[0017] Additionally, the formulation should deliver the active ingredient with reasonable efficiency. One measure of efficiency is the ability to minimize the concentration of active ingredient in the finished product and still maintain the desired therapeutic effect. This has implications for manufacturability, cost of goods, and local safety and tolerability. Another measure of efficiency is the ability to minimize the dose frequency and still maintain the desired therapeutic effect, which has implications for patient convenience and product marketability.

[0018] As well, the formulation must cause little or no skin irritation. If applied to skin near the eye, *e.g.,* the eyelid, the formulation is considered an ophthalmic formulation. Generally, an ophthalmic formulation must be sterile, *e.g.,* according to Chapter <71> of the U.S. Pharmacopeia. Preferably, an ophthalmic formulation must also be free or essentially free of bacterial endotoxin, *e.g.* according to Chapter <85> of the U.S. Pharmacopeia, *e.g.,* an endotoxin level of <10 EU (endotoxin units) per gram of composition. If applied to skin near the eye, the formulation must be ophthalmically compatible, *i.e,* the formulation must not cause clinically significant eye irritation, and must not be toxic to the eye, *e.g.,* the ocular surface, *e.g.* the cornea. Irritation potential and ocular toxicity are studied empirically by standard preclinical models, or in human trials. Although the skin or eye irritation potential of individual inactive ingredients is generally known, combinations of inactive and active ingredients can cause unexpected irritation, which must be tested empirically.

[0019] Furthermore, the formulation must possess other qualities necessary to make a topical formulation and market it to consumers: ease of manufacture, physical and chemical stability, and commercially acceptable appearance, odor, and tactile qualities.

[0020] Therefore, there is a need for new compositions for topically delivering a PFPRA compound to adipose tissue under the skin.

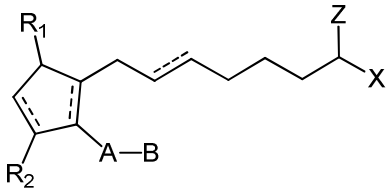
Summary

[0021] It has now been discovered experimentally that certain topical compositions comprising a PFPRA compound *(e.g.,* latanoprost or tafluprost) and certain fatty acid esters *(e.g.,* isopropyl myristate) provide exceptionally efficient delivery of the compound and its active metabolite into subcutaneous fat, and thus have particular uses and advantages, as described herein. In theory, this efficiency may owe to the similar structure and polarity between the PFPRA compound *(e.g.,* latanoprost or tafluprost) and the fatty acid ester *(e.g.,* isopropyl myristate), as described herein.

[0022] Thus, in one example, provided is a composition useful in the reduction of

subcutaneous fat comprising a PFPRA compound, e.g. latanoprost or tafluprost, and a fatty acid ester, e.g., isopropyl myristate. In certain examples, the concentration of the PFPRA compound in the composition is between about 0.0001 percent to about 1 percent by weight, as a proportion of the total weight of the composition, e.g., between about 0.05 percent and about 0.5 percent by weight, or between about 0.01 percent and about 0.1 percent by weight of the final composition. In some examples, the final concentration of the fatty acid ester (e.g., isopropyl myristate) is between about 1 percent to about 20 percent by weight, e.g., between about 1 percent and about 10 percent by weight of the composition. In certain examples, the composition further comprises an ointment base, e.g., a hydrocarbon base such as petroleum jelly. In some examples, the final concentration of the ointment base is between about 50 percent and about 99 percent by weight, e.g., between about 70 percent and about 99 percent by weight, of the total weight of the composition. In some examples, the composition further comprises an organic alcohol (e.g., propylene glycol). In some examples, the final concentration of the organic alcohol is between about 5 percent and about 50 percent by weight, e.g., between about 5 percent and about 20 percent by weight, of the total weight of the composition. In some examples, the composition is not an emulsion. In some examples, the composition is immiscible in water. In some examples, the composition is an ophthalmic composition and is ophthalmically compatible. In some examples, the composition is sterile.

[0022a] In one aspect, the present disclosure refers to a composition comprising a compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof; wherein:

each instance of ------ independently represents a single bond or a double bond, which can be in the *cis* or *trans* configuration;

A is optionally substituted $C_{1–10}$ alkylene, optionally substituted $C_{2–10}$ alkenylene, or optionally substituted $C_{2–10}$ alkynylene, wherein the alkylene, alkenylene, or alkynylene group is optionally interrupted by one or more –O– or –S– groups;

B is hydrogen, optionally substituted $C_{3–7}$ carbocyclyl, optionally substituted 3–8–membered heterocyclyl, optionally substituted 5–14–membered heteroaryl, optionally substituted $C_{6–10}$ aryl, optionally substituted $C_{1–30}$ alkyl, optionally substituted $C_{2–30}$ alkenyl, or optionally substituted $C_{2–30}$ alkynyl;

X is $–OR_4$, $–SR_4$, or $–N(R_4)_2$, wherein each instance of R_4 is independently hydrogen,

optionally substituted $C_{1–30}$ alkyl, optionally substituted $C_{2–30}$ alkenyl, optionally substituted $C_{2–30}$ alkynyl, –C(=O)R_5, or –C(=O)OR_5, wherein R_5 is optionally substituted $C_{1–30}$ alkyl, optionally substituted $C_{2–30}$ alkenyl, or optionally substituted $C_{2–30}$ alkynyl, or two R_4 groups are joined to form an optionally substituted 3–8–membered heterocyclyl or optionally substituted 5–14–membered heteroaryl ring;

Z is =O, =S, or =NR_Z, wherein R_Z is selected from hydrogen, an amino protecting group, –OH, substituted hydroxyl, optionally substituted $C_{1–10}$ alkyl, optionally substituted $C_{2–10}$ alkenyl, optionally substituted $C_{2–10}$ alkynyl, optionally substituted $C_{3–7}$ carbocyclyl, optionally substituted 3–8–membered heterocyclyl, optionally substituted $C_{6–10}$ aryl, or optionally substituted 5–14-membered heteroaryl, or Z represents two hydrogen atoms; and

one of R_1 and R_2 is =O, –OH, or a −O(CO)R_6 group, and the other one is −OH or −O(CO)R_6, or R_1 is =O and R_2 is H, wherein R_6 is an optionally substituted $C_{1–20}$ alkyl, optionally substituted $C_{2–20}$ alkenyl, optionally substituted $C_{2–20}$ alkynyl, or $-(CH_2)_mR_7$, wherein m is 0 or an integer of between 1–10, inclusive, and R_7 is optionally substituted $C_{3–7}$ carbocyclyl, optionally substituted 3–8–membered heterocyclyl, optionally substituted $C_{6–10}$ aryl, or optionally substituted 5–14–membered heteroaryl; and isopropyl myristate

[0022b] In another aspect, the present disclosure refers to use of composition as described herein in the manufacture of a medicament for reducing body fat in a subject, wherein the composition is to be administered to the subject.

[0022c] In yet another aspect, the present disclosure refers to composition as described herein for use in therapy.

[0023] In another example, provided is a method of reducing body fat in a subject, comprising topically administering a composition as described herein to a subject in need thereof. In certain examples, the method is a therapeutic method. In other examples, the method is a cosmetic method.

[0024] In another example, provided is a composition as described herein for use in a method of reducing body fat in a subject. In another example, provided is use of a composition as described herein in the manufacture of a medicament for reducing body fat in a subject.

[0025] In another example, provided is a composition for use in for reducing fat in a subject suffering from steatoblepharon. In another example, provided is a method of treating steatoblepharon in a subject, comprising topically administering *(e.g.,* applying to an eyelid of the subject) a composition as described herein to a subject in need thereof. In another example, provided is a composition as described herein for use in a method of treating steatoblepharon in a subject. In another example, provided is use a composition as described herein in the manufacture of a medicament for treating steatoblepharon in a subject.

[0026] In yet another example, provided is a kit comprising a composition as described

herein and instructions for use.

[0027] In another example, provided is a process for manufacturing one or more of the inventive compositions in a sterile fashion, whereby the composition is sterile, endotoxin-free, and ophthalmically compatible, and therefore suitable for use on the eyelid or near the eye. For example, in one example, provided is a process for manufacturing a sterile ointment, comprising the steps of dissolving a PFPRA compound *(e.g.* latanoprost or tafluprost) in a fatty acid ester *(e.g.,* isopropyl myristate) to make a solution; microfiltration of the solution to make a filtrate; and combining the filtrate with an ointment base *(e.g.,* a hydrocarbon base such as petroleum jelly). In certain examples, the method further comprises dissolving a preservative (e.g., chlorobutanol) in the fatty acid ester *(e.g.,*isopropyl myristate).

[0028] Other objects and advantages will become apparent to those skilled in the art from consideration of the ensuing Detailed Description, Examples, and Claims.

Description of the Drawings

[0029] *Figure 1* depicts three-dimensional molecular models of isopropyl myristate and latanoprost in energy-minimized conformations (solved *in vacuo).* Carbon atoms are shown in gray and oxygen atoms in red; hydrogens are not shown. Measured end-to-end distances (between heavy atom centers) are 19.9 Å for isopropyl myristate and 17.7 Å for latanoprost.

Definitions

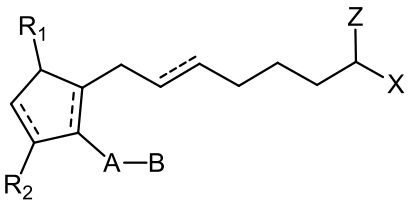
Chemical definitions

[0030] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

Claims

What is claimed is:

1. A composition comprising a compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof; wherein:

each instance of ------ independently represents a single bond or a double bond, which can be in the *cis* or *trans* configuration;

A is optionally substituted $C_{1–10}$ alkylene, optionally substituted $C_{2–10}$ alkenylene, or optionally substituted $C_{2–10}$ alkynylene, wherein the alkylene, alkenylene, or alkynylene group is optionally interrupted by one or more –O– or –S– groups;

B is hydrogen, optionally substituted $C_{3–7}$ carbocyclyl, optionally substituted 3–8–membered heterocyclyl, optionally substituted 5–14–membered heteroaryl, optionally substituted $C_{6–10}$ aryl, optionally substituted $C_{1–30}$ alkyl, optionally substituted $C_{2–30}$ alkenyl, or optionally substituted $C_{2–30}$ alkynyl;

X is $-OR_4$, $–SR_4$, or $-N(R_4)_2$, wherein each instance of R_4 is independently hydrogen, optionally substituted $C_{1–30}$ alkyl, optionally substituted $C_{2–30}$ alkenyl, optionally substituted $C_{2–30}$ alkynyl, $–C(=O)R_5$, or $–C(=O)OR_5$, wherein R_5 is optionally substituted $C_{1–30}$ alkyl, optionally substituted $C_{2–30}$ alkenyl, or optionally substituted $C_{2–30}$ alkynyl, or two R_4 groups are joined to form an optionally substituted 3–8–membered heterocyclyl or optionally substituted 5–14–membered heteroaryl ring;

Z is =O, =S, or $=NR_Z$, wherein R_Z is selected from hydrogen, an amino protecting group, –OH, substituted hydroxyl, optionally substituted $C_{1–10}$ alkyl, optionally substituted $C_{2–10}$ alkenyl, optionally substituted $C_{2–10}$ alkynyl, optionally substituted $C_{3–7}$ carbocyclyl, optionally substituted 3–8–membered heterocyclyl, optionally substituted $C_{6–10}$ aryl, or optionally substituted 5–14-membered heteroaryl, or Z represents two hydrogen atoms; and

one of R_1 and R_2 is =O, –OH, or a $-O(CO)R_6$ group, and the other one is −OH or $-O(CO)R_6$, or R_1 is =O and R_2 is H, wherein R_6 is an optionally substituted $C_{1–20}$ alkyl, optionally substituted $C_{2–20}$ alkenyl, optionally substituted $C_{2–20}$ alkynyl, or $-(CH_2)_mR_7$, wherein

m is 0 or an integer of between 1–10, inclusive, and R_7 is optionally substituted $C_{3–7}$ carbocyclyl, optionally substituted 3–8–membered heterocyclyl, optionally substituted $C_{6–10}$ aryl, or optionally substituted 5–14–membered heteroaryl;

and isopropyl myristate.

2. The composition of claim 1 further comprising petroleum jelly.

3. The composition of claim 2, wherein the composition consists essentially of the compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, isopropyl myristate, and petroleum jelly.

4. The composition of claim 1, wherein the concentration of the compound of Formula (**I**), or the pharmaceutically acceptable salt thereof, is between about 0.001% and about 1% w/w, inclusive.

5. The composition of claim 1, wherein the concentration of the compound of Formula (**I**), or the pharmaceutically acceptable salt thereof, is between about 0.01% and about 0.5% w/w, inclusive.

6. The composition of claim 1, wherein the concentration of isopropyl myristate is between about 1% and about 20% w/w, inclusive.

7. The composition of claim 1, wherein the concentration of isopropyl myristate is between about 1% and about 10% w/w, inclusive.

8. The composition of claim 2, wherein the concentration of petroleum jelly is between about 70% and about 99% w/w, inclusive.

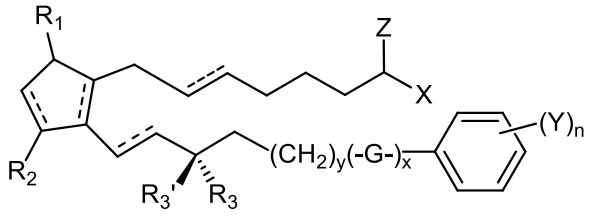
9. The composition of claim 1, wherein the concentration the compound of Formula (**I**), or the pharmaceutically acceptable salt thereof, is between about 0.001% and 1% w/w, inclusive; and the concentration of isopropyl myristate is between about 1% and about 10% w/w, inclusive.

10. The composition of claim 2, wherein the concentration of the compound of Formula (**I**), or the pharmaceutically acceptable salt thereof, is between about 0.001% and 1% w/w, inclusive; the concentration of isopropyl myristate is between about 1% and about 10% w/w, inclusive; and the concentration of petroleum jelly is between about 70% and about 99% w/w, inclusive.

11. The composition of claim 1, further comprising a preservative.

12. The composition of claim 1, wherein the composition is sterile.

13. The composition of claim 1, wherein the compound of Formula (**I**) is of Formula (**I–a**):



(**I–a**),

or a pharmaceutically acceptable salt thereof; wherein:

each instance of ------ independently represents a single bond or a double bond which can be in the *cis* or *trans* configuration;

each instance of R_3 and R_3' is independently hydrogen, halogen, −OH, substituted hydroxyl, or $-O(CO)R_8$, wherein R_8 is optionally substituted $C_{1–20}$ alkyl, optionally substituted $C_{2–20}$ alkenyl, optionally substituted $C_{2–20}$ alkynyl, or $-(CH_2)_mR_9$ wherein m is 0 or an integer between 1–10, inclusive, and R_9 is optionally substituted $C_{3–7}$ carbocyclyl, optionally substituted $C_{6–10}$ aryl, or optionally substituted 5–14–membered–heteroaryl, or R_3 and R_3' are joined to form =O;

Y is selected from the group consisting of optionally substituted $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, optionally substituted $C_{2–10}$ alkenyl, optionally substituted $C_{2–10}$ alkynyl, halo, nitro, cyano, thiol, substituted thiol, hydroxyl, substituted hydroxyl, amino, monosubstituted amino, and disubstituted amino;

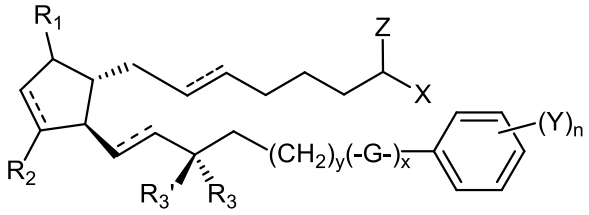
G is –O– or –S–;

y is 0, 1, or 2;

x is 0 or 1; and

n is 0 or an integer of from 1–5, inclusive.

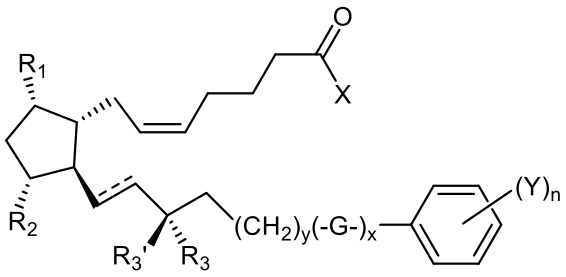
14. The composition of claim 13, wherein the compound of Formula (**I–a**) is of Formula (**I–d**):



(**I–d**),

or a pharmaceutically acceptable salt thereof.

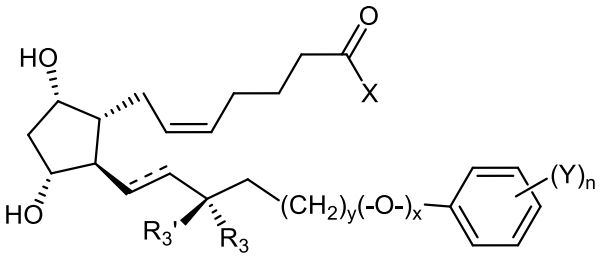
15. The composition of claim 13, wherein the compound of Formula (**I–a**) is of Formula (**I–d3**):



(**I–d3**),

or a pharmaceutically acceptable salt thereof.

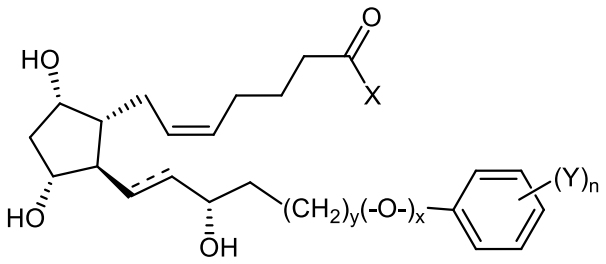
16. The composition of claim 13, wherein the compound of Formula (**I–a**) is of Formula (**I–h**):



(**I–h**),

or a pharmaceutically acceptable salt thereof.

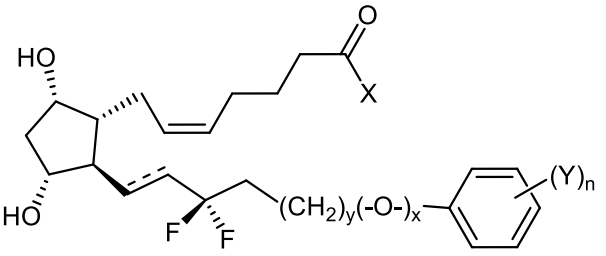
17. The composition of claim 13, wherein the compound of Formula (**I–a**) is of Formula (**I–j**):



(**I–j**),

or a pharmaceutically acceptable salt thereof.

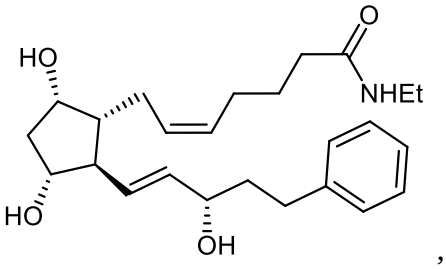
18. The composition of claim 13, wherein the compound of Formula (**I–a**) is of Formula (**I–j**):



(**I–j**),

or a pharmaceutically acceptable salt thereof.

19. The composition of claim 1, wherein the compound of Formula (**I**) is selected from the group consisting of:



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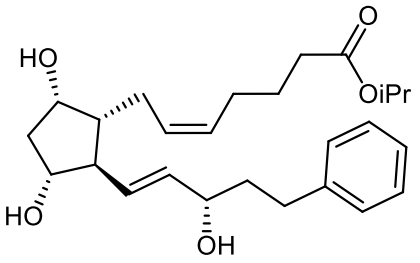

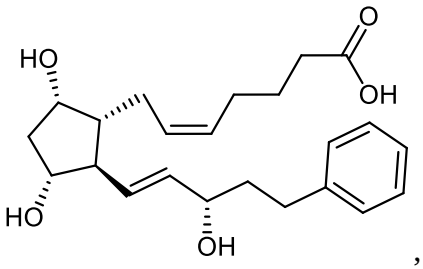

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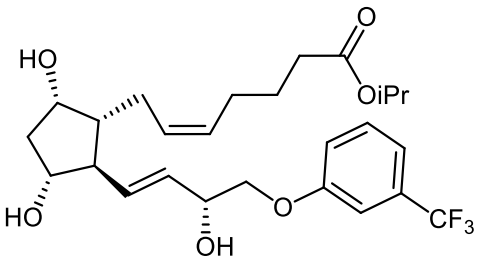

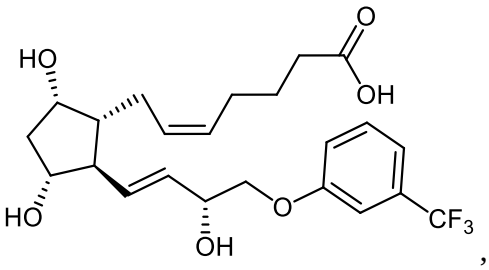

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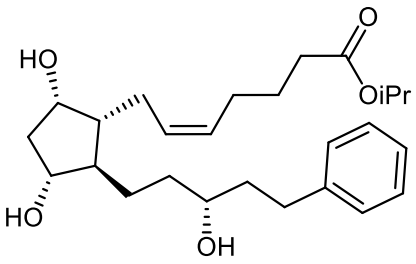

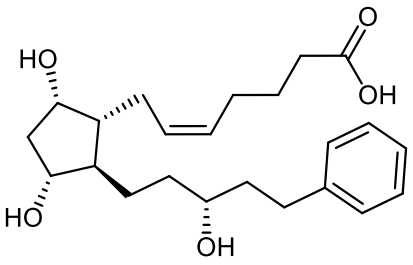

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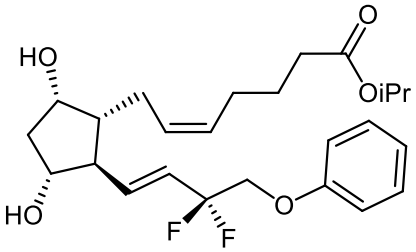

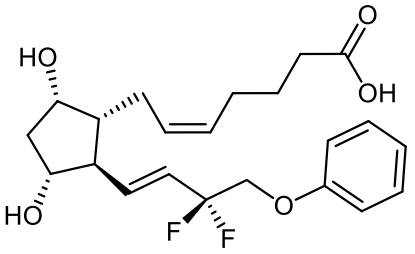

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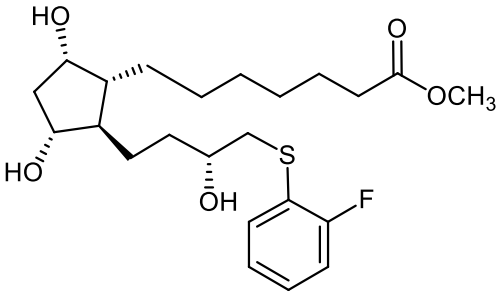

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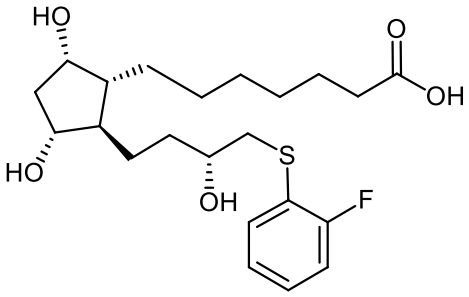

,

and pharmaceutically acceptable salts thereof.

20. Use of the composition of claim 1 in the manufacture of a medicament for reducing body fat in a subject, wherein the composition is to be administered to the subject.

21. The use of claim 20, wherein the composition is to be administered topically.

22. The use of claim 21, wherein the composition is to be administered to the face, chin, neck, arms, abdomen, chest, breast, buttocks, hips, thighs, legs, and/or knees.

23. The use of claim 21, wherein the composition is to be administered to the eyelids.

24. The use of claim 21, wherein the composition is to be administered to the submental region.

25. The use of claim 20, wherein body fat in the subject is locally reduced.

26. The use of claim 20, wherein subcutaneous fat in the subject is reduced.

27. The use of claim 20, wherein the composition is to be administered about once a day.

28. The composition of claim 1 for use in therapy.