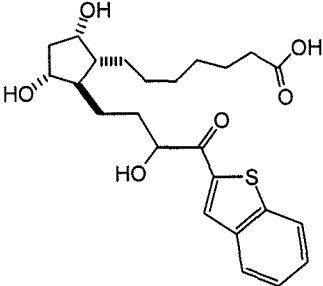
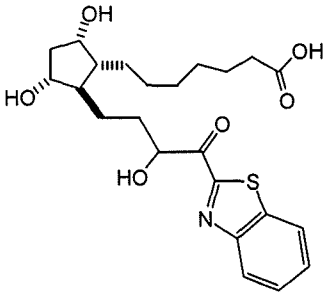
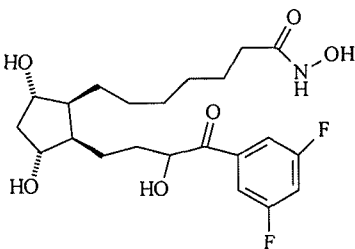
Table 1: Examples of Suitable PGF's for Component A)

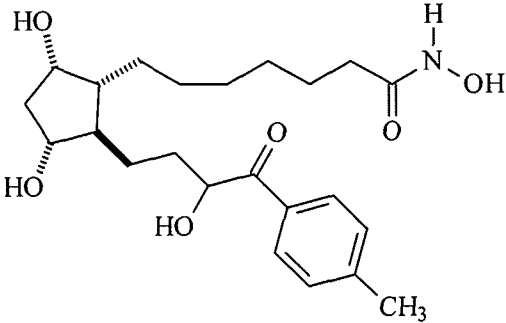
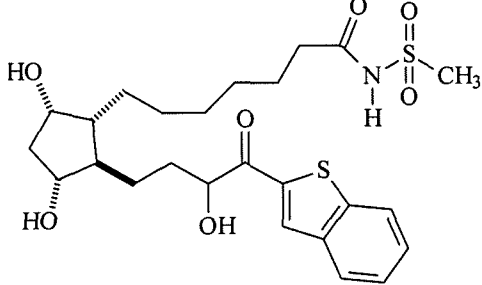
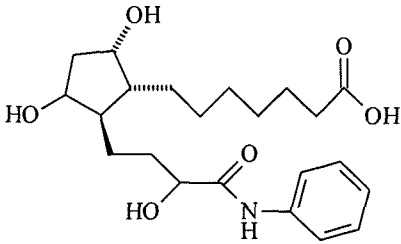
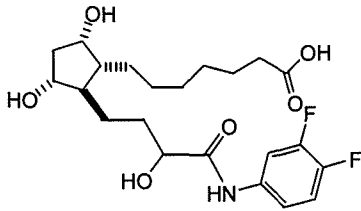
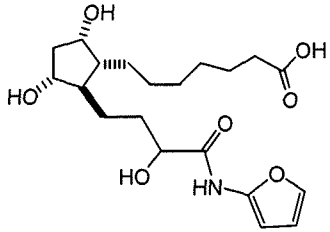
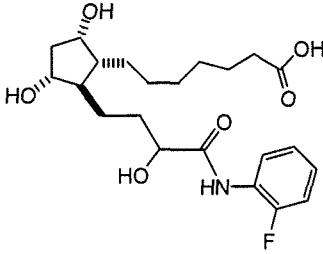
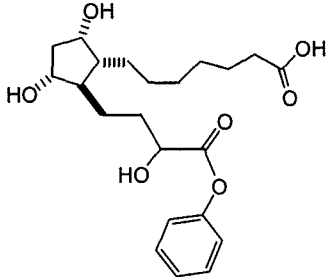
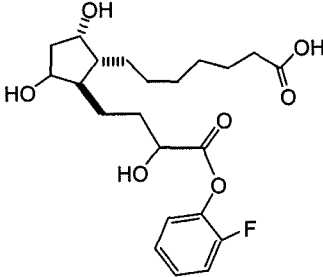
13,14-dihydro-16,17-<i>Z</i>-didehydro-17-(2-fluorophenyl)-17-trinor PGF_{1α}	13,14-dihydro-16,17-<i>E</i>-didehydro-17-(2-fluorophenyl)-17-trinor PGF_{1α}
13,14-dihydro-<i>E</i>-16,17-didehydro-17-phenyl-17-trinor PGF_{1α}	13,14-dihydro-<i>E</i>-16,17-didehydro-17-(2,4-dichlorophenyl)-17-trinor PGF_{1α}

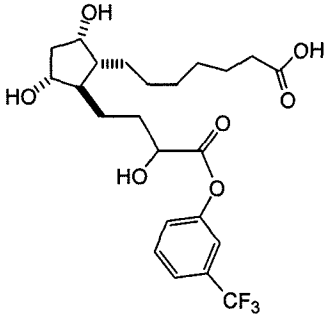
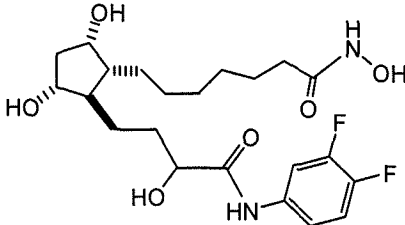
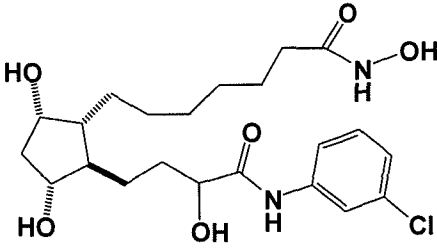
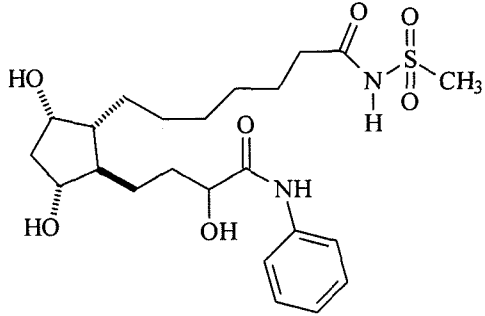
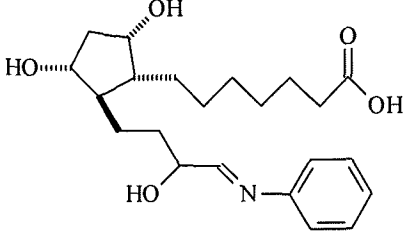
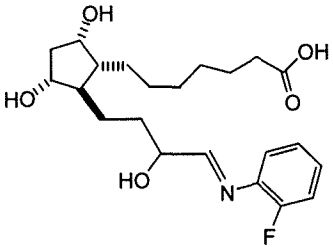
13,14-dihydro-<i>E</i>-16,17-didehydro-17-(2-fluoro-4-methylphenyl)-17-trinor PGF_{1α} 	13,14-dihydro-<i>E</i>-16,17-didehydro-17-(2-fluoro-5-chlorophenyl)-17-trinor PGF_{1α} 
13,14-dihydro-<i>E</i>-16,17-didehydro-17-(2,5-difluorophenyl)-17-trinor PGF_{1α} 	13,14-dihydro-<i>E</i>-16,17-didehydro-17-(2-fluoro-3-chlorophenyl)-17-trinor PGF_{1α} 
13,14-dihydro-<i>E</i>-16,17-didehydro-17-(2-fluoro-3-methoxyphenyl)-17-trinor PGF_{1α} 	13,14-dihydro-16,17-didehydro-17-(3-fluorophenyl)-17-trinor PGF_{1α} 

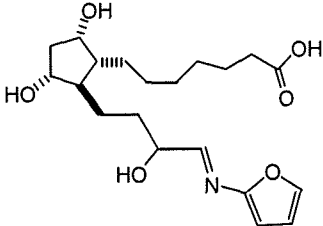
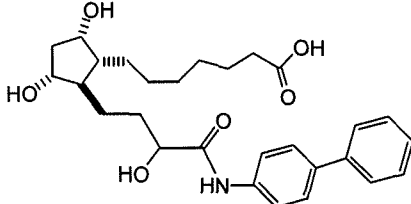
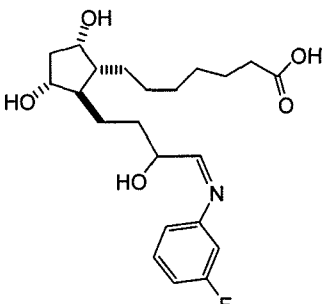
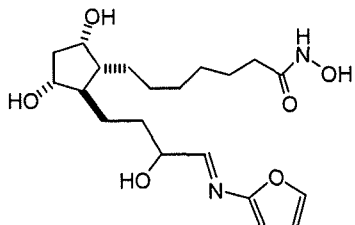
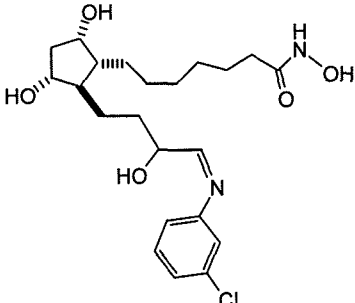
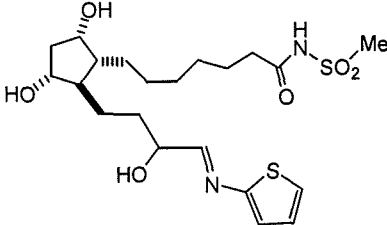
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13,14-dihydro-16,17,17,18-dienyl-18-phenyl-18-dinor PGF_{1α} 	13,14-dihydro-16,17,17,18-dienyl-18-(2-fluorophenyl)-18-dinor PGF_{1α} 
13,14-dihydro-16,17,17,18-dienyl-18-(2,4-difluorophenyl)-18-dinor PGF_{1α} 	13,14-dihydro-16,17,17,18-dienyl-18-(3-trifluoromethylphenyl)-18-dinor PGF_{1α} 

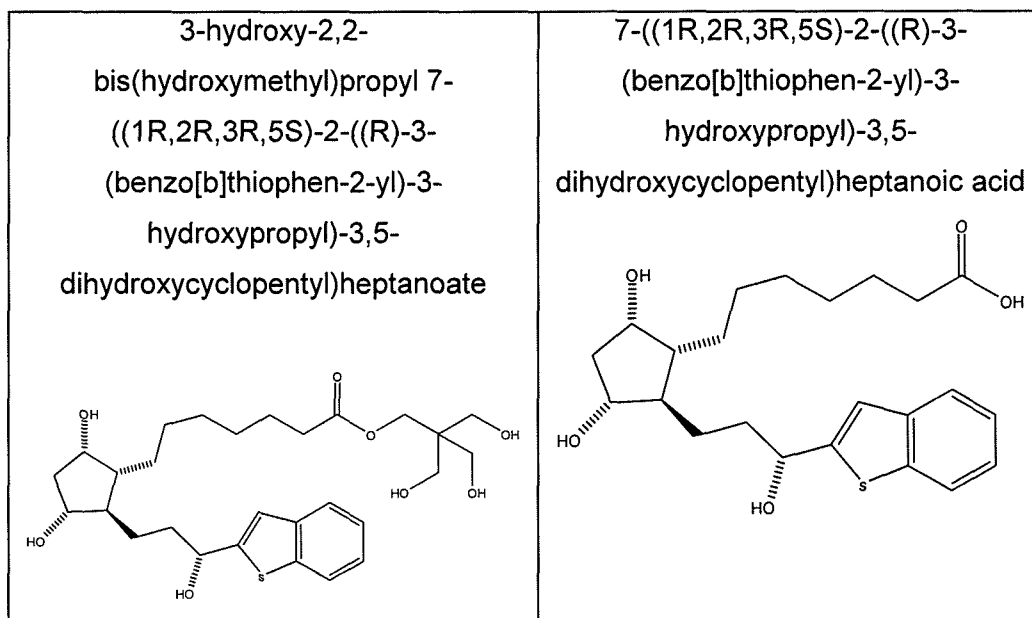
13,14-dihydro-16,17,17,18-dienyl-18-(4-methoxyphenyl)-18-dinor PGF_{1α} 	13,14-dihydro-16,17-didehydro-17-(2-fluorophenyl)-17-trinor PGF_{1α} 1-hydroxamic acid 
13,14-dihydro-16,17,17,18-dienyl-18-phenyl-18-dinorPGF_{2α} 1-hydroxamic acid 	13,14-dihydro-16,17-didehydro-17-3-fluorophenyl-17-trinor PGF_{1α} 1-N-methanesulfonamide 
13,14-dihydro-16-oxo-16-phenyl-16-tetranorPGF_{1α} 	13,14-dihydro-16-oxo-16-(3,5-difluorophenyl)-16-tetranor PGF_{1α} 

13,14-dihydro-16-oxo-16-(2-furanyl)-16-tetranor PGF_{1α} 	13,14-dihydro-16-oxo-16-(3-chloro-5-methylphenyl)-16-tetranor PGF_{1α} 
13,14-dihydro-16-oxo-16-(6-fluorobenzo[b]furanyl)-16-tetranor PGF_{1α} 	13,14-dihydro-16-oxo-16-(2-benzo[b]thienyl)-16-tetranor PGF_{1α} 
13,14-dihydro-16-oxo-16-(2-benzothiazolyl)-16-tetranor PGF_{1α} 	13,14-dihydro-16-oxo-16-(3,5-difluorophenyl)-16-tetranor PGF_{1α} 1-hydroxamic acid 

13,14-dihydro-16-oxo-16-(4-methylphenyl)-16-tetranor PGF_{1α} 1-hydroxamic acid 	13,14-dihydro--16-oxo-16-(2-benzo[b]thienyl)-16-tetranor PGF_{1α} 1-N-methanesulfonamide 
13,14-dihydro-16-oxo-17-aza-17-phenyl-17-trinor PGF_{1α} 	13,14-dihydro-16-oxo-17-aza-17-(3,4-difluorophenyl)-17-trinor PGF_{1α} 
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13,14-dihydro-16-oxo-16-phenoxy-16-tetranor PGF_{1α} 	13,14-dihydro-16-oxo-16-(2-fluorophenoxy)-16-tetranor PGF_{1α} 

13,14-dihydro-16-oxo-16-(3-trifluoromethylphenoxy)-16-tetranor PGF_{1α} 	13,14-dihydro-16-oxo-17-aza-17-(3,4-difluorophenyl)-17-trinor PGF_{1α} 1-hydroxamic acid 
13,14-dihydro-16-oxo-17-amino-17-(3-chlorophenyl)-17-trinor PGF_{1α} 1-hydroxamic acid: 	13,14-dihydro-16-oxo-17-amino-17-phenyl-17-trinor PGF_{1α} 1-methane sulfonamide 
13,14-dihydro-16,17-didehydro-17-aza-17-phenyl-17-trinor PGF_{1α} 	13,14-dihydro-16,17-didehydro-17-aza-17-(2-fluorophenyl)-17-trinor PGF_{1α} 

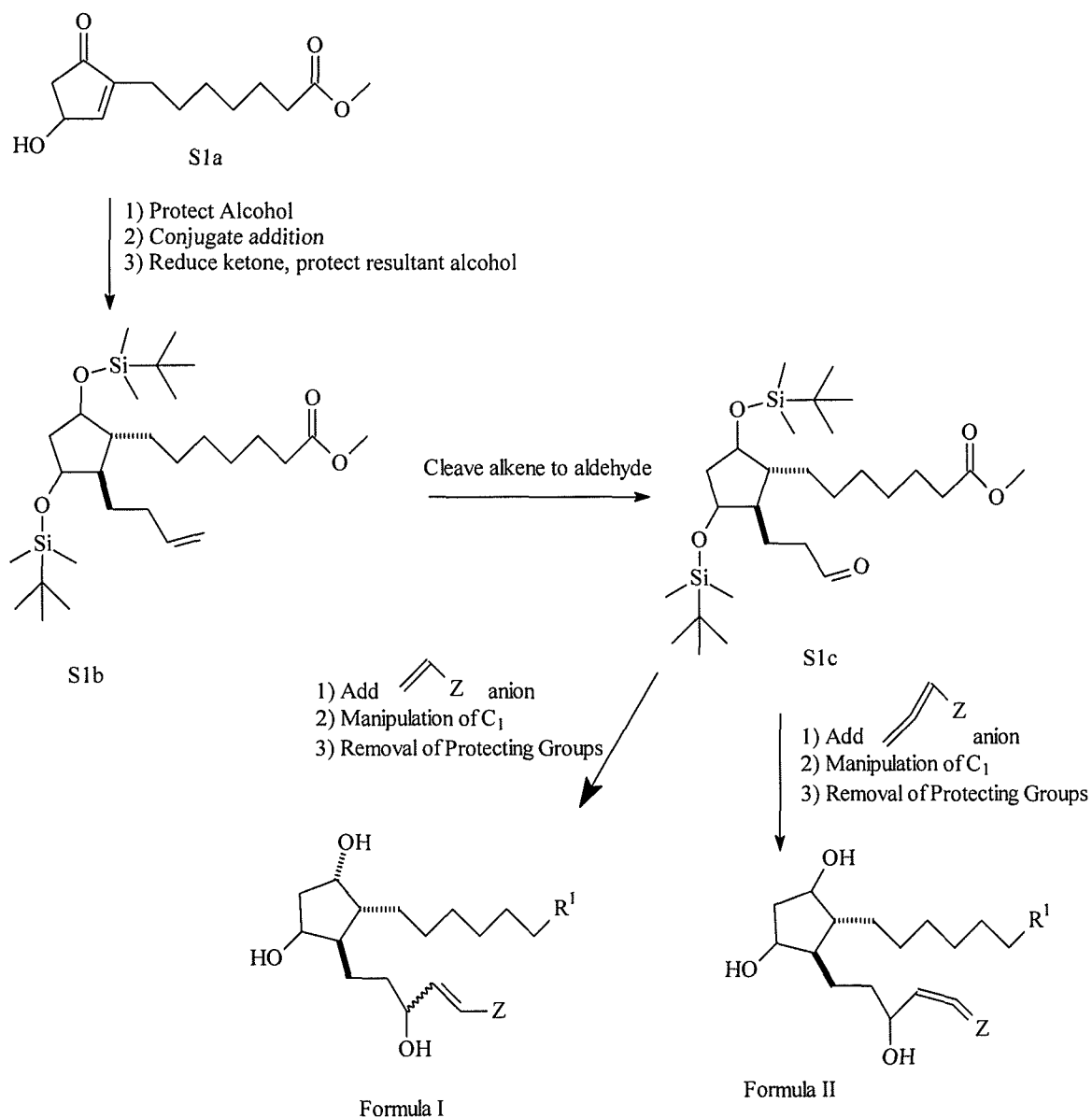
13,14-dihydro-16,17-didehydro-17-aza-17-(2-furanyl)-17-trinor PGF_{1α} 	13,14-dihydro-16-oxo-17-aza--17-(4-phenylphenyl)-17-trinor PGF_{1α} 
13,14-dihydro-16,17-didehydro-17-aza-17-(3-fluorophenyl)-17-trinor PGF_{1α} 	13,14-dihydro-16,17-didehydro-17-aza-17-(2-furanyl)-17- trinor PGF_{1α} 1-hydroxamic acid 
13,14-dihydro-16,17-didehydro-17-aza-17-(3-chlorophenyl)-17-trinor PGF_{1α} 1-hydroxamic acid 	13,14-dihydro-16,17-didehydro-17-aza-17-(2-thienyl)-17-trinor PGF_{1α} 1-methanesulfonamide 



Where Me in the table above represents a methyl group.

The PGF's in Table 1 can be prepared using conventional organic syntheses. Preferred syntheses are carried out using reaction schemes 1, 2, and 3. **Scheme 1** describes a general reaction scheme for making PGFs wherein X is -CH=CH- (**Formula I**) or -CH=C=CH- (**Formula II**). **Scheme 2** describes a general reaction scheme for making PGFs wherein X is -C(O)- (**Formula III**) or -C(O)Y- (**Formula IV**). **Scheme 3** describes a general reaction scheme for making PGFs wherein X is -CH=N- (**Formula V**).

Scheme 1



In **Scheme 1**, R^1 and Z are as defined above. The methyl 7(3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl) heptanoate (**S1a**) depicted as starting material for **Scheme 1** is commercially available (such as from Sumitomo Chemical or Cayman Chemical).

In **Scheme 1**, methyl 7-(3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl) heptanoate (**S1a**) is reacted with a silylating agent and base in a solvent that will allow the silylation to proceed. Preferred silylating agents include tert-butyldimethylsilyl chloride and tert-butyldimethylsilyl trifluoromethanesulphonate. The most preferred silylating agent is tert-butyldimethylsilyl trifluoromethanesulphonate. Preferred bases include triethylamine,

trimethylamine, and 2,6-lutidine. More preferred bases include triethylamine and 2,6-lutidine. The most preferred base is 2,6-lutidine. Preferred solvents include halogenated hydrocarbon solvents with dichloromethane being the most preferred solvent. The reaction is allowed to proceed at a temperature of preferably -100°C to 100°C , more preferably -80°C to 80°C , and most preferably -70°C to 23°C .

The resulting silylated compound is isolated by methods known to one of ordinary skill in the art. Such methods include extraction, solvent evaporation, distillation, and crystallization. Preferably, the silyl ether is purified after isolation by distillation under vacuum.

The silylated compound is then reacted with the cuprate generated *via* Grignard formation of the appropriate alkenyl bromide as disclosed, for example, in the following references: H.O. House et. al., "The Chemistry of Carbanions: A Convenient Precursor for the Generation of Lithium Organocuprates", J. Org. Chem. Vol. 40 (1975) pp. 1460-69 ; and P. Knochel et. al., "Zinc and Copper Carbenoids as Efficient and Selective α/δ Multicoupling Reagents", J. Amer. Chem. Soc. Vol. 111 (1989) p. 6474-76. Preferred alkenyl bromides include 4-bromo-1-butene, 4-bromo-1-butyne, 4-bromo-2-methyl-1-butene, and 4-bromo-2-ethyl-1-butene. The most preferred alkenyl bromide is 4-bromo-1-butene. Preferred solvents include ethereal solvents, of which diethyl ether and tetrahydrofuran are preferred. The most preferred solvent is tetrahydrofuran. The Grignard reagent is allowed to form at a temperature of 100°C to 23°C , more preferably 85°C to 30°C , and most preferably 75°C to 65°C . The reaction time is preferably 1 to 6 hours, more preferably 2 to 5 hours, and most preferably 3 to 4 hours.

Once the Grignard reagent is formed, the cuprate is generated from the alkenyl magnesium species. The temperature range for cuprate formation is -100°C to 0°C . The preferred temperature range is -80°C to -20°C . The more preferred temperature range is -75°C to -50°C . The preferred reaction time is 30 minutes to 6 hours, more preferably 45 minutes to 3 hours. The most preferred reaction time is 1 to 1.5 hours.

The alkene thus formed is isolated by methods known to one of ordinary skill in the art. Such methods include extraction, solvent evaporation, distillation, and crystallization. Preferably, the alkene is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 10% EtOAc/hexanes as the eluent. (EtOAc represents ethyl acetate.)

The alkene is then reacted with a hydride reducing agent and a polar, protic solvent to give the C-9 alcohol. Preferred reducing agents include lithium aluminum

hydride, sodium borohydride, and L-selectride. More preferred reducing agents include sodium borohydride, and L-selectride. The most preferred reducing agent is sodium borohydride. Preferred solvents include methanol, ethanol, and butanol. The most preferred solvent is methanol. The reduction is carried out at a temperature of -100°C to 23°C. The preferred temperature range is -60°C to 0°C. The most preferred temperature range is -45°C to -20°C.

The resulting alcohol is isolated by methods known to one of ordinary skill in the art. Such methods include extraction, solvent evaporation, distillation, and crystallization. Preferably, the alcohol is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent.

The resultant alcohol can be protected as described previously herein. Preferred silylating agents in this case also include tert-butyldimethylsilyl chloride and tert-butyldimethylsilyl trifluoromethanesulfonate. The most preferred silylating agent is tert-butyldimethylsilyl trifluoromethanesulfonate. Preferred bases include triethylamine, trimethylamine, and 2,6-lutidine. More preferred bases include triethylamine and 2,6-lutidine. The most preferred base is 2,6-lutidine. Preferred solvents include halogenated hydrocarbon solvents with dichloromethane being the most preferred solvent. The reaction is allowed to proceed at a temperature of preferably -100°C to 100°C, more preferably -80°C to 80°C, and most preferably -70°C to 23°C.

The resulting silylated compound, **S1b** is isolated by methods known to one of ordinary skill in the art. Such methods include extraction, solvent evaporation, distillation, and crystallization. Preferably, the silyl ether is purified after isolation by distillation under vacuum, giving compound **S1b**.

The protected alcohol is then treated with a form of osmium and sodium periodate in a solvent in which both are soluble. Preferred forms of osmium include osmium tetroxide and potassium osmate. Preferred solvent systems include 1:1 mixtures of acetic acid and water and 1:1:2 mixtures of water, acetic acid and THF. (THF represents tetrahydrofuran.) The result of this treatment is the aldehyde, **S1c**.

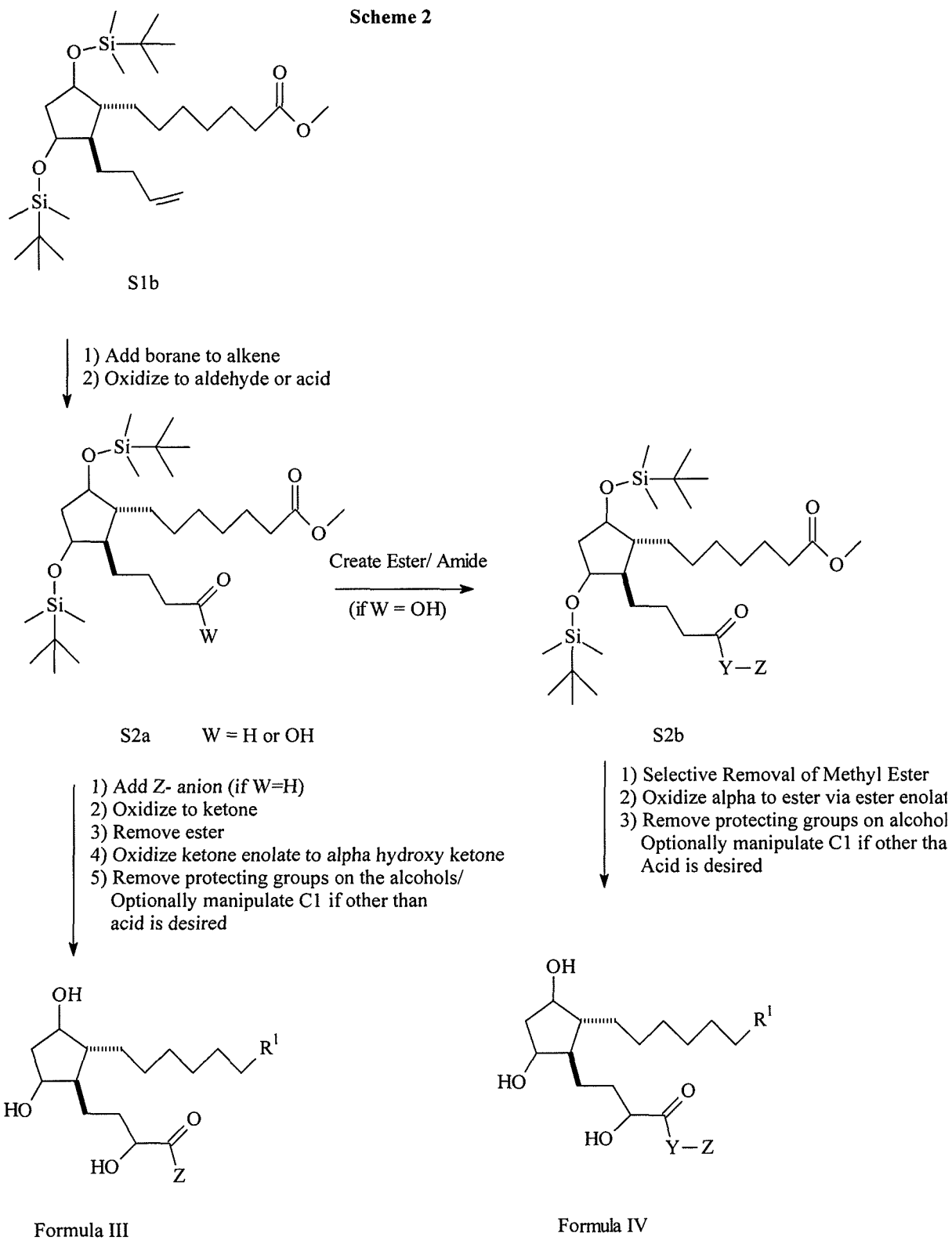
The compound **S1c** is isolated by methods known to one of ordinary skill in the art. Such methods include extraction, solvent evaporation, distillation, and crystallization. Preferably, **S1c** is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent.

The key intermediate aldehyde depicted as **S1c** can be reacted with a variety of unsaturated alkenyl anion nucleophiles to provide the C-9 and C-11-protected 13,14-dihydro-prostaglandin $F_{1\alpha}$ derivatives.

The resulting compounds can be isolated, but are generally deprotected using techniques known to one of ordinary skill in the art, and optionally, manipulated at C-1 to provide the desired acid derivative at R^1 . For example, the condensation of a methyl ester with an amine or a hydroxylamine provides an amide or a hydroxamic acid compound, respectively. After any such manipulation at C-1, the compounds are isolated as the final 13,14-dihydro-15-substituted-15-pentanor prostaglandin $F_{1\alpha}$ derivative, **Formula I**.

Compounds depicted by **Formula II** can be made directly from intermediate **S1c** in a manner similar to that for compounds depicted by **Formula I** substituting the appropriate allene anion. With allene nucleophiles, the reaction is carried out preferably at -80°C to 0°C , more preferably -80°C to -20°C , and most preferably -80°C to -40°C . Preferred bases for the reaction include *n*-butyl lithium, *s*-butyl lithium, and *t*-butyl lithium. The most preferred base is *n*-butyl lithium. Preferred solvents for the reaction are ether solvents. Preferred solvents include diethyl ether, and tetrahydrofuran. The most preferred solvent is tetrahydrofuran. With heterocyclic nucleophiles, preferred solvents include ethereal solvents. More preferred ethereal solvents include diethyl ether, dibutyl ether and tetrahydrofuran. The most preferred ethereal solvent is tetrahydrofuran. After isolation, similar C-1 manipulations and/or deprotection of the functional groups ensues using techniques known to one of ordinary skill in the art.

Scheme 2



In **Scheme 2**, R¹, Y, and Z are as defined above. The protected alcohol **S1b** (from **Scheme 1**) is treated with a hydroborating reagent in an ethereal solvent, followed by oxidative removal of the boron reagent with a suitable oxidant to give a compound of the type **S2a**. Preferred hydroborating reagents include monochloroborane-dimethylsulfide, diborane, borane-tetrahydrofuran and borane-dimethylsulfide. The most preferred hydroborating reagent is borane-dimethylsulfide. Preferred ethereal solvents include THF and diethyl ether. The most preferred solvent is THF. The reaction is carried out from about 1 to about 24 hours at a temperature of about -20 °C to about +30 °C. The preferred temperature range is about 0 °C to about +20 °C. The hydroborated product of this reaction may then be oxidatively removed to the alcohol using alkaline hydrogen peroxide (See *Boranes in Organic Chemistry*, H. C. Brown, Cornell University Press, Ithaca, NY 1972, pp. 321-325), which may then be oxidized to either the aldehyde (W= H) or to the acid (W= OH) using methods known to one of ordinary skill in the art. Alternatively, the hydroborated product may be directly oxidized to the aldehyde or acid by treatment with chromic acid or a Cr(VI) salt. Such salts include pyridinium chlorochromate (PCC) and dichlorochromate. See Brown, H. C.; Kulkarni, Rao, and Patil, *Tetrahedron*, 1986, 45515. The preferred method is treatment of the hydroborated product with PCC in dichloromethane at room temperature. The result of these manipulations is a compound of the type **S2a**.

The compound **S2a** is isolated by methods known to one of ordinary skill in the art. Such methods include extraction, solvent evaporation, distillation, and crystallization. Preferably, **S2a** is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent with 0.1% acetic acid added if W = OH.

The key intermediate aldehyde depicted as **S2a** can be reacted with a variety unsaturated carbon nucleophiles to provide the C-9 and C-11-protected 13,14-dihydro-16-tetranor prostaglandin F_{1α} derivatives of **Formula III**.

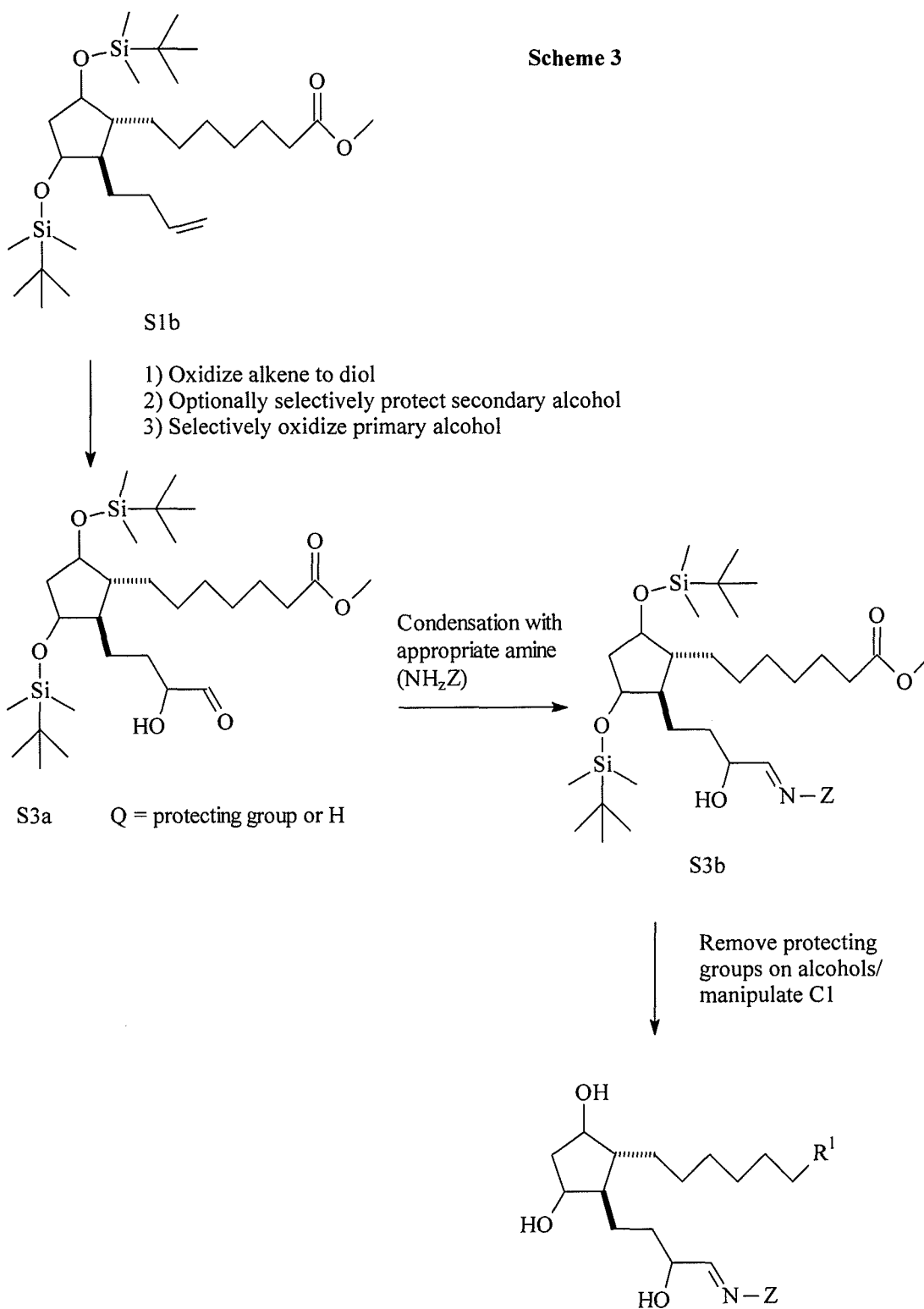
With aromatic and heteroaromatic nucleophiles, the reaction is carried out preferably at -80°C to 0°C, more preferably -80°C to -20°C, and most preferably -80°C to -40°C. Preferred bases for the reaction include *n*-butyl lithium, *s*-butyl lithium, lithium diisopropylamide, and *t*-butyl lithium. The most preferred base is *n*-butyl lithium. Preferred solvents for the reaction are ether solvents. Preferred solvents include diethyl ether, and tetrahydrofuran. The most preferred solvent is tetrahydrofuran. With

heterocyclic nucleophiles, preferred solvents include ethereal solvents. More preferred ethereal solvents include diethyl ether, dibutyl ether and tetrahydrofuran. The most preferred ethereal solvent is tetrahydrofuran.

The resulting alcohol can be isolated, but is generally oxidized as a crude isolate. The oxidation of benzylic alcohols to benzylic ketones is well known in the art. The preferred reagents to effect this reaction include KMnO_4 , MnO_2 , chromic acid, Jones' reagent, Collins' reagent, and PCC. The most preferred method is oxidation at room temperature in dichloromethane with PCC for about 4 hours. The ketones are isolated by column chromatography using 20% hexanes/ethyl acetate as solvent. The ester is then removed using standard conditions. See Greene and Wuts, Protecting Groups in Organic Synthesis, Wiley Interscience, NY pp. 224-276. The free acid is then treated with 2.1 equivalents of a strong nitrogen base to effect deprotonation both of the acid and adjacent to the benzylic ketone. Such bases include LDA. This enolate is reacted with a peroxidizing agent which has the effect of oxidizing the compound to deliver the alpha-hydroxy ketone. Such reagents include *meta*-chloroperoxybenzoic acid, dimethyl dioxirane, Davis' reagent and peracetic acid. The crude product may be isolated or the remaining protecting groups may be removed. At this point manipulation of the acid at C-1 may take place. For example, re-esterifying, making the amide, the hydroxamic acid or the sulfonamide using methods known to one of ordinary skill in the art may be performed to yield compounds according to **Formula III**.

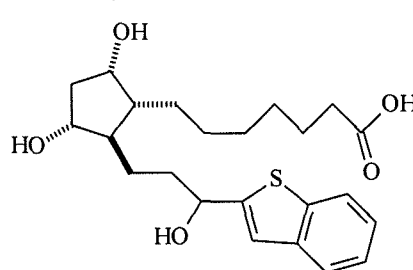
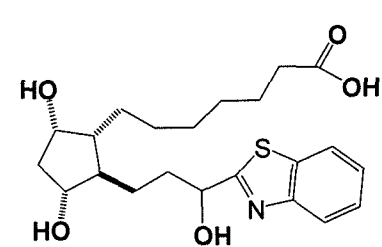
Compounds depicted by **Formula IV** can be made from intermediate **S2b**. In this case, condensation of the free acid is readily achieved with a variety of alcohols and amines, either by the use of coupling agents such as dicyclohexylcarbodiimide ("DCC"), or by activating the acid with, for example, oxalyl chloride. Following this is the selective removal of the methyl esters as described in Greene and Wuts, Protecting Groups in Organic Synthesis, Wiley Interscience, NY pp. 224-276, and the oxidation of the ester enolates using the same technique described above for the ketone intermediates. Similarly, as described above, the remaining protecting groups are removed and the desired manipulation of C-1 is affected, yielding compounds of **Formula IV**.

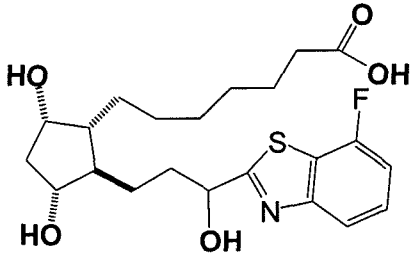
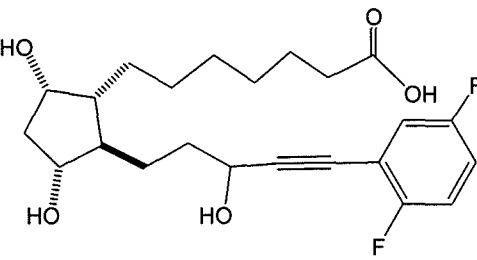
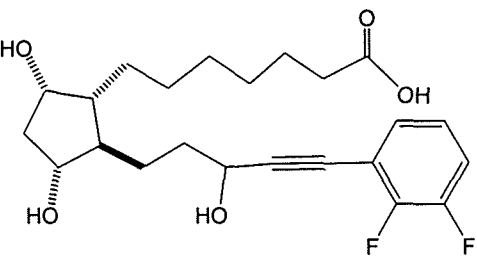
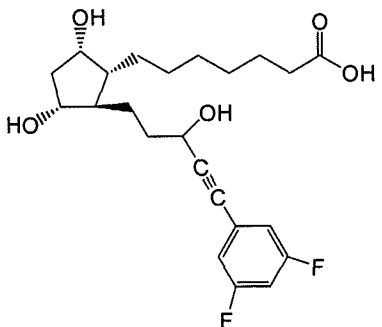
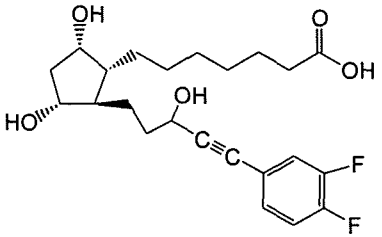
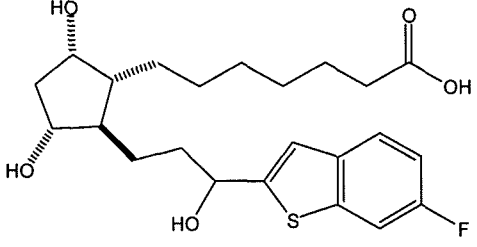
Scheme 3

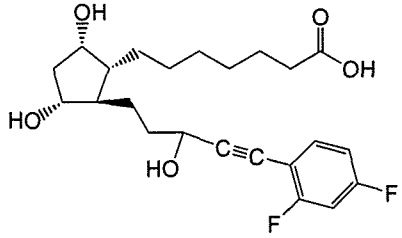
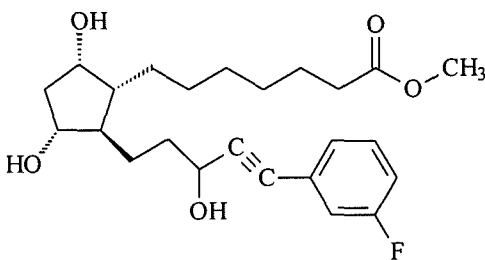
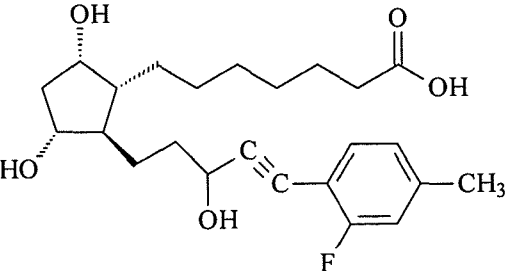
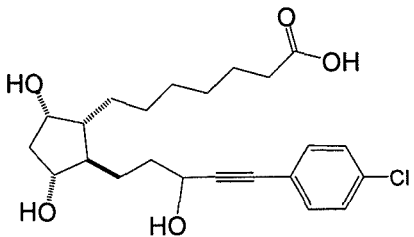
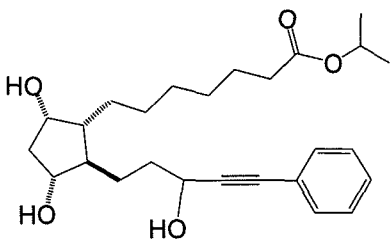
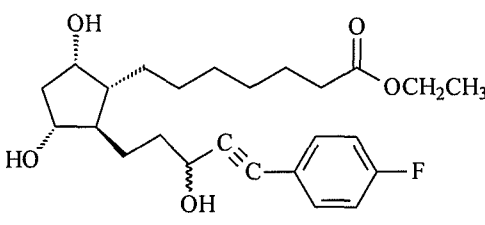


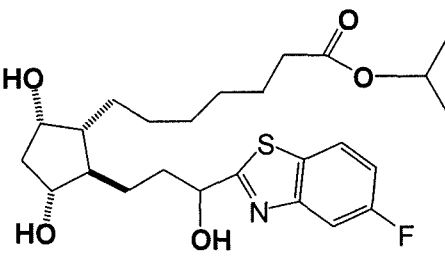
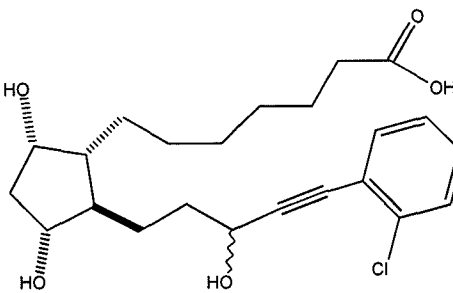
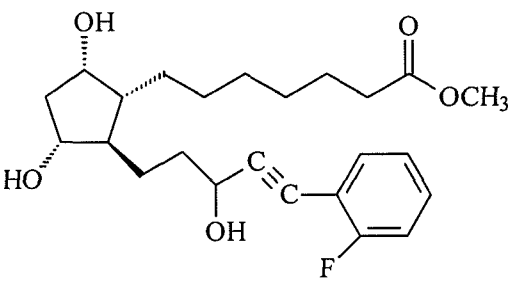
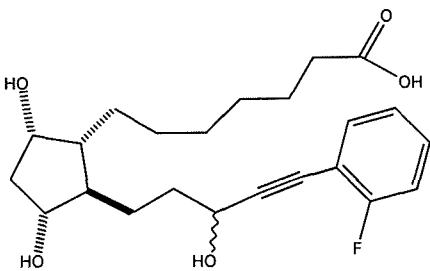
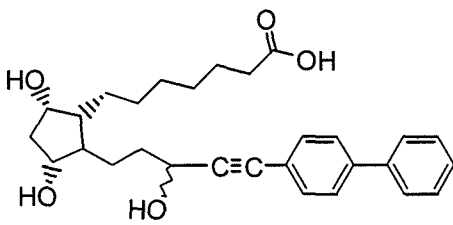
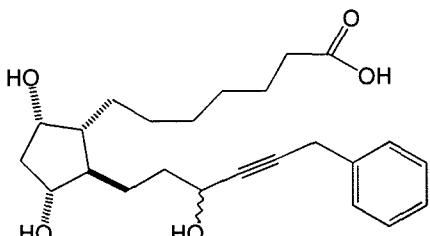
In **Scheme 3**, R^1 and Z are as defined above. The alkene **S1b** (from **Scheme 1**) is treated with an osmium salt and with an optional catalyst reoxidant, preferably *N*-methyl morpholine *N*-oxide ("NMO"), to give the diol. This diol is isolated by extraction and purified by silica gel chromatography. The diol is then oxidized selectively to the *alpha* hydroxy aldehyde. This may be accomplished in several ways. For example, a selective oxidant such as DMSO-oxalyl chloride may be used. ("DMSO" represents dimethylsulfoxide.) Alternatively, the primary alcohol may be selectively protected, then the secondary alcohol protected, then the protection on the primary alcohol may then be removed and the alcohol oxidized as described above in **Scheme II**. However, the preferred method is the addition of a *o*-bromo-benzyl bromide protecting group, which can be removed with concomitant oxidation by tributyl tin hydride and like reagents. This technique yields compounds of the type **S3a**, wherein Q = H. From this step follows the condensation of the aldehyde with an amine to form an imine of the type **S3b**. Appropriate removal of protecting groups and manipulation of C-1 as stated above in **Schemes I** and **II** yields compounds of **Formula V**.

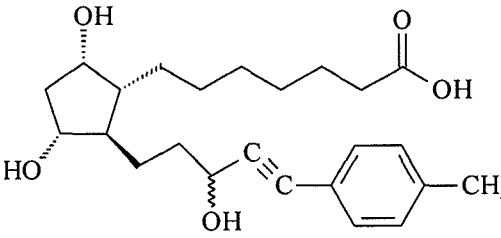
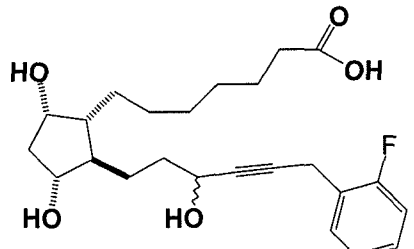
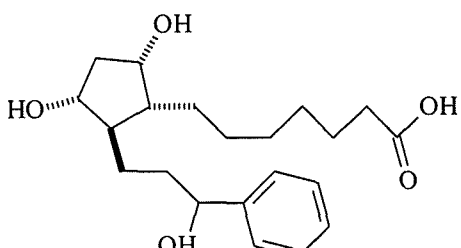
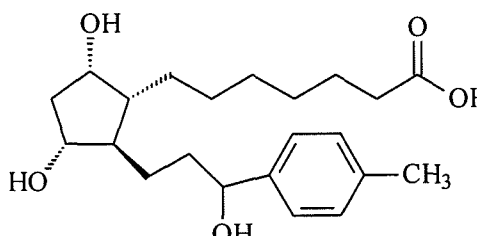
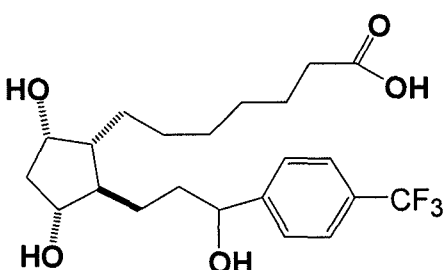
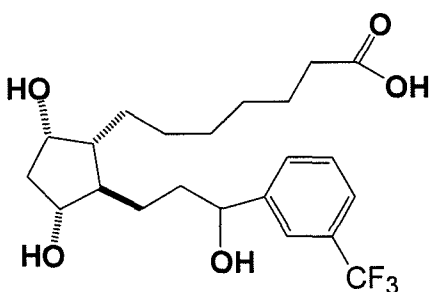
Table 2: Examples of Suitable PGF's

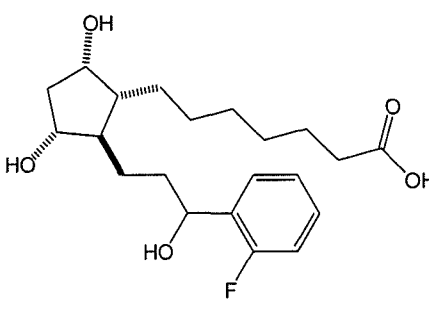
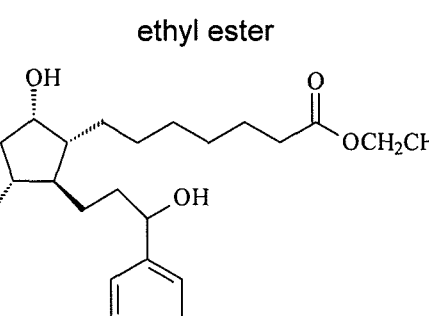
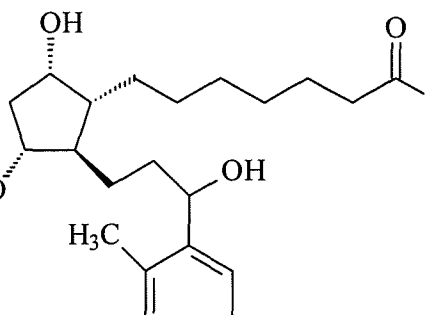
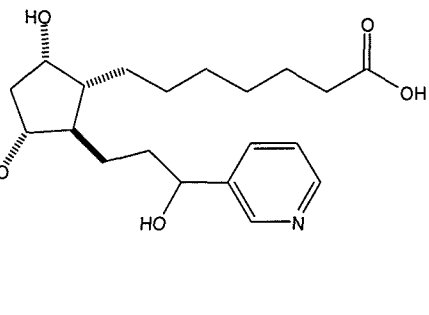
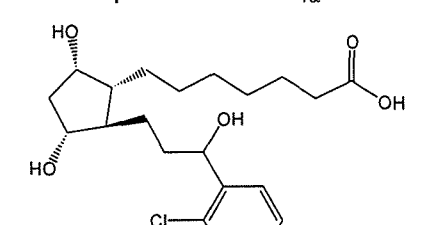
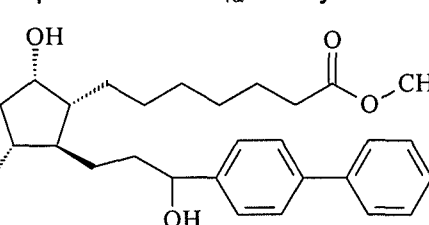
13,14-dihydro-15-(2-benzothienyl)-15-pentanor PGF_{1α} 	13,14-dihydro-15-(2-benzothiazolyl)-15-pentanor PGF_{1α} 
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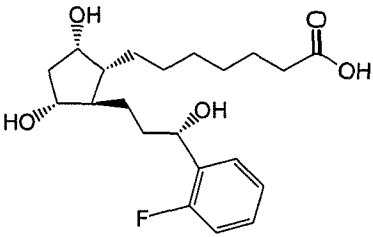
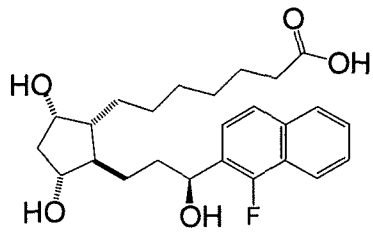
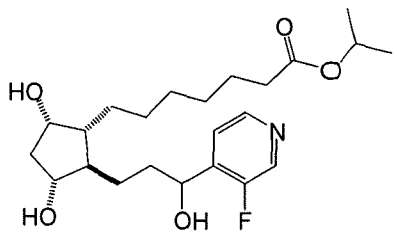
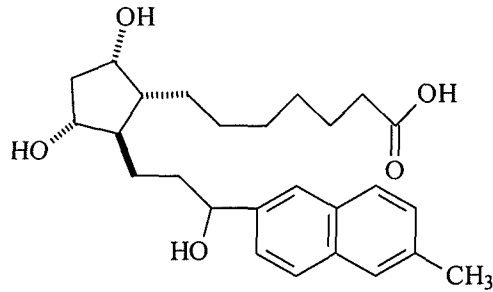
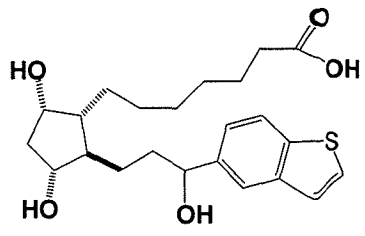
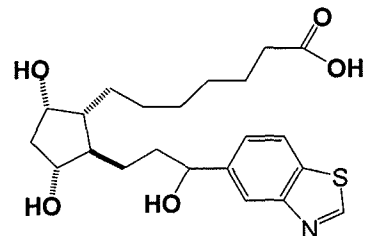
13,14-dihydro-15-(8-fluoro-2-benzothiazolyl)-15-pentanor PGF_{1α} 	13,14-dihydro-16,17-ynyl-17-(2,5-difluorophenyl)-17-trinor PGF_{1α} 
13,14-dihydro-16,17-ynyl-17-(2,3-difluorophenyl)-17-trinor PGF_{1α} 	13,14-dihydro-16,17-ynyl-17-(3,5-difluorophenyl)-17-trinor PGF_{1α} 
13,14-dihydro-16,17-ynyl-17-(3,4-difluorophenyl)-17-trinor PGF_{1α} 	13,14-dihydro-15-(6-fluoro-2-benzothieryl)-15-pentanor PGF_{1α} 

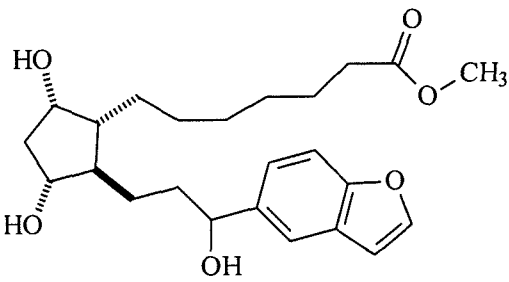
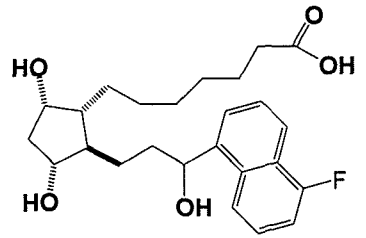
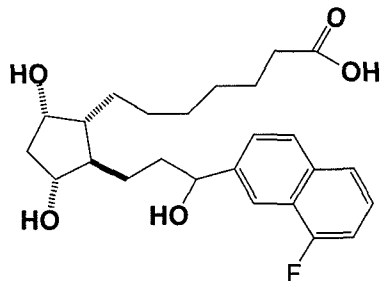
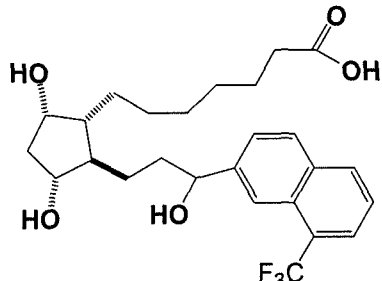
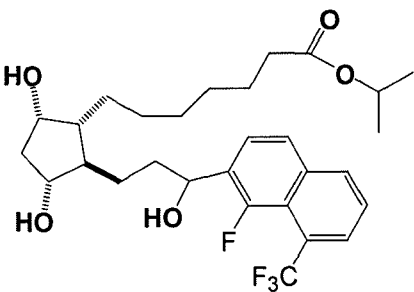
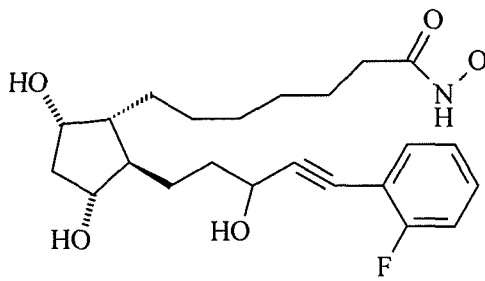
3,14-dihydro-16,17-ynyl-17-(2,4-difluorophenyl)-17-trinor PGF_{1α} 	13,14-dihydro-16,17-ynyl-17-(3-fluorophenyl)-17-trinor PGF_{1α} methyl ester 
13,14-dihydro-16,17-ynyl-17-(2-fluoro-4-methylphenyl)-17-trinor PGF_{1α} 	13,14-dihydro-16,17-ynyl-17-(4-chlorophenyl)-17-trinor PGF_{1α} 
13,14-dihydro-16,17-ynyl-17-phenyl-17-trinor PGF_{1α} isopropyl ester 	13,14-dihydro-16,17-ynyl-17-(4-fluorophenyl)-17-trinor PGF_{1α} ethyl ester 

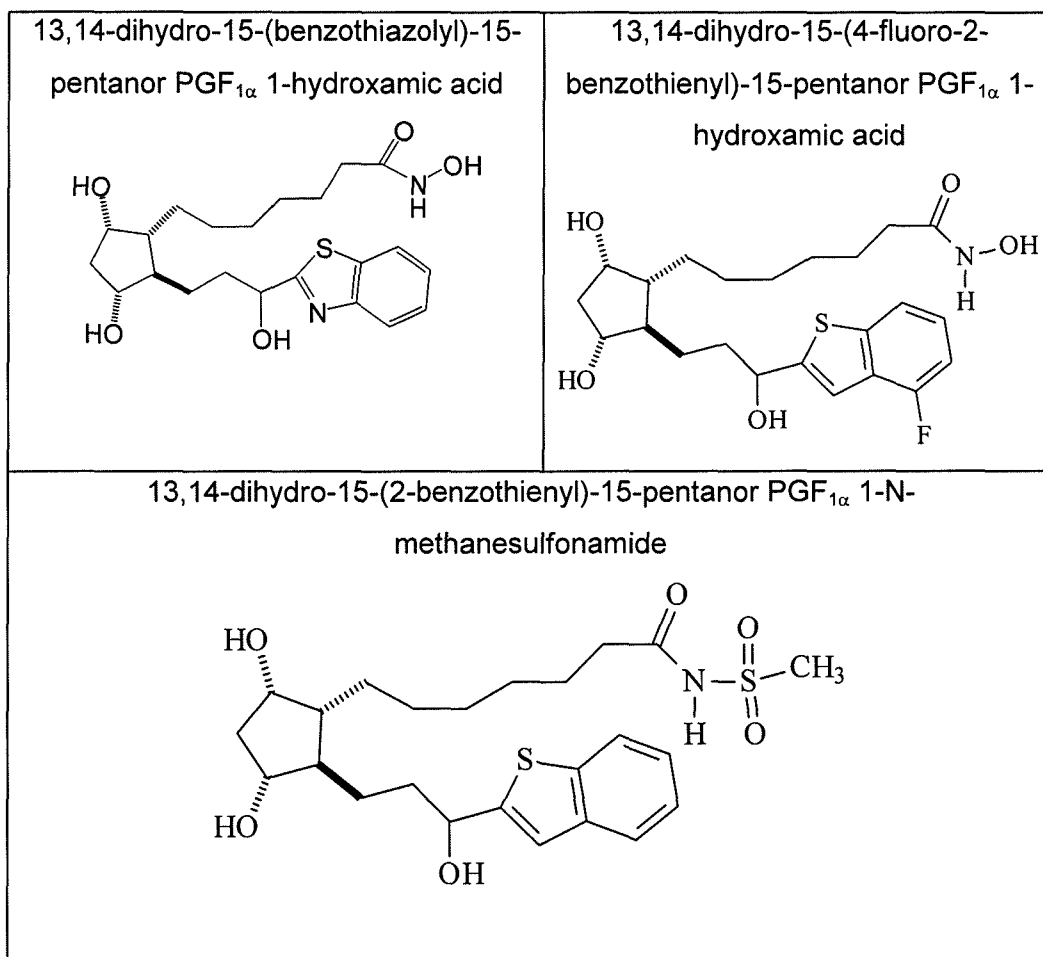
13,14-dihydro-15-(5-fluoro-2-benzothiazolyl)-15-pentanor $\text{PGF}_{1\alpha}$ isopropyl ester 	13,14-dihydro-16,17-ynyl-17-(2-chlorophenyl)-17-trinor $\text{PGF}_{1\alpha}$ 
13,14-dihydro-16,17-ynyl-17-(2-fluorophenyl)-17-trinor $\text{PGF}_{1\alpha}$ methyl ester 	13,14-dihydro-16,17-ynyl-17-(2-fluorophenyl)-17-trinor $\text{PGF}_{1\alpha}$ 
13,14-dihydro-16,17-ynyl-17-(4-phenyl-phenyl)-17-trinor $\text{PGF}_{1\alpha}$ 	13,14-dihydro-16,17-ynyl-18-phenyl-18-dinor $\text{PGF}_{1\alpha}$ 

13,14-dihydro-16,17-ynyl-17-(4-methylphenyl)-17-trinor $\text{PGF}_{1\alpha}$ 	13,14-dihydro-16,17-ynyl-18-(2-fluorophenyl)-18-dinor $\text{PGF}_{1\alpha}$ 
13,14-dihydro-15-phenyl-15-pentanor $\text{PGF}_{1\alpha}$ 	13,14-dihydro-15-(4-methylphenyl)-15-pentanor $\text{PGF}_{1\alpha}$ 
13,14-dihydro-15-(4-trifluoromethylphenyl)-15-pentanor $\text{PGF}_{1\alpha}$ 	13,14-dihydro-15-(3-trifluoromethylphenyl)-15-pentanor $\text{PGF}_{1\alpha}$ 

13,14-dihydro-15-(2-fluorophenyl)-15-pentanoic acid $\text{PGF}_{1\alpha}$ 	13,14-dihydro-15-(3,5-difluorophenyl)-15-pentanoic acid ethyl ester $\text{PGF}_{1\alpha}$ 
13,14-dihydro-15-(3-chloro-4-fluoro-6-methylphenyl)-15-pentanoic acid $\text{PGF}_{1\alpha}$ 	13,14-dihydro-15-(3-pyridinyl)-15-pentanoic acid $\text{PGF}_{1\alpha}$ 
13,14-dihydro-15-(2-chlorophenyl)-15-pentanoic acid $\text{PGF}_{1\alpha}$ 	13,14-dihydro-15-(4-phenylphenyl)-15-pentanoic acid methyl ester $\text{PGF}_{1\alpha}$ 

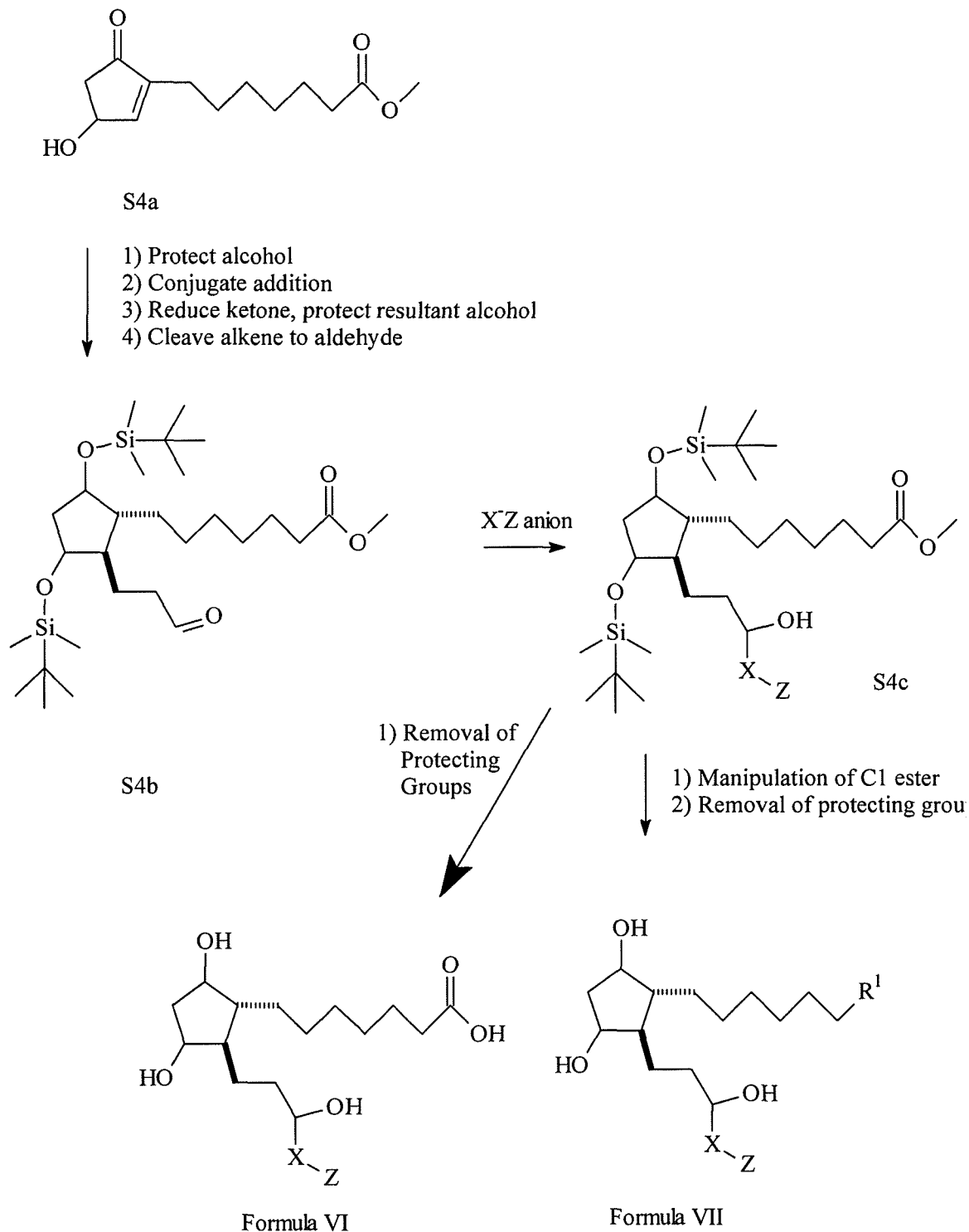
13,14-dihydro-15-S-(2-fluorophenyl)- 15-pentanoic acid $\text{PGF}_{1\alpha}$ 	13,14-dihydro-15-S-(2-fluoronaphthyl)-15-pentanoic acid $\text{PGF}_{1\alpha}$ 
13,14-dihydro-15-(3-fluoro-4-pyridyl)- 15-pentanoic acid $\text{PGF}_{1\alpha}$ isopropyl ester 	13,14-dihydro-15-(6-methylnaphth-2-yl)-15-pentanoic acid $\text{PGF}_{1\alpha}$ 
13,14-dihydro-15-(benzo(b)thiophen-5-yl)-15-pentanoic acid $\text{PGF}_{1\alpha}$ 	13,14-dihydro-15-(6-benzothiazol-5-yl)-15-pentanoic acid $\text{PGF}_{1\alpha}$ 

13,14-dihydro-15-(benzofuran-5-yl)-15-pentanoic acid methyl ester 	13,14-dihydro-15-(5-fluoronaphth-1-yl)-15-pentanoic acid 
13,14-dihydro-15-(8-fluoro-2-naphthyl)-15-pentanoic acid 	13,14-dihydro-15-(8-trifluoromethyl-2-naphthyl)-15-pentanoic acid 
13,14-dihydro-15-(1-fluoro-3-trifluoromethyl-2-naphthyl)-15-pentanoic acid isopropyl ester 	13,14-dihydro-16,17-ynyl-17-(2-fluorophenyl)-17-trinor PGF_{1α} 1-hydroxamic acid 



The PGF's in Table 2 can be prepared by conventional organic syntheses. A preferred synthesis is reaction scheme 4.

Scheme 4



In **Scheme 4**, R¹, R², X, and Z are as defined above. The methyl 7(3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl) heptanoate (**S4a**) depicted as starting material for

Scheme 4 is commercially available (such as from Sumitomo Chemical or Cayman Chemical).

The C₁₁ alcohol of methyl 7-(3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl) heptanoate (**S4a**) is protected with a suitable protecting group. The most preferred protecting group is a silyl group. In the above **Scheme 4**, methyl 7-(3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl) heptanoate (**S4a**) is reacted with a silylating agent and base in a solvent that will allow the silylation to proceed. Preferred silylating agents include tert-butyldimethylsilyl chloride and tert-butyldimethylsilyl trifluoromethanesulphonate. The most preferred silylating agent is tert-butyldimethylsilyl trifluoromethanesulphonate. Preferred bases include triethylamine, trimethylamine, and 2,6-lutidine. More preferred bases include triethylamine and 2,6-lutidine. The most preferred base is 2,6-lutidine. Preferred solvents include halogenated hydrocarbon solvents with dichloromethane being the most preferred solvent. The reaction is allowed to proceed at a temperature of preferably -100°C to 100°C, more preferably -80°C to 80°C, and most preferably -70°C to 23°C.

The resulting silylated compound is isolated by methods known to those of ordinary skill in the art. Such methods include extraction, solvent evaporation, distillation, and crystallization. Preferably, the silyl ether is purified after isolation by distillation under vacuum.

The silylated compound is then reacted with the cuprate generated via Grignard formation of the appropriate alkenyl bromide as disclosed, for example, in the following references: H.O. House et. al., "The Chemistry of Carbanions: A Convenient Precursor for the Generation of Lithium Organocuprates", J. Org. Chem., Vol. 40, pp. 1460-69 (1975); and P. Knochel et. al., "Zinc and Copper Carbenoids as Efficient and Selective a'/d' Multicoupling Reagents", J. Amer. Chem. Soc., Vol. 111, p. 6474-76 (1989). Preferred alkenyl bromides include 4-bromo-1-butene, 4-bromo-1-butyne, 4-bromo-2-methyl-1-butene, and 4-bromo-2-ethyl-1-butene. The most preferred alkenyl bromide is 4-bromo-1-butene.

Preferred solvents include ethereal solvents, of which diethyl ether and tetrahydrofuran are preferred. The most preferred solvent is tetrahydrofuran. The Grignard reagent is allowed to form at a temperature of 100°C to 23°C, more preferably 85°C to 30°C, and most preferably 75°C to 65°C. The reaction time is preferably 1 to 6 hours, more preferably 2 to 5 hours, and most preferably 3 to 4 hours.

Once the Grignard reagent is formed, the cuprate is generated from the alkenyl magnesium species. The temperature range for cuprate formation is -100°C and 0°C. The preferred temperature range is -80°C to -20°C, more preferably -75°C to -50°C. The preferred reaction time is 30 minutes to 6 hours, more preferably 45 minutes to 3 hours, and most preferably 1 to 1.5 hours.

The alkene thus formed is isolated by methods known to one of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, the alkene is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 10% EtOAc/hexanes as the eluent. The alkene is then reacted with a hydride reducing agent and a polar, protic solvent to give the C-9 alcohol. Preferred reducing agents include lithium aluminum hydride, sodium borohydride, and L-selectride. More preferred reducing agents include sodium borohydride, and L-selectride. The most preferred reducing agent is sodium borohydride. Preferred solvents include methanol, ethanol, and butanol. The most preferred solvent is methanol. The reduction is carried out at a temperature between -100°C and 23°C. The preferred temperature range is -60°C to 0°C. The most preferred temperature range is -45°C to -20°C.

The resulting alcohol is isolated by methods known to one of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, the alcohol is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent.

The resultant alcohol can be protected as described previously herein. Preferred silylating agents in this case also include tert-butyldimethylsilyl chloride and tert-butyldimethylsilyl trifluoromethanesulfonate. The most preferred silylating agent is tert-butyldimethylsilyl trifluoromethanesulfonate. Preferred bases include triethylamine, trimethylamine, and 2,6-lutidine. More preferred bases include triethylamine and 2,6-lutidine. The most preferred base is 2,6-lutidine. Preferred solvents include halogenated hydrocarbon solvents with dichloromethane being the most preferred solvent. The reaction is allowed to proceed at a temperature of preferably -100°C to 100°C, more preferably -80°C to 80°C, and most preferably -70°C to 23°C.

The resulting silylated compound is isolated by methods known to those of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent

evaporation, distillation, and crystallization. Preferably, the silyl ether is purified after isolation by distillation under vacuum

The protected or alcohol is then treated with a form of osmium, and sodium periodate in a solvent where they are both soluble. Preferred forms of osmium include osmium tetroxide and potassium osmate. Preferred solvent systems include 1:1 mixtures of acetic acid and water and 1:1:2 mixtures of water, acetic acid and THF. The result of this treatment is the aldehyde, **S4b**.

The compound **S4b** is isolated by methods known to one of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, **S4b** is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent.

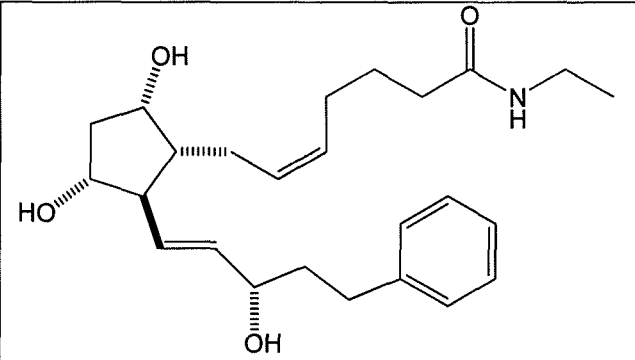
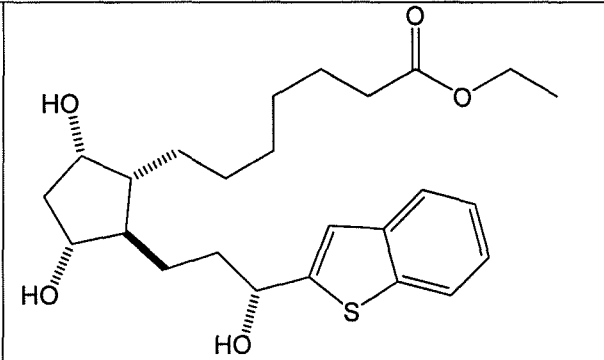
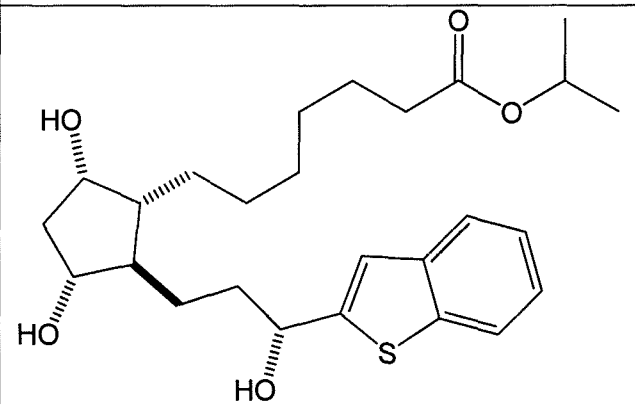
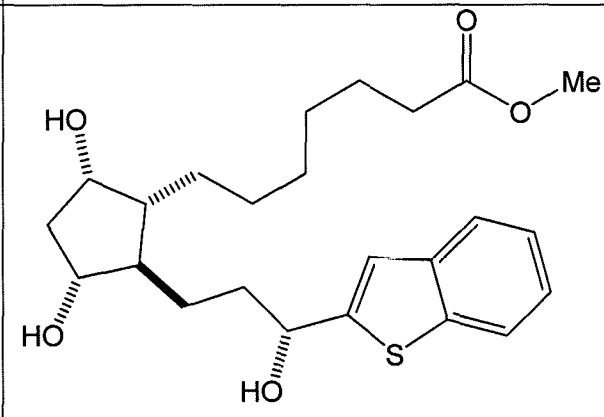
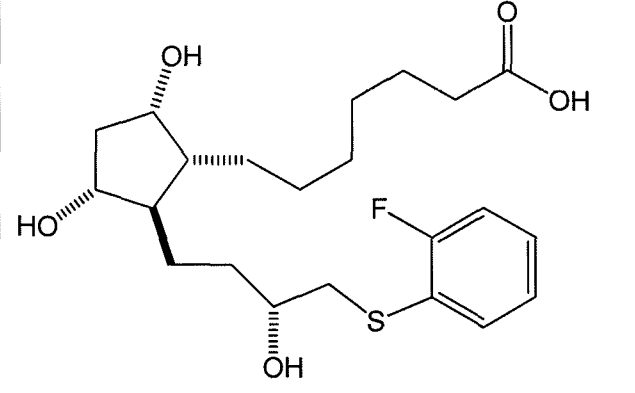
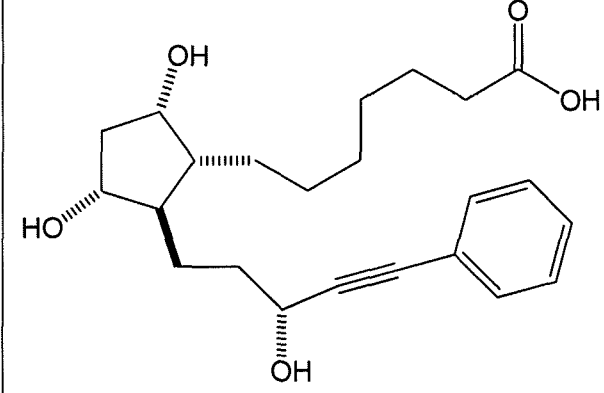
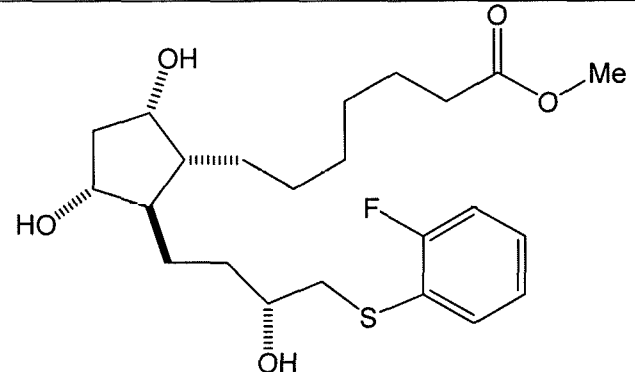
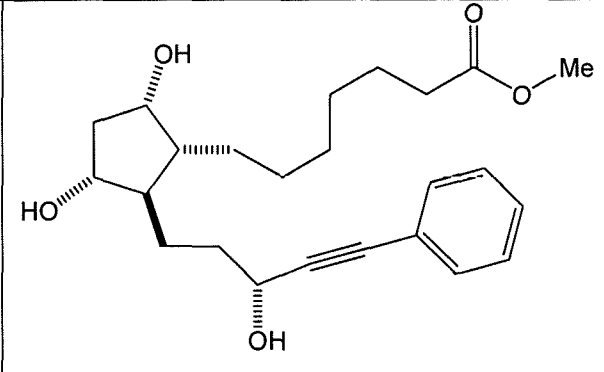
The key intermediate aldehyde depicted as **S4b** can be reacted with a variety unsaturated carbon nucleophiles to provide the C-9 and C-11-protected 13,14-dihydro-16-tetranor prostaglandin $F_{1\alpha}$ derivatives depicted as **S4c**.

With alkyne nucleophiles, the reaction is carried out preferably at -80°C to 0°C , more preferably -80°C to -20°C , and most preferably -80°C to -40°C . Preferred bases for the reaction include *n*-butyl lithium, *s*-butyl lithium, *t*-butyl lithium, and lithium diisopropyl amide ("LDA"). Preferred solvents for the reaction are ether solvents. Preferred solvents include diethyl ether, and tetrahydrofuran. The most preferred solvent is tetrahydrofuran. With heterocyclic nucleophiles, preferred solvents include ethereal solvents. More preferred ethereal solvents include diethyl ether, dibutyl ether and tetrahydrofuran. The most preferred ethereal solvent is tetrahydrofuran.

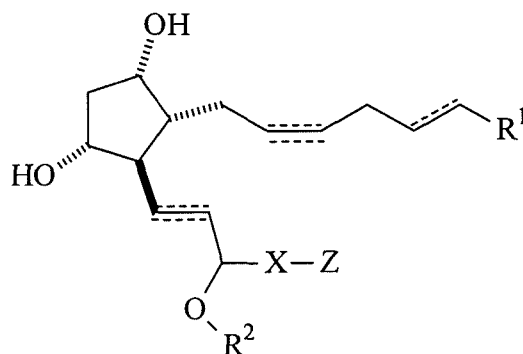
The resulting compounds depicted as **S4c** can then be deprotected using techniques known to one of ordinary skill in the art, and isolated yielding the 13,14-dihydro-15-substituted-15-pentanor prostaglandin $F_{1\alpha}$ derivatives depicted by **Formula VI**.

Compounds depicted by **Formula VII** can be made directly from the C-9 and C-11-protected 13,14-dihydro-16-tetranor prostaglandin $F_{1\alpha}$ derivatives depicted as **S4c** by methods known to one of ordinary skill in the art. For example, the condensation of methyl esters of **S4c** with amines or hydroxylamine provides compounds depicted by **Formula VII**. These compounds are isolated by methods known to one of ordinary skill in the art. Such methods include extraction, solvent evaporation, distillation, and crystallization.

Table 3: Examples of Suitable PGF's

Examples of PGF's having the structure:



which are suitable for component A) include: cloprostenol (estrumate), fluprostenol (equimate), tiaprost, alfaprostol, delprostenate, froxiprost, 9- α , 11- α , 15- α -trihydroxy-16-(3-chlorophenoxy)- ω -tetranor-prosta-4-cis-13-trans-dienoic acid, latanoprost and their analogs; and 13,14-dihydro-16-((3-trifluoromethyl)phenoxy)-16-tetranor prostaglandin $F_{1\alpha}$, 17-((3-trifluoromethyl)phenyl)-17-trinor-prostaglandin $F_{2\alpha}$ and its analogs, 13,14-dihydro-18-thienyl-18-dinor prostaglandin $F_{1\alpha}$ and their analogs. Additional PGF's are also disclosed in CRC Handbook of Eicosanoids: Prostaglandins and Related Lipids, Volume I, Chemical and Biochemical Aspects, Part B. Ed. by Anthony L. Willis, CRC Press, Boca Raton, Table Four, pp. 80-97 (1987) and references therein.

Preferred PGF's of the present invention are further selective for the FP receptor over an excitatory prostaglandin receptor in a ratio of 1:10, preferably from 1:20, more preferably from 1:50.

Compositions of the Invention

This invention further relates to compositions for maintaining or promoting patency; relieving nasal congestion; treating neurogenic bladder; treating, relieving or reducing symptoms of neurogenic bladder; and/or treating or relieving respiratory disorders. The composition comprises component A) the PGF described above and component B) a carrier. The composition may further comprise component C) one or more optional activity enhancers.

The composition can be a pharmaceutical or cosmetic composition, administered to maintain nasal patency. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa (1990).

The composition further comprises component B) a carrier. "Carrier" means one or more compatible substances that are suitable for administration to a mammal. Carrier includes solid or liquid diluents, hydrotopes, surface-active agents, and encapsulating substances. "Compatible" means that the components of the composition are capable of being commingled with the PGF's, and with each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the composition under ordinary use situations. Carriers must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the mammal being treated. The carrier can be inert, or it can possess pharmaceutical benefits, cosmetic benefits, or both.

The choice of carrier for component B) depends on the route by which A) the PGF will be administered and the form of the composition. The composition may be in a variety of forms, suitable, for example, for systemic administration (e.g., oral, rectal, nasal, sublingual, buccal, or parenteral) or topical administration (e.g., local application on the skin, mucous membranes, liposome delivery systems, or iontophoresis). Topical administration directly to the nasal mucous membranes is preferred.

Carriers for systemic administration typically comprise one or more ingredients selected from the group consisting of a) diluents, b) lubricants, c) binders, d) disintegrants, e) colorants, f) flavors, g) sweeteners, h) antioxidants, j) preservatives, k) glidants, m) solvents, n) suspending agents, o) surfactants, combinations thereof, and others.

Ingredient a) is a diluent. Suitable diluents include sugars such as glucose, lactose, dextrose, and sucrose; polyols such as propylene glycol; calcium carbonate; sodium carbonate; glycerin; mannitol; sorbitol; and maltodextrin.

Ingredient b) is a lubricant. Suitable lubricants are exemplified by solid lubricants including silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate; and liquid lubricants such as polyethylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma.

Ingredient c) is a binder. Suitable binders include polyvinylpyrrolidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethylcellulose, methylcellulose, microcrystalline cellulose, and

hydroxypropylmethylcellulose; carbomer; providone; acacia; guar gum; and xanthan gum.

Ingredient d) is a disintegrant. Suitable disintegrants include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmellose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins.

Ingredient e) is a colorant such as an FD&C dye.

Ingredient f) is a flavor such as menthol, peppermint, and fruit flavors.

Ingredient g) is a sweetener such as saccharin and aspartame.

Ingredient h) is an antioxidant such as butylated hydroxyanisole, butylated hydroxytoluene, and vitamin E.

Ingredient j) is a preservative such as phenol, alkyl esters of parahydroxybenzoic acid, benzoic acid and the salts thereof, boric acid and the salts thereof, sorbic acid and the salts thereof, chlorbutanol, benzyl alcohol, thimerosal, phenylmercuric acetate and nitrate, nitromersol, benzalkonium chloride, cetylpyridinium chloride, methyl paraben, and propyl paraben. Particularly preferred are the salts of benzoic acid, cetylpyridinium chloride, methyl paraben and propyl paraben, and sodium benzoate.

Ingredient k) is a glidant such as silicon dioxide.

Ingredient m) is a solvent, such as water, isotonic saline, ethyl oleate, alcohols such as ethanol, glycerin, glycols (e.g., polypropylene glycol and polyethylene glycol), and buffer solutions (e.g., phosphate, potassium acetate, boric carbonic, phosphoric, succinic, malic, tartaric, citric, acetic, benzoic, lactic, glyceric, gluconic, glutaric and glutamic).

Ingredient n) is a suspending agent. Suitable suspending agents include AVICEL® RC-591 from FMC Corporation of Philadelphia, Pennsylvania and sodium alginate.

Ingredient o) is a surfactant such as lecithin, polysorbate 80, sodium lauryl sulfate, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene monoalkyl ethers, sucrose monoesters, lanolin esters, and lanolin ethers. Suitable surfactants are known in the art and commercially available, e.g., the TWEENS® from Atlas Powder Company of Wilmington, Delaware.

Compositions for parenteral administration typically comprise A) 0.1 to 10% of a PGF and B) 90 to 99.9% of a carrier comprising a) a diluent, and m) a solvent. Preferably, component a) is propylene glycol and m) is ethanol or ethyl oleate.

Compositions for oral administration can have various dosage forms. For example, solid forms include tablets, capsules, granules, and bulk powders. These oral dosage forms comprise a safe and effective amount, usually at least 5%, and preferably from 25% to 50%, of A) the PGF. The oral dosage compositions further comprise B) 50 to 95% of a carrier, preferably 50 to 75%.

Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed. Tablets typically comprise A) the PGF, and B) a carrier comprising ingredients selected from the group consisting of a) diluents, b) lubricants, c) binders, d) disintegrants, e) colorants, f) flavors, g) sweeteners, k) glidants, and combinations thereof. Preferred diluents include calcium carbonate, sodium carbonate, mannitol, lactose and cellulose. Preferred binders include starch, gelatin, and sucrose. Preferred disintegrants include alginic acid, and croscarmellose. Preferred lubricants include magnesium stearate, stearic acid, and talc. Preferred colorants are the FD&C dyes, which can be added for appearance. Chewable tablets preferably contain g) sweeteners such as aspartame and saccharin, or f) flavors such as menthol, peppermint, and fruit flavors.

Capsules (including time release and sustained release formulations) typically comprise A) the PGF, and B) a carrier comprising one or more a) diluents disclosed above in a capsule comprising gelatin. Granules typically comprise A) the PGF, and preferably further comprise k) glidants such as silicon dioxide to improve flow characteristics.

The selection of ingredients in the carrier for oral compositions depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this invention. One skilled in the art can optimize appropriate ingredients without undue experimentation.

The solid compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that A) the PGF is released in the gastrointestinal tract at various times to extend the desired action. The coatings typically comprise one or more components selected from the group consisting of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, acrylic resins such as EUDRAGIT® coatings (available from Rohm & Haas G.M.B.H. of Darmstadt, Germany), waxes, shellac, polyvinylpyrrolidone, and other commercially available film-coating preparations such as Dri-Klear, manufactured by

Crompton & Knowles Corp., Mahwah, NJ or OPADRY® manufactured by Colorcon, Inc., of West Point, Pennsylvania.

Compositions for oral administration can also have liquid forms. For example, suitable liquid forms include aqueous solutions, emulsions, suspensions, solutions reconstituted from non-effervescent granules, suspensions reconstituted from non-effervescent granules, effervescent preparations reconstituted from effervescent granules, elixirs, tinctures, syrups, and the like. Liquid orally administered compositions typically comprise A) the PGF and B) a carrier comprising ingredients selected from the group consisting of a) diluents, e) colorants, and f) flavors, g) sweeteners, j) preservatives, m) solvents, n) suspending agents, and o) surfactants. *Peroral* liquid compositions preferably comprise one or more ingredients selected from the group consisting of e) colorants, f) flavors, and g) sweeteners.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as a) diluents including sucrose, sorbitol and mannitol; and c) binders such as acacia, microcrystalline cellulose, carboxymethylcellulose, and hydroxypropylmethylcellulose. Such compositions may further comprise b) lubricants, e) colorants, f) flavors, g) sweeteners, h) antioxidants, and k) glidants.

Component ii) is a penetration enhancer that can be added to all of the compositions for systemic administration. The amount of component ii), when present in the composition, is typically 1 to 5 %. Examples of penetration enhancers include 2-methyl propan-2-ol, propan-2-ol, ethyl-2-hydroxypropanoate, hexan-2,5-diol, polyoxyethylene(2) ethyl ether, di(2-hydroxypropyl) ether, pentan-2,4-diol, acetone, polyoxyethylene(2) methyl ether, 2-hydroxypropionic acid, 2-hydroxyoctanoic acid, propan-1-ol, 1,4-dioxane, tetrahydrofuran, butan-1,4-diol, propylene glycol dipelargonate, polyoxypropylene 15 stearyl ether, octyl alcohol, polyoxyethylene ester of oleyl alcohol, oleyl alcohol, lauryl alcohol, dioctyl adipate, dicapryl adipate, di-isopropyl adipate, di-isopropyl sebacate, dibutyl sebacate, diethyl sebacate, dimethyl sebacate, dioctyl sebacate, dibutyl suberate, dioctyl azelate, dibenzyl sebacate, dibutyl phthalate, dibutyl azelate, ethyl myristate, dimethyl azelate, butyl myristate, dibutyl succinate, didecyl phthalate, decyl oleate, ethyl caproate, ethyl salicylate, isopropyl palmitate, ethyl laurate, 2-ethyl-hexyl pelargonate, isopropyl isostearate, butyl laurate, benzyl benzoate, butyl benzoate, hexyl laurate, ethyl caprate, ethyl caprylate, butyl stearate, benzyl

salicylate, 2-hydroxypropanoic acid, 2-hydroxyoctanoic acid, dimethyl sulphoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, phosphine oxides, sugar esters, tetrahydrofurfural alcohol, urea, diethyl-m-toluamide, 1-dodecylazacycloheptan-2-one, omega three fatty acids and fish oils, and combinations thereof.

In a preferred embodiment of the invention, the PGF's are topically administered. Topical compositions that can be applied locally to the skin may be in any form including solutions, oils, creams, ointments, gels, lotions, milks, cleansers, moisturizers, sprays, skin patches, and the like. Topical compositions comprise: component A) the PGF described above and component B) a carrier.

The exact amounts of each component in the topical composition depend on various factors. The amount of component A) depends on the IC_{50} of the PGF selected. " IC_{50} " means inhibitory concentration 50th percentile. The amount of component A) added to the topical composition is:

$$IC_{50} \times 10^{-2} \geq \% \text{ of component A) } \geq IC_{50} \times 10^{-3},$$

where IC_{50} is expressed in nanomolar units. For example, if the IC_{50} of the PGF is 1 nM, the amount of component A) will be 0.001 to 0.01%. If the IC_{50} of the PGF is 10 nM, the amount of component A) will be 0.01 to 0.1%. If the IC_{50} of the PGF is 100 nM, the amount of component A) will be 0.1 to 1.0%. If the IC_{50} of the PGF is 1000 nM, the amount of component A) will be 1.0 to 10%, preferably 1.0 to 5%. If the amount of component A) is outside the ranges specified above (i.e., either higher or lower), efficacy of the treatment may be reduced. IC_{50} can be calculated according to the method in Reference Example 1, below. One skilled in the art can calculate IC_{50} without undue experimentation.

The topical composition preferably further comprises 1 to 20% component C), and a sufficient amount of component B) such that the amounts of components A), B), and C), combined equal 100%. The amount of B) the carrier employed in conjunction with the PGF is sufficient to provide a practical quantity of composition for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

Component B) the carrier may comprise a single ingredient or a combination of two or more ingredients. In the topical compositions, component B) is a topical carrier. Preferred topical carriers comprise one or more ingredients selected from the group consisting of water, alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, polypropylene glycol-2 myristyl propionate, dimethyl isosorbide, combinations thereof, and the like. More preferred carriers include propylene glycol, dimethyl isosorbide, and water.

The topical carrier may comprise one or more ingredients selected from the group consisting of q) emollients, r) propellants, s) solvents, t) humectants, u) thickeners, v) powders, and w) fragrances in addition to, or instead of, the preferred topical carrier ingredients listed above. One skilled in the art would be able to optimize carrier ingredients for the topical compositions without undue experimentation.

Ingredient q) is an emollient. The amount of ingredient q) in the topical composition is typically 5 to 95%. Suitable emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petrolatum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate, polydimethylsiloxane, and combinations thereof. Preferred emollients include stearyl alcohol and polydimethylsiloxane.

Ingredient r) is a propellant. The amount of ingredient r) in the topical composition is typically 5 to 95%. Suitable propellants include propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide, and combinations thereof.

Ingredient s) is a solvent. The amount of ingredient s) in the topical composition is typically 5 to 95 %. Suitable solvents include water, ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulfoxide, dimethyl formamide, tetrahydrofuran, and combinations thereof. Preferred solvents include ethyl alcohol.

Ingredient t) is a humectant. The amount of ingredient t) in the topical composition is typically 5 to 95 %. Suitable humectants include glycerin, sorbitol, sodium

2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and combinations thereof. Preferred humectants include glycerin.

Ingredient u) is a thickener. The amount of ingredient u) in the topical composition is typically 0 to 95%.

Ingredient v) is a powder. The amount of ingredient v) in the topical composition is typically 0 to 95 %. Suitable powders include chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminum silicate, organically modified montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, and combinations thereof.

Ingredient w) is a fragrance. The amount of ingredient w) in the topical composition is typically 0.001 to 0.5%, preferably 0.001 to 0.1%.

In an alternative embodiment of the invention, topical pharmaceutical compositions for nasal administration are prepared by conventional methods. Topical pharmaceutical compositions for nasal administration typically comprise A) a PGF, B) a carrier, such as purified water, and one or more ingredients selected from the group consisting of y) sugars such as dextrans, particularly dextran 70, z) cellulose or a derivative thereof, aa) a salt, bb) disodium EDTA (Edetate disodium), and cc) a pH adjusting additive.

Examples of z) cellulose derivatives suitable for use in the topical pharmaceutical composition for nasal administration include sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and hydroxypropylmethylcellulose. Hydroxypropylmethylcellulose is preferred.

Examples of aa) salts suitable for use in the for use in the topical pharmaceutical composition for nasal administration include sodium chloride, potassium chloride, and combinations thereof.

Examples of cc) pH adjusting additives include HCl or NaOH in amounts sufficient to adjust the pH of the topical pharmaceutical composition for nasal administration to 7.2-7.5.

The PGF's may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The PGF's may also be administered by iontophoresis. See, e.g., Internet site www.unipr.it/arpa/dipfarm/erasmus/erasm14.html; Banga et al., "Hydrogel-based Iontotherapeutic Delivery Devices for Transdermal Delivery of Peptide/Protein Drugs", Pharm. Res., Vol. 10 (5), pp. 697-702 (1993); Ferry, "Theoretical Model of Iontophoresis Utilized in Transdermal Drug Delivery", Pharmaceutical Acta Helvetiae, Vol 70, pp. 279-287 (1995); Gangarosa et al., "Modern Iontophoresis for Local Drug Delivery", Int. J. Pharm., Vol. 123, pp. 159-171 (1995); Green et al., "Iontophoretic Delivery of a Series of Tripeptides Across the Skin *in vitro*", Pharm. Res., Vol 8, pp. 1121-1127 (1991); Jadoul et al., "Quantification and Localization of Fentanyl and TRH Delivered by Iontophoresis in the Skin", Int. J. Pharm., Vol. 120, pp. 221-8 (1995); O'Brien et al., "An Updated Review of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Efficacy", Drugs, Vol. 37, pp. 233-309 (1989); Parry et al., "Acyclovir Bioavailability in Human Skin", J. Invest. Dermatol., Vol. 98 (6), pp. 856-63 (1992); Santi et al., "Drug Reservoir Composition and Transport of Salmon Calcitonin in Transdermal Iontophoresis", Pharm. Res., Vol 14 (1), pp. 63-66 (1997); Santi et al., "Reverse Iontophoresis - Parameters Determining Electroosmotic Flow: I. pH and Ionic Strength", J. Control. Release, Vol. 38, pp. 159-165 (1996); Santi et al., "Reverse Iontophoresis - Parameters Determining Electroosmotic Flow: II. Electrode Chamber Formulation", J. Control. Release, Vol. 42, pp. 29-36 (1996); Rao et al., "Reverse Iontophoresis: Noninvasive Glucose Monitoring *in vivo* in Humans", Pharm. Res., Vol. 12 (12), pp. 1869-1873 (1995); Thysman et al., "Human Calcitonin Delivery in Rats by Iontophoresis", J. Pharm. Pharmacol., Vol. 46, pp. 725-730 (1994); and Volpato et al., "Iontophoresis Enhances the Transport of Acyclovir through Nude Mouse Skin by Electorepulsion and Electroosmosis", Pharm. Res., Vol. 12 (11), pp. 1623-1627 (1995).

The PGF's may be included in kits comprising a PGF, a systemic or topical composition described above, or both; and information, instructions, or both that use of the kit will maintain nasal patency in mammals (particularly humans). The information and instructions may be in the form of words, pictures, or both, and the like. In addition or in the alternative, the kit may comprise a PGF, a composition, or both; and information, instructions, or both, regarding methods of application of the PGF or composition, preferably with the benefit of maintaining nasal patency in mammals.

Methods of the Invention

This invention further relates to methods for maintaining or promoting patency; relieving nasal congestion; treating neurogenic bladder; treating, relieving or reducing

symptoms of neurogenic bladder; and/or treating or relieving respiratory disorders. The method comprises administering to a mammal (preferably a human) suffering from the above, a PGF described above. Preferably, a systemic or topical composition comprising A) the PGF and B) a carrier is administered to the mammal. More preferably, the composition is a topical composition.

The dosage of the PGF administered depends on the method of administration. For systemic administration, (e.g., oral, rectal, nasal, sublingual, buccal, or parenteral), typically, 0.5 mg to 300 mg, preferably 0.5 mg to 100 mg, more preferably 0.1 mg to 10 mg, of a PGF described above is administered per day. These dosage ranges are merely exemplary, and daily administration can be adjusted depending on various factors. The specific dosage of the PGF to be administered, as well as the duration of treatment, and whether the treatment is topical or systemic are interdependent. The dosage and treatment regimen will also depend upon such factors as the specific PGF used, the treatment indication, the efficacy of the compound, the personal attributes of the subject (such as, for example, weight, age, sex, and medical condition of the subject), compliance with the treatment regimen, and the presence and severity of any side effects of the treatment.

For topical administration (e.g., local application on the skin, mucous membranes, liposome delivery systems, or iontophoresis), the topical composition is typically administered once per day. The topical compositions are administered daily for a relatively short amount of time (i.e., on the order of weeks). Generally, 6 to 12 weeks is sufficient. The topical compositions are preferably leave-on compositions. In general, the topical composition should not be removed for at least several hours after administration.

EXAMPLES

These examples are intended to illustrate the invention to those skilled in the art and should not be interpreted as limiting the scope of the invention set forth in the claims.

Reference Example 1 - Radioligand Binding Assay

IC₅₀ of a PGF can be determined relative to PGF_{2α} using the Radioligand Binding Assay. As a control, the IC₅₀ for PGF_{2α} itself should be no lower than 1.0 nM and no higher than 5.0 nM.

In this assay, COS-7 cells are transiently transfected with the hFP recombinant plasmid using LipofectAMINE Reagent. Forty-eight hours later, the transfected cells are washed with Hank's Balanced Salt Solution (HBSS, without CaCl_2 , MgCl_2 , MgSO_4 , or phenol red). The cells are detached with versene, and HBSS is added. The mixture is centrifuged at 200g for 10 minutes, at 4°C to pellet the cells. The pellet is resuspended in Phosphate-Buffered Saline-EDTA buffer (PBS; 1 mM EDTA; pH 7.4; 4°C). The cells are disrupted by nitrogen cavitation (Parr model 4639), at 800 psi, for 15 minutes at 4°C. The mixture is centrifuged at 1000g for 10 minutes at 4°C. The supernatant is centrifuged at 100,000g for 60 minutes at 4°C. The pellet is resuspended to 1 mg protein/mL TME buffer (50 mM Tris; 10 mM MgCl_2 ; 1 mM EDTA; pH 6.0; 4°C) based on protein levels measured using the Pierce BCA Protein Assay kit. The homogenate is mixed for 10 seconds using a Kinematica POLYTRON® (available from KINEMATICA AG, Luzernerstrasse 147A CH-6014 Littau, Switzerland). The membrane preparations are then stored at -80°C, until thawed for assay use.

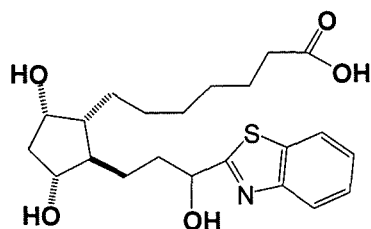
The receptor competition binding assays are developed in a 96 well format. Each well contains 100 g of hFP membrane, 5 nM (3 H) PGF₂, and the various competing compounds in a total volume of 200 L. The plates are incubated at 23°C for 1 hour. The incubation is terminated by rapid filtration using the Packard Filtermate 196 harvester through Packard UNIFILTER® GF/B filters (available from Packard Instrument Co., Inc. of Downers Grove Illinois) pre-wetted with TME buffer. The filter is washed four times with TME buffer. Packard Microscint 20, a high efficiency liquid scintillation cocktail, is added to the filter plate wells and the plates remain at room temperature for three hours prior to counting. The plates are read on a Packard TOPCOUNT® Microplate Scintillation Counter (also available from Packard Instrument Co., Inc.)

Reference Example 2 – Assay

Functional Receptor Assays: Compounds are evaluated for functional activity in a fibroblastic rat cell line (RAT-1 cells), transiently-transfected with the human FP prostanoid receptor (hFP) or the other excitatory human prostaglandin receptors. This cell line has a constitutively-expressed b-galactosidase proliferation reporter gene (stably-transfected) and the EC₅₀ measured is for a timed hydrolysis of a galactosidase pseudosubstrate. See Messier, T., et al., Pharmacol. and Toxicol. 76: 308-311 (1995).

Example 1

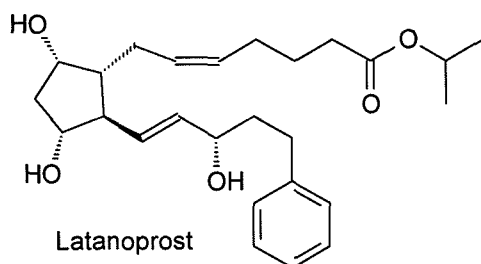
13,14-dihydro-15-(2-benzathiazolyl) pentanor Prostaglandin F₁ α , having the structure:



was tested according to the method Reference Example 1. 13,14-dihydro-15-(2-benzathiazolyl) pentanor Prostaglandin F₁ α had IC₅₀ of 45nM.

Comparative Example 1

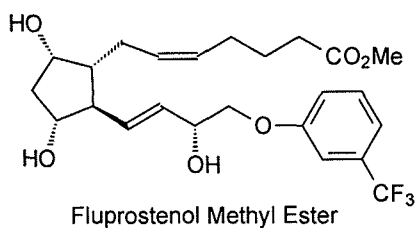
Latanoprost, having the structure:



was tested according to the method Reference Example 1. Latanoprost was active at 0.01% and 0.1%. However, latanoprost is nonselective. Although latanoprost does not negate the effect of activating the FP receptor, latanoprost also activates the EP₁ receptor, which results in the side effect of causing pain.

Example 2

Fluprostenol Methyl Ester having the structure:



was tested according to the method Reference Example 1.

Comparative Example 2

A composition containing 0.01% of a T3 compound was prepared and tested according to the method of Reference Example 1.

Example 3

Compositions for topical administration are made, comprising:

Component	3-1	3-2	3-3
PGF (wt %)	0.019	0.027	0.045
IC ₅₀ the PGF (nM)	19	27	45
Ethanol (wt %)	59.988	59.983	59.973
Propylene Glycol (wt %)	19.996	19.995	19.991
Dimethyl Isosorbide (wt %)	19.996	19.995	19.991

The PGFs in the compositions are as follows:

Sample	PGF
3-1	
3-2	
3-3	

A human male subject suffering from diminished nasal patency is treated by a method of this invention.

Example 4

Pharmaceutical 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>
PGF	0.5
Microcrystalline Cellulose	100
Sodium Starch Glycollate	30
Magnesium Stearate	3

The PGF is the same as that used in Example 3-3.

The above composition is administered orally to a subject once daily for 6 to 12 weeks to promote nasal patency.

Example 5

Pharmaceutical compositions in liquid form are prepared by conventional methods, formulated as follows:

<u>Ingredient</u>	<u>Quantity</u>
PGF	0.1 mg
Phosphate buffered physiological saline	10 ml
Methyl Paraben	0.05ml

The PGF is the same as that used in Example 3-3.

Example 6

A topical pharmaceutical composition is prepared by conventional methods and formulated as follows:

<u>Ingredient</u>	<u>Amount (wt %)</u>
PGF	0.004
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.3

Sodium Chloride	0.77
Potassium chloride	0.12
Disodium EDTA (Edetate disodium)	0.05
Benzalkonium chloride	0.01
HCL and/or NaOH	pH 7.2-7.5
Purified water	q.s. to 100%

The PGF is the same as that used in Example 3-3.

Example 7

The topical pharmaceutical composition of Example 6 is bottled in a conventional nasal spray applicator and given to a patient with nasal congestion due to a cold virus. After inserting into each nostril and squeezing the bottle to spray the material into the nasal passages, the patient experiences an increase in nasal patency.

Example 8

The composition of Example 7 is repeated with a patient suffering from nasal congestion due to an allergy. After inserting into each nostril and squeezing the bottle to spray the material into the nasal passages, the patient experiences an increase in nasal patency.

Example 9

Topical pharmaceutical compositions for instillation into the bladder are prepared by conventional methods and formulated as follows:

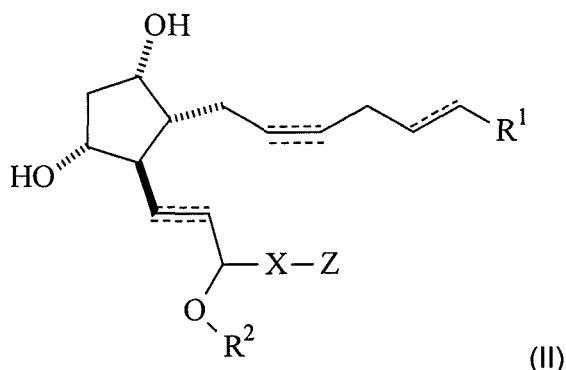
<u>Ingredient</u>	<u>Amount (wt %)</u>
FP selective prostaglandin	0.4
Sodium Chloride	0.77
Potassium chloride	0.12
Disodium EDTA (Edetate disodium)	0.05
Benzalkonium chloride	0.01
HCl and/or NaOH	q.s. to bring pH to 7.2-7.5
Purified water	q.s. to 100%

Intravesical instillation of 1.0 mL of the above solution into the bladder of a patient suffering from neurogenic bladder results in reflex voiding within a few minutes. The procedure is repeated as needed until bladder control is reestablished.

CLAIMS

We claim:

1. A method for maintaining or promoting nasal patency comprising administering to a subject in need thereof an effective amount of at least one prostaglandin F analog (PGF) according to Formula II:



wherein R^1 is selected from the group consisting of $C(O)OH$, $C(O)NHOH$, $C(O)OR^3$, CH_2OH , $S(O)_2R^3$, $C(O)NHR^3$, $C(O)NHS(O)_2R^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogenous group, and lower monovalent hydrocarbon groups;

R^3 is selected from the group consisting of unsubstituted or substituted lower alkyl, lower heteroalkyl, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R^4 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

X is selected from the group consisting of $-C\equiv C-$, $-C\equiv C-CH_2-$, a covalent bond, $-CH=C=CH-$, $-CH=CH-$, $-CH=N-$, $-C(O)-$, $-C(O)Y-$, $-(CH_2)_n-$ wherein n is 2 to 4,

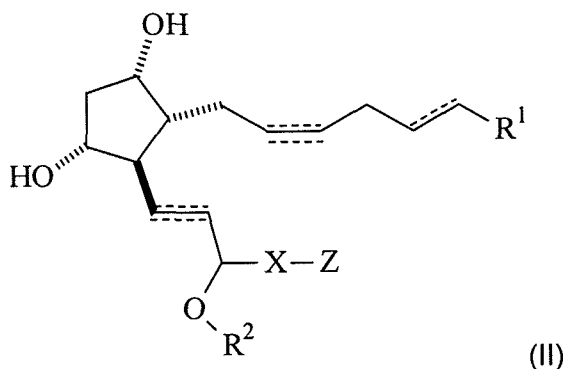
-CH₂NH-, -CH₂S-, and -CH₂O-;

Y is selected from the group consisting of O, S, and NH; and

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

and pharmaceutically acceptable salts and hydrates of the structures above; biohydrolyzable amides, esters, and imides of the structures above; and optical isomers, diastereomers, and enantiomers thereof.

2. A method for relieving nasal congestion comprising administering to a subject in need thereof an effective amount of at least one PGF according to Formula II:



wherein R¹ is selected from the group consisting of C(O)OH, C(O)NHOH, C(O)OR³, CH₂OH, S(O)₂R³, C(O)NHR³, C(O)NHS(O)₂R⁴, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R² is selected from the group consisting of a hydrogen atom, a lower heterogenous group, and lower monovalent hydrocarbon groups;

R³ is selected from the group consisting of unsubstituted or substituted lower alkyl, lower heteroalkyl, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R⁴ is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a

heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

X is selected from the group consisting of $-\text{C}\equiv\text{C}-$, $-\text{C}\equiv\text{C}-\text{CH}_2-$, a covalent bond, $-\text{CH}=\text{C}=\text{CH}-$, $-\text{CH}=\text{CH}-$, $-\text{CH}=\text{N}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{Y}-$, $-(\text{CH}_2)_n-$ wherein n is 2 to 4, $-\text{CH}_2\text{NH}-$, $-\text{CH}_2\text{S}-$, and $-\text{CH}_2\text{O}-$;

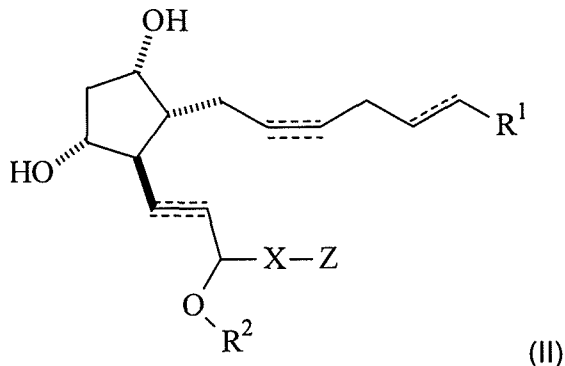
Y is selected from the group consisting of O, S, and NH; and

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

and pharmaceutically acceptable salts and hydrates of the structures above;

biohydrolyzable amides, esters, and imides of the structures above; and optical isomers, diastereomers, and enantiomers thereof.

3. A method of treating neurogenic bladder comprising administering to a subject in need thereof an effective amount of at least one PGF according to Formula II:



wherein R^1 is selected from the group consisting of $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{O})\text{NHOH}$, $\text{C}(\text{O})\text{OR}^3$, CH_2OH , $\text{S}(\text{O})_2\text{R}^3$, $\text{C}(\text{O})\text{NHR}^3$, $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogeneous group, and lower monovalent hydrocarbon groups;

R^3 is selected from the group consisting of unsubstituted or substituted lower alkyl, lower heteroalkyl, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent

hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R^4 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

X is selected from the group consisting of $-C\equiv C-$, $-C\equiv C-CH_2-$, a covalent bond, $-CH=C=CH-$, $-CH=CH-$, $-CH=N-$, $-C(O)-$, $-C(O)Y-$, $-(CH_2)_n-$ wherein n is 2 to 4, $-CH_2NH-$, $-CH_2S-$, and $-CH_2O-$;

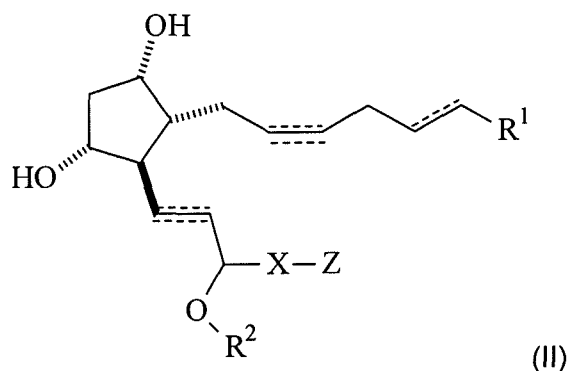
Y is selected from the group consisting of O, S, and NH; and

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

and pharmaceutically acceptable salts and hydrates of the structures above;

biohydrolyzable amides, esters, and imides of the structures above; and optical isomers, diastereomers, and enantiomers thereof.

4. A method of treating, relieving, or reducing the symptoms of neurogenic bladder comprising administering to a subject in need thereof an effective amount of at least one PGF according to Formula II:



wherein R^1 is selected from the group consisting of $C(O)OH$, $C(O)NHOH$, $C(O)OR^3$, CH_2OH , $S(O)_2R^3$, $C(O)NHR^3$, $C(O)NHS(O)_2R^4$, tetrazole, a cationic salt

moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogenous group, and lower monovalent hydrocarbon groups;

R^3 is selected from the group consisting of unsubstituted or substituted lower alkyl, lower heteroalkyl, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R^4 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

X is selected from the group consisting of $-C\equiv C-$, $-C\equiv C-CH_2-$, a covalent bond, $-CH=C=CH-$, $-CH=CH-$, $-CH=N-$, $-C(O)-$, $-C(O)Y-$, $-(CH_2)_n-$ wherein n is 2 to 4, $-CH_2NH-$, $-CH_2S-$, and $-CH_2O-$;

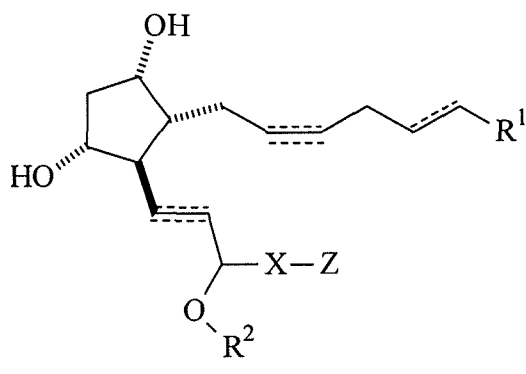
Y is selected from the group consisting of O, S, and NH; and

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

and pharmaceutically acceptable salts and hydrates of the structures above;

biohydrolyzable amides, esters, and imides of the structures above; and optical isomers, diastereomers, and enantiomers thereof.

5. A method of treating or relieving a respiratory disorder comprising administering to a subject in need thereof an effective amount of at least one PGF according to Formula II:



wherein R^1 is selected from the group consisting of $C(O)OH$, $C(O)NHOH$, $C(O)OR^3$, CH_2OH , $S(O)_2R^3$, $C(O)NHR^3$, $C(O)NHS(O)_2R^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogenous group, and lower monovalent hydrocarbon groups;

R^3 is selected from the group consisting of unsubstituted or substituted lower alkyl, lower heteroalkyl, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R^4 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

X is selected from the group consisting of $-C\equiv C-$, $-C\equiv C-CH_2-$, a covalent bond, $-CH=CH-$, $-CH=CH-$, $-CH=N-$, $-C(O)-$, $-C(O)Y-$, $-(CH_2)_n-$ wherein n is 2 to 4, $-CH_2NH-$, $-CH_2S-$, and $-CH_2O-$;

Y is selected from the group consisting of O, S, and NH; and

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

and pharmaceutically acceptable salts and hydrates of the structures above; biohydrolyzable amides, esters, and imides of the structures above; and optical isomers, diastereomers, and enantiomers thereof.

6. The method of any one of claims 1-5, wherein R^1 is selected from the group consisting of CO_2H , $\text{C}(\text{O})\text{NHOH}$, CO_2R^3 , $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}^4$, and tetrazole.

7. The method of any one of claims 1-5, wherein R^2 is a hydrogen atom.

8. The method of any one of claims 1-5, wherein R^4 is a phenyl group.

9. The method of any one of claims 1-5, wherein X is a covalent bond, and Z is selected from the group consisting of an aromatic group, a heteroaromatic group, a substituted aromatic group, and a substituted heteroaromatic group.

10. The method of any one of claims 1-5, wherein X is a covalent bond, and Z is a bicyclic heteroaromatic group.

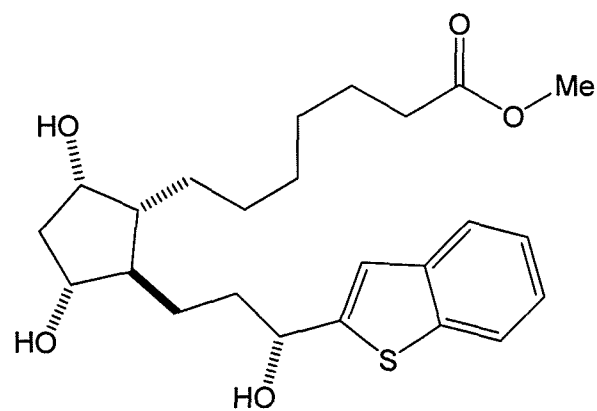
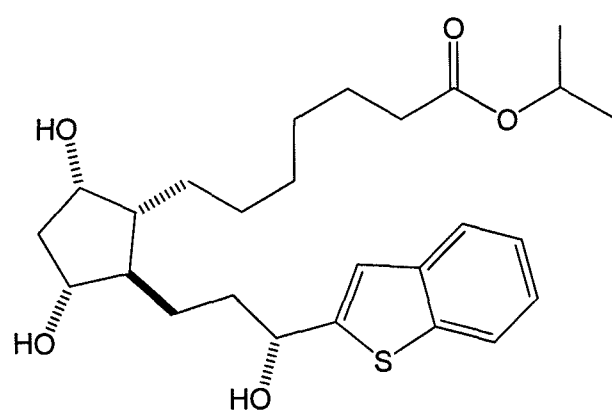
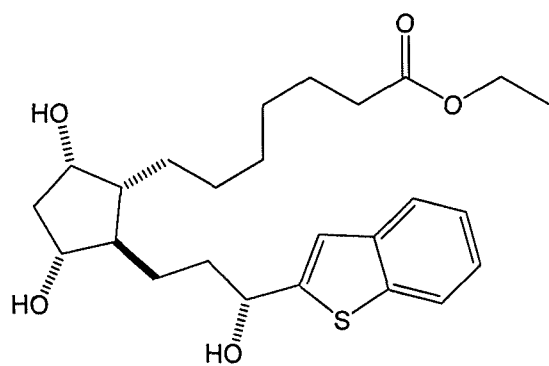
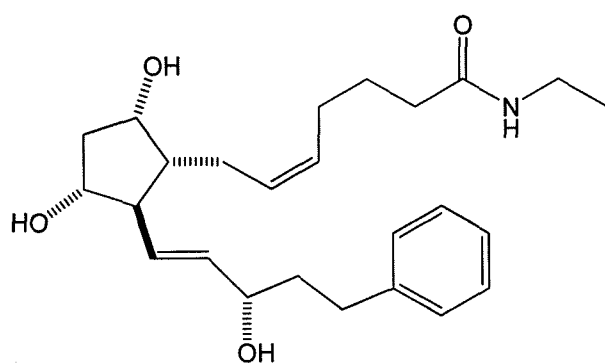
11. The method of any one of claims 1-5, wherein X is $-\text{C}\equiv\text{C}-$, and Z is selected from the group consisting of furanyl, thienyl, and phenyl.

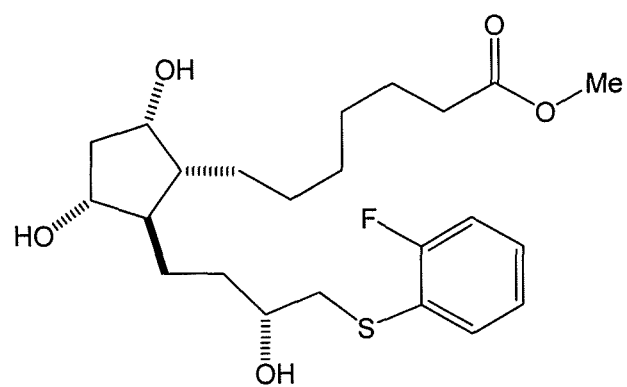
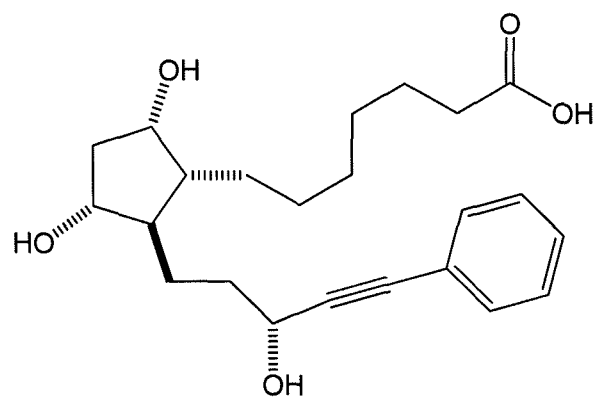
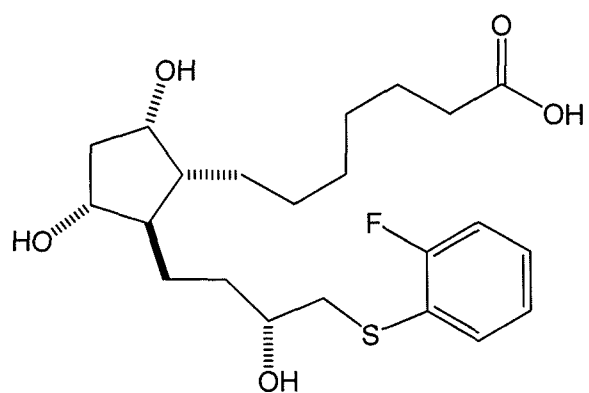
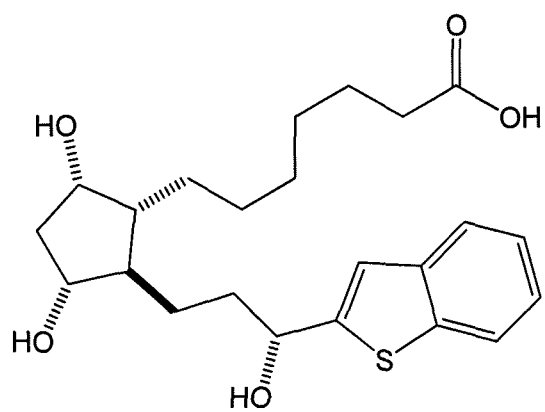
12. The method of any one of claims 1-5, wherein R_2 is H, X is a covalent bond, and Z is benzo(β)thiazolyl, benzo(β)thiophenyl, thianaphthyl, or benzoxazolyl.

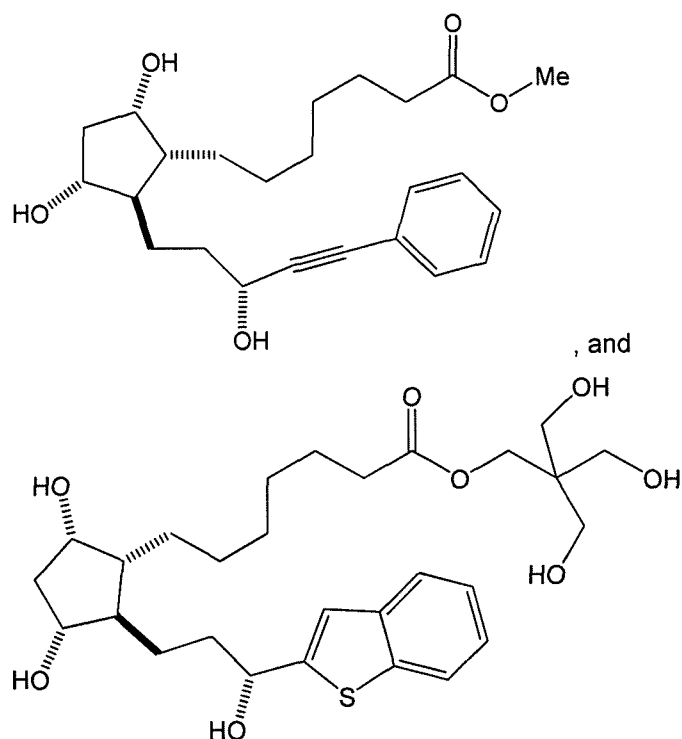
13. The method of any one of claims 1-5, wherein R_3 is unsubstituted or substituted monocyclic aromatic ring, monocyclic heteroaromatic ring, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, or phenyl.

14. The method of any one of claims 1-5, wherein R_1 is CO_2R_3 and R_3 is a lower alkyl substituted with from 1 to 4 OH groups.

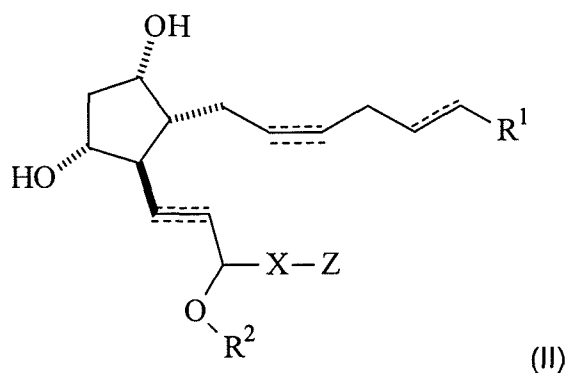
15. The method of any one of claims 1-5, wherein the prostaglandin F analog is selected from the following:







16. A composition for maintaining or promoting nasal patency, the composition comprising at least one prostaglandin F analog (PGF) according to Formula II:



wherein R^1 is selected from the group consisting of $C(O)OH$, $C(O)NHOH$, $C(O)OR^3$, CH_2OH , $S(O)_2R^3$, $C(O)NHR^3$, $C(O)NHS(O)_2R^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogenous group, and lower monovalent hydrocarbon groups;

R^3 is selected from the group consisting of unsubstituted or substituted lower alkyl, lower heteroalkyl, a heterogeneous group, a carbocyclic group, a heterocyclic

group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R^4 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

X is selected from the group consisting of $-C\equiv C-$, $-C\equiv C-CH_2-$, a covalent bond, $-CH=C=CH-$, $-CH=CH-$, $-CH=N-$, $-C(O)-$, $-C(O)Y-$, $-(CH_2)_n-$ wherein n is 2 to 4, $-CH_2NH-$, $-CH_2S-$, and $-CH_2O-$;

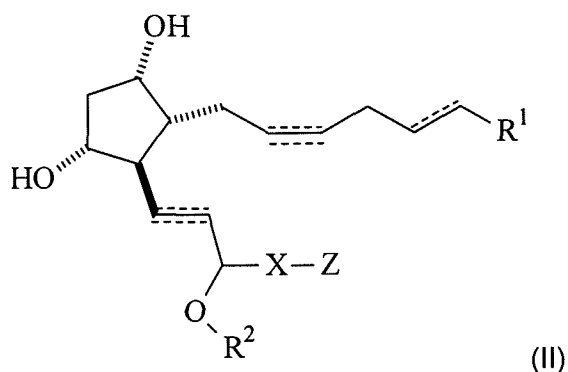
Y is selected from the group consisting of O, S, and NH; and

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

and pharmaceutically acceptable salts and hydrates of the structures above; biohydrolyzable amides, esters, and imides of the structures above; and optical isomers, diastereomers, and enantiomers thereof; and

a carrier.

17. A composition for relieving nasal congestion, the composition comprising at least one prostaglandin F analog (PGF) according to Formula II:



wherein R^1 is selected from the group consisting of $C(O)OH$, $C(O)NHOH$, $C(O)OR^3$, CH_2OH , $S(O)_2R^3$, $C(O)NHR^3$, $C(O)NHS(O)_2R^4$, tetrazole, a cationic salt

moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogenous group, and lower monovalent hydrocarbon groups;

R^3 is selected from the group consisting of unsubstituted or substituted lower alkyl, lower heteroalkyl, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R^4 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

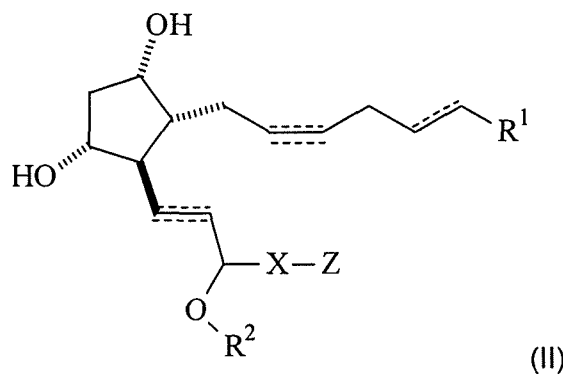
X is selected from the group consisting of $-C\equiv C-$, $-C\equiv C-CH_2-$, a covalent bond, $-CH=C=CH-$, $-CH=CH-$, $-CH=N-$, $-C(O)-$, $-C(O)Y-$, $-(CH_2)_n-$ wherein n is 2 to 4, $-CH_2NH-$, $-CH_2S-$, and $-CH_2O-$;

Y is selected from the group consisting of O, S, and NH; and

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

and pharmaceutically acceptable salts and hydrates of the structures above; biohydrolyzable amides, esters, and imides of the structures above; and optical isomers, diastereomers, and enantiomers thereof; and
a carrier.

18. A composition for treating neurogenic bladder, the composition comprising at least one prostaglandin F analog (PGF) according to Formula II:



wherein R^1 is selected from the group consisting of $C(O)OH$, $C(O)NHOH$, $C(O)OR^3$, CH_2OH , $S(O)_2R^3$, $C(O)NHR^3$, $C(O)NHS(O)_2R^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogenous group, and lower monovalent hydrocarbon groups;

R^3 is selected from the group consisting of unsubstituted or substituted lower alkyl, lower heteroalkyl, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R^4 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

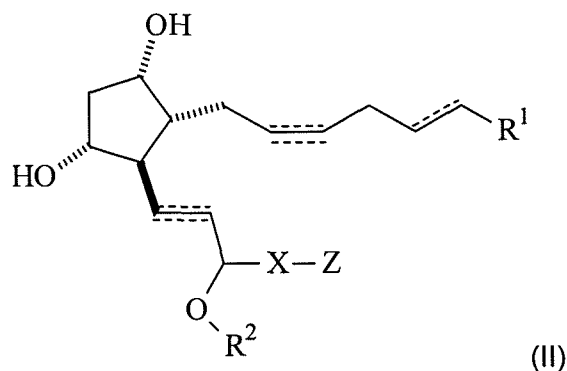
X is selected from the group consisting of $-C\equiv C-$, $-C\equiv C-CH_2-$, a covalent bond, $-CH=C=CH-$, $-CH=CH-$, $-CH=N-$, $-C(O)-$, $-C(O)Y-$, $-(CH_2)_n-$ wherein n is 2 to 4, $-CH_2NH-$, $-CH_2S-$, and $-CH_2O-$;

Y is selected from the group consisting of O, S, and NH; and

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

and pharmaceutically acceptable salts and hydrates of the structures above; biohydrolyzable amides, esters, and imides of the structures above; and optical isomers, diastereomers, and enantiomers thereof; and a carrier.

19. A composition for treating, relieving, or reducing the symptoms of neurogenic bladder, the composition comprising at least one prostaglandin F analog (PGF) according to Formula II:



wherein R^1 is selected from the group consisting of $C(O)OH$, $C(O)NHOH$, $C(O)OR^3$, CH_2OH , $S(O)_2R^3$, $C(O)NHR^3$, $C(O)NHS(O)_2R^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogenous group, and lower monovalent hydrocarbon groups;

R^3 is selected from the group consisting of unsubstituted or substituted lower alkyl, lower heteroalkyl, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R^4 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

X is selected from the group consisting of $-C\equiv C-$, $-C\equiv C-CH_2-$, a covalent bond,

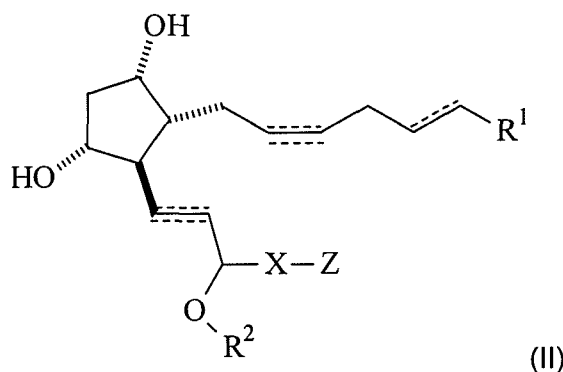
-CH=C=CH-, -CH=CH-, -CH=N-, -C(O)-, -C(O)Y-, -(CH₂)_n- wherein n is 2 to 4, -CH₂NH-, -CH₂S-, and -CH₂O-;

Y is selected from the group consisting of O, S, and NH; and

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

and pharmaceutically acceptable salts and hydrates of the structures above; biohydrolyzable amides, esters, and imides of the structures above; and optical isomers, diastereomers, and enantiomers thereof; and a carrier.

20. A composition for treating or relieving a respiratory disorder, the composition comprising at least one prostaglandin F analog (PGF) according to Formula II:



wherein R¹ is selected from the group consisting of C(O)OH, C(O)NHOH, C(O)OR³, CH₂OH, S(O)₂R³, C(O)NHR³, C(O)NHS(O)₂R⁴, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R² is selected from the group consisting of a hydrogen atom, a lower heterogenous group, and lower monovalent hydrocarbon groups;

R³ is selected from the group consisting of unsubstituted or substituted lower alkyl, lower heteroalkyl, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R⁴ is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

X is selected from the group consisting of -C≡C-, -C≡C-CH₂-, a covalent bond, -CH=C=CH-, -CH=CH-, -CH=N-, -C(O)-, -C(O)Y-, -(CH₂)_n- wherein n is 2 to 4, -CH₂NH-, -CH₂S-, and -CH₂O-;

Y is selected from the group consisting of O, S, and NH; and

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

and pharmaceutically acceptable salts and hydrates of the structures above; biohydrolyzable amides, esters, and imides of the structures above; and optical isomers, diastereomers, and enantiomers thereof; and a carrier.

21. The composition of any one of claims 16-20, wherein the composition is a topical composition.

22. The composition of any one of claims 16-20, wherein R¹ is selected from the group consisting of CO₂H, C(O)NHOH, CO₂R³, C(O)NHS(O)₂R⁴, and tetrazole.

23. The composition of any one of claims 16-20, wherein R² is a hydrogen atom.

24. The composition of any one of claims 16-20, wherein R⁴ is a phenyl group.

25. The composition of any one of claims 16-20, wherein X is a covalent bond, and Z is selected from the group consisting of an aromatic group, a heteroaromatic group, a substituted aromatic group, and a substituted heteroaromatic group.

26. The composition of any one of claims 16-20, wherein X is a covalent bond, and Z is a bicyclic heteroaromatic group.

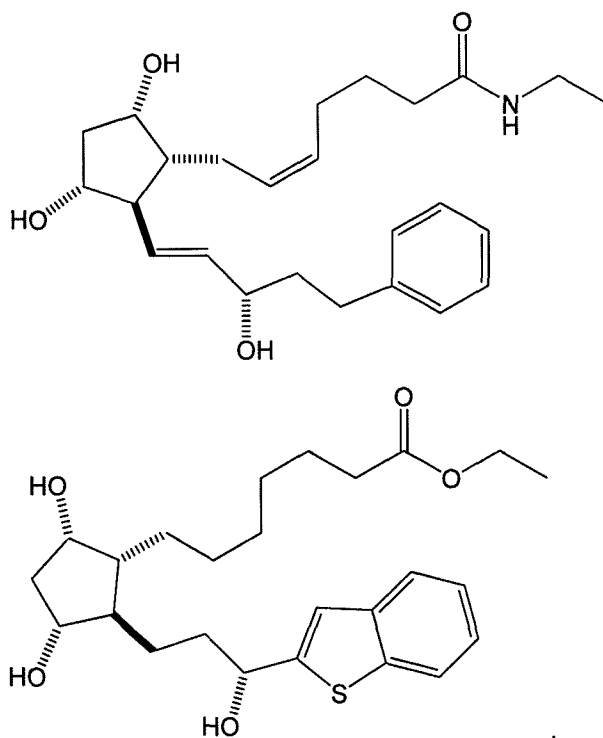
27. The composition of any one of claims 16-20, wherein X is $-C\equiv C-$, and Z is selected from the group consisting of furanyl, thienyl, and phenyl.

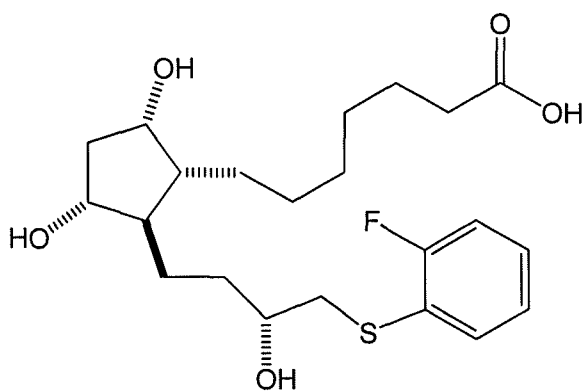
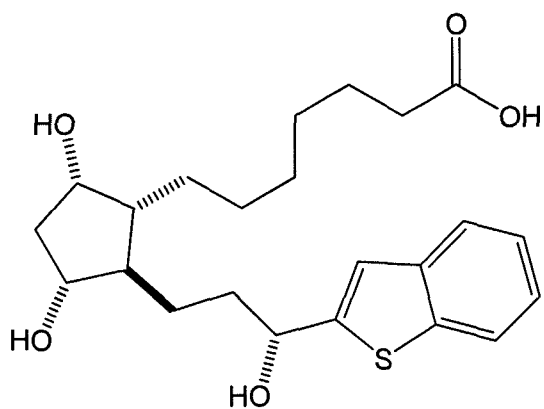
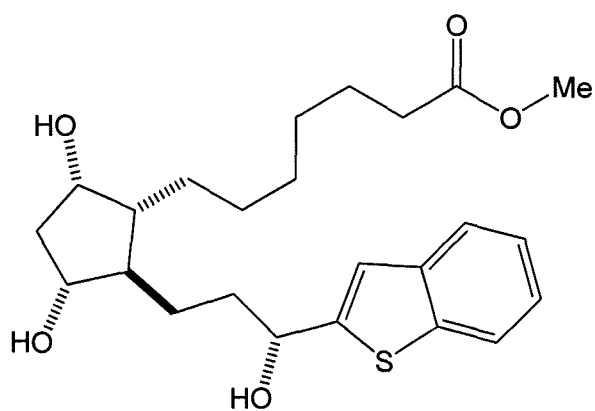
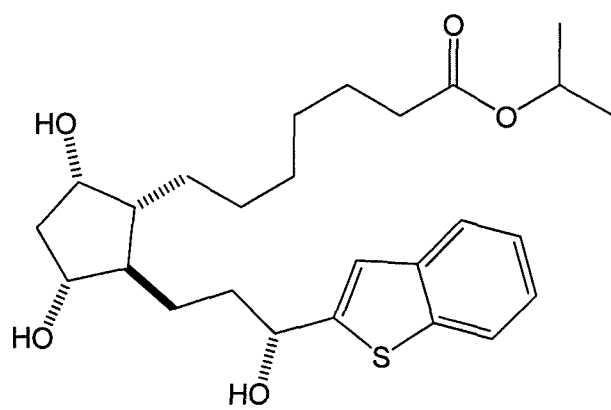
28. The composition of any one of claims 16-20, wherein R_2 is H, X is a covalent bond, and Z is benzo(β)thiazolyl, benzo(β)thiophenyl, thianaphthyl, or benzoxazolyl.

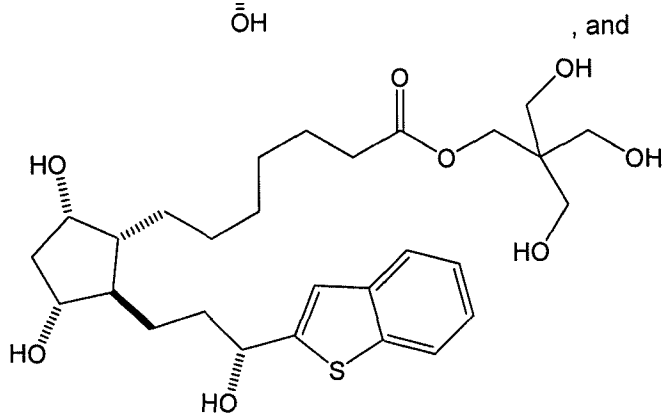
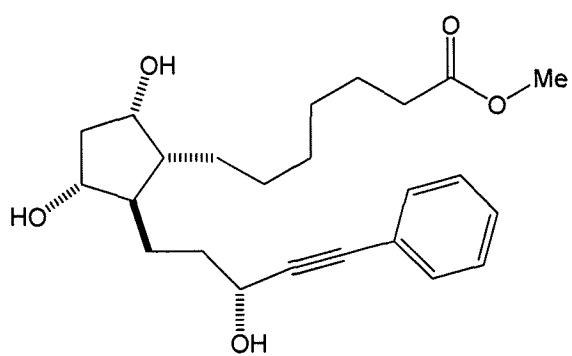
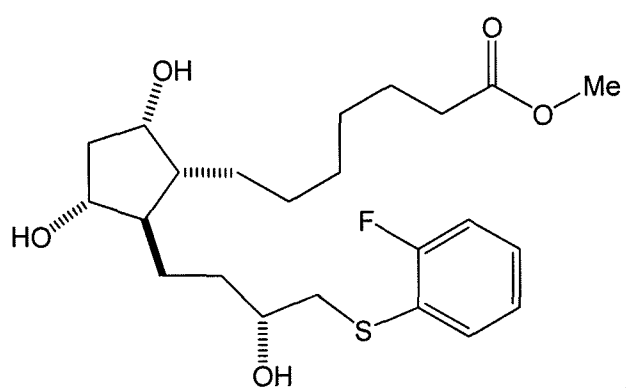
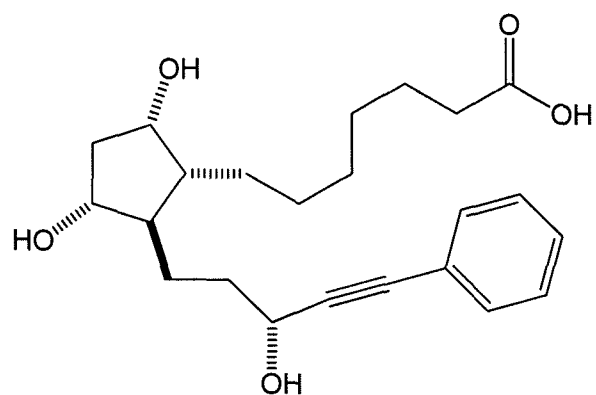
29. The composition of any one of claims 16-20, wherein R_3 is unsubstituted or substituted monocyclic aromatic ring, monocyclic heteroaromatic ring, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, or phenyl.

30. The composition of any one of claims 16-20, wherein R_1 is CO_2R_3 and R_3 is a lower alkyl substituted with from 1 to 4 OH groups.

31. The composition of any one of claims 16-20, wherein the prostaglandin F analog is selected from the following:







, and

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/27831

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 29/04 (2010.01)

USPC - 514/747

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/747

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/763,429; 544/264 (text search) Find search terms below.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,EPAB,JPAB), Google Scholar
prostaglandin F, PGF\$, analog, nasal, patency, airflow, congestion, increas\$, neurogenic bladder, respiratory, disorder

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 6,451,859 B1 (DELONG et al.) 17 September 2002 (17.09.2002) col 1, ln 9-13; col 3, ln 5-12; ln 30; col 4, ln 8-11; ln 27-32; col 4, ln 66 to col 5, ln 30; col 42, ln 50-54	1-4, 6-8, 11, 13, 14, 16-19, 21-24, 27, 29, 30 ----- 9, 10, 12, 15, 25, 26, 28, 31
X	US 4,116,989 A (NELSON) 26 September 1978 (26.09.1978) col 4, ln 1-8; col 7, ln 31-36; col 8, ln 20-25; col 9, ln 25-45; col 13, ln 44-60	5, 20
Y	US 2007/0254920 A1 (DELONG et al.) 01 November 2007 (01.11.2007) para [0086]-[0088], [0091], [0166]	9, 10, 12, 15, 25, 26, 28, 31

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

17 April 2010 (17.04.2010)

Date of mailing of the international search report

26 APR 2010

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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