TOPICAL FORMULATIONS OF DGAT1 INHIBITORS AND THEIR METHODS OF USE

Cross Reference To Related Application:

[0001] The present application claims benefit of and priority to U.S. Provisional No. 62/688,180 entitled "TOPICAL FORMULATIONS OF DGAT1 INHIBITORS AND THEIR METHODS OF USE" filed June 21, 2018 and to U.S. Provisional No. 62/695,441 entitled "TOPICAL FORMULATIONS OF DGAT1 INHIBITORS AND THEIR METHODS OF USE" filed July 9, 2018, the contents of which is hereby incorporated by reference in its entirety.

Summary:

[0002] Examples herein are directed to a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, benzyl alcohol, , diisopropyl adipate, diethyl sebacate, dimethyl isosorbide, 2-(2-ethoxyethoxy)ethanol, hexylene glycol, polysorbate 80, and optionally one or more pharmaceutically acceptable topical excipients such as but not limited to PEG 400, ethanol, isopropanol.

[0003] Examples herein are directed to a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, benzyl alcohol, PEG 400, 2-(2-ethoxyethoxy)ethanol, polysorbate 80, and optionally one or more pharmaceutically acceptable topical excipients. In some examples, the topical composition further comprises diisopropyl adipate. In some examples, the topical composition further comprises diethyl sebacate. In some examples, the topical composition further comprises dimethyl isosorbide. In some examples, the topical composition further comprises hexylene glycol.

[0004] Examples herein are directed to a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, PEG 400, dimethyl isosorbide, 2-(2-ethoxyethoxy)ethanol, DMSO, and optionally one or more pharmaceutically acceptable topical excipients.

[0005] Examples herein are directed to a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, propylene glycol,

oleic acid, polysorbate 80, isopropyl myristate, phenoxyethanol, and optionally one or more pharmaceutically acceptable topical excipients.

[0006] Examples herein are directed to a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, benzyl alcohol, glycerin, and optionally one or more pharmaceutically acceptable topical excipients.

[0007] Examples herein are directed to a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, DMSO, water, and optionally one or more pharmaceutically acceptable topical excipients.

[0008] Examples herein are directed to a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, propylene glycol, water, and optionally one or more pharmaceutically acceptable topical excipients.

[0009] Examples herein are directed to a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, propylene glycol, glycerin, and optionally one or more pharmaceutically acceptable topical excipients.

[0010] Examples herein are directed to a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, propylene glycol, 2-(2-ethoxyethoxy)ethanol, PEG400, butylated hydroxytoluene, and optionally one or more pharmaceutically acceptable topical excipients. In some examples, the topical composition further comprises glycerin. In some examples, the topical composition further comprises cellulose polymers. In some examples, the topical composition further comprises Carbomer Homopolymer Types A, B or C. In some examples, the topical composition further comprises Poloxamer.

[0011] Examples herein are directed to a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, 2-(2-ethoxyethoxy)ethanol, PEG400, glycerin, cellulose polymers , butylated hydroxytoluene, and optionally one or more pharmaceutically acceptable topical excipients.

[0012] Examples herein are directed to a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, propylene glycol, 2-(2-ethoxyethoxy)ethanol, glycerin, dimethyl isosorbide, butylated hydroxytoluene, and optionally one or more pharmaceutically acceptable topical excipients. In some examples, the topical composition further comprises cellulose polymers. In some examples, the topical composition further comprises Carbomer Homopolymer Types A, B or C.

[0012a] In a first aspect, the present disclosure refers to a topical composition comprising about 0.1% to about 1.0% 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid by weight of the topical composition, about 10.0% to about 50.0% propylene glycol by weight of the topical composition, about 30.0% to about 75.0% 2-(2-ethoxyethoxy)ethanol by weight of the topical composition, about 15.0% to about 50.0% PEG400 by weight of the topical composition, about 0.01% to about 5.0% butylated hydroxytoluene by weight of the topical composition, and optionally one or more pharmaceutically acceptable topical excipients.

[0012b] In a second aspect, the present disclosure refers to a topical composition comprising about 0.1% to about 1.0% 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid by weight of the topical composition, about 30.0% to about 75.0% 2-(2-ethoxyethoxy)ethanol by weight of the topical composition, about 15.0% to about 65.0% PEG400 by weight of the topical composition, about 5.0% to about 25.0% glycerin by weight of the topical composition, about 0.1% to about 5.0% cellulose polymer(s) by weight of the topical composition, about 0.01% to about 5.0% butylated hydroxy toluene by weight of the topical composition, and optionally one or more pharmaceutically acceptable topical excipients.

[0012c] In a third aspect, the present disclosure refers to a topical composition comprising about 0.1% to about 1.0% 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid by weight of the topical composition, about 20.0% to about 50.0% propylene glycol by weight of the topical composition, about 25.0% to about 65.0% 2-(2-ethoxyethoxy)ethanol by weight of the topical composition, about 5.0% to about 25.0% glycerin by weight of the topical composition, about 5.0% to about 25.0% dimethyl isosorbide by weight of the topical composition, about 0.01% to about 5.0% butylated hydroxy toluene by weight of the topical composition, and optionally one or more pharmaceutically acceptable topical excipients.

[0012d] In a fourth aspect, the present disclosure refers to a topical composition comprising about 0.1% to about 1.0% 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid by weight of the topical composition, about 0.5% to about 5.0% benzyl alcohol by weight of the topical composition, about 1.0% to about 10.0% PEG 400 by weight of the topical composition, about 1.0% to about 20.0% diisopropyl adipate by weight of the topical composition, about 1.0% to about 20.0% diethyl sebacate by weight of the topical composition, about 1.0% to about 20.0% dimethyl isosorbide by weight of the topical composition, about 1.0% to about 30.0% 2-(2-ethoxyethoxy)ethanol by weight of the topical composition, about 1.0% to about 15.0% hexylene glycol by weight of the topical composition, about 1.0% to about 10.0% polysorbate 80 by weight of the topical composition, and optionally one or more pharmaceutically acceptable topical excipients.

[0012e] In a fifth aspect, the present disclosure refers to a topical composition comprising about 0.1% to about 1.0% 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid by weight of the topical composition, about 0.5% to about 5.0% benzyl alcohol by weight of the topical composition, about 30.0% to about 60.0% PEG 400 by weight of the topical composition, about 1.0% to about 30.0% 2-(2-ethoxyethoxy)ethanol by weight of the topical composition, about 1.0% to about 10.0% polysorbate 80 by weight of the topical composition, and optionally one or more pharmaceutically acceptable topical excipients.

[0013] Some examples herein are directed to a method of treating skin conditions in a patient in need thereof comprising topically applying a topical composition

comprising a therapeutically effective amount of 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, benzyl alcohol, diisopropyl adipate, diethyl sebacate, dimethyl isosorbide, 2-(2-ethoxyethoxy)ethanol, hexylene glycol, polysorbate 80, and optionally one or more pharmaceutically acceptable topical excipients such as but not limited to PEG 400, ethanol, isopropanol.

[0014] Some examples herein are directed to a method of treating skin conditions in a patient in need thereof comprising topically applying a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, benzyl alcohol, PEG 400, 2-(2-ethoxyethoxy)ethanol, polysorbate 80, and optionally one or more pharmaceutically acceptable topical excipients.

[0015] Some examples herein are directed to a method of treating skin conditions in a patient in need thereof comprising topically applying a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, PEG 400, dimethyl isosorbide, 2-(2-ethoxyethoxy)ethanol, DMSO, and optionally one or more pharmaceutically acceptable topical excipients.

[0016] Some examples herein are directed to a method of treating skin conditions in a patient in need thereof comprising topically applying a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, propylene glycol, oleic acid, polysorbate 80, isopropyl myristate, phenoxyethanol, and optionally one or more pharmaceutically acceptable topical excipients.

[0017] Some examples herein are directed to a method of treating skin conditions in a patient in need thereof comprising topically applying a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, benzyl alcohol, glycerin, and optionally one or more pharmaceutically acceptable topical excipients.

[0018] Some examples herein are directed to a method of treating skin conditions in a patient in need thereof comprising topically applying a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, DMSO, water, and optionally one or more pharmaceutically acceptable topical excipients.

[0019] Some examples herein are directed to a method of treating skin conditions in a patient in need thereof comprising topically applying a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, propylene glycol, water, and optionally one or more pharmaceutically acceptable topical excipients.

[0020] Some examples herein are directed to a method of treating skin conditions in a patient in need thereof comprising topically applying a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, propylene glycol, glycerin, and optionally one or more pharmaceutically acceptable topical excipients.

[0021] Some examples herein are directed to a method of treating skin conditions in a patient in need thereof comprising topically applying a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, propylene glycol, 2-(2-ethoxyethoxy)ethanol, PEG400, butylated hydroxytoluene, and optionally one or more pharmaceutically acceptable topical excipients. In some examples, the topical composition further comprises cellulose polymers. In some examples, the topical composition further comprises Carbomer Homopolymer Types A, B or C. In some examples, the topical composition further comprises Poloxamer.

[0022] Some examples herein are directed to a method of treating skin conditions in a patient in need thereof comprising topically applying a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, 2-(2-ethoxyethoxy)ethanol, PEG400, glycerin, cellulose polymer, butylated hydroxytoluene, and optionally one or more pharmaceutically acceptable topical excipients.

[0023] Some examples herein are directed to a method of treating skin conditions in a patient in need thereof comprising topically applying a topical composition comprising 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid, propylene glycol, 2-(2-ethoxyethoxy)ethanol, glycerin, dimethyl isosorbide, butylated hydroxytoluene, and optionally one or more pharmaceutically acceptable topical excipients. In some examples, the topical composition further comprises cellulose polymers. In some examples, the topical composition further comprises Carbomer Homopolymer Types A, B or C.

[0023a] In a sixth aspect, the present disclosure refers to use of a topical composition of the first aspect in the manufacture of a medicament for treating skin conditions in a patient in need thereof, wherein the medicament is to be topically applied to the patient.

[0023b] In a seventh aspect, the present disclosure refers to use of a topical composition of the second aspect in the manufacture of medicament for treating skin conditions in a patient in need thereof, wherein the medicament is to be topically applied to the patient.

[0023c] In an eighth aspect, the present disclosure refers to use of a topical composition of the third aspect in the manufacture of a medicament for treating skin conditions in a patient in need thereof, wherein the medicament is to be topically applied to the patient.

[0023d] In a ninth aspect, the present disclosure refers to use of a topical composition of the fourth aspect in the manufacture of a medicament for treating skin conditions in a patient in need thereof, wherein the medicament is to be topically applied to the patient.

[0023e] In a tenth aspect, the present disclosure refers to use of a topical composition of the fifth aspect in the manufacture of a medicament for treating skin conditions in a patient in need thereof, wherein the medicament is to be topically applied to the patient.

Description of the Drawings:

[0024] For a fuller understanding of the nature and advantages of the present invention, reference should be had to the following detailed description taken in connection with the accompanying drawings, in which:

[0025] FIG. 1A provides cell viability data measured by CTB at day 3 of treatment. FIG. 1B provides cell viability data measured by CTB at day 5 of treatment.

Claims

1. A topical composition comprising about 0.1% to about 1.0% 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid by weight of the topical composition, about 10.0% to about 50.0% propylene glycol by weight of the topical composition, about 30.0% to about 75.0% 2-(2-ethoxyethoxy)ethanol by weight of the topical composition, about 15.0% to about 50.0% PEG400 by weight of the topical composition, about 0.01% to about 5.0% butylated hydroxytoluene by weight of the topical composition, and optionally one or more pharmaceutically acceptable topical excipients.

2. The topical composition of claim 1, wherein the topical composition further comprises glycerin, cellulose polymers, Carbomer Homopolymer Type A, Carbomer Homopolymer Type B, Carbomer Homopolymer Type C, or combinations thereof.

3. The topical composition of claim 2, wherein the glycerin is at a concentration from about 5.0% to about 25.0% by weight of the topical composition.

4. The topical composition of claim 2, wherein the cellulose polymer is at a concentration from about 0.1% to about 5.0% by weight of the topical composition.

5. The topical composition of claim 2, wherein the Carbomer Homopolymer Type A, Carbomer Homopolymer Type B, or Carbomer Homopolymer Type C is at a concentration from about 0.1% to about 5.0% by weight of the topical composition.

6. A topical composition comprising about 0.1% to about 1.0% 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid by weight of the topical composition, about 30.0% to about 75.0% 2-(2-ethoxyethoxy)ethanol by weight of the topical composition, about 15.0% to about 65.0% PEG400 by weight of the topical composition, about 5.0% to about 25.0% glycerin by weight of the topical composition, about 0.1% to about 5.0% cellulose polymer(s) by weight of the topical composition, about 0.01% to about 5.0% butylated hydroxy toluene by weight of the topical composition, and optionally one or more pharmaceutically acceptable topical excipients.

7. A topical composition comprising about 0.1% to about 1.0% 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid by weight of the topical composition, about 20.0% to about 50.0% propylene glycol by weight of the topical

composition, about 25.0% to about 65.0% 2-(2-ethoxyethoxy)ethanol by weight of the topical composition, about 5.0% to about 25.0% glycerin by weight of the topical composition, about 5.0% to about 25.0% dimethyl isosorbide by weight of the topical composition, about 0.01% to about 5.0% butylated hydroxy toluene by weight of the topical composition, and optionally one or more pharmaceutically acceptable topical excipients.

8. The topical composition of claim 7, wherein the topical composition further comprises cellulose polymers, , Carbomer Homopolymer Type A, Carbomer Homopolymer Type B, Carbomer Homopolymer Type C, or combinations thereof.

9. The topical composition of claim 8, wherein the cellulose polymer is at a concentration from about 0.1% to about 5.0% by weight of the topical composition.

10. The topical composition of claim 8, wherein the Carbomer Homopolymer Type A, Carbomer Homopolymer Type B, or Carbomer Homopolymer Type C is at a concentration from about 0.1% to about 5.0% by weight of the topical composition.

11. A topical composition comprising about 0.1% to about 1.0% 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid by weight of the topical composition, about 0.5% to about 5.0% benzyl alcohol by weight of the topical composition, about 1.0% to about 10.0% PEG 400 by weight of the topical composition, about 1.0% to about 20.0% diisopropyl adipate by weight of the topical composition, about 1.0% to about 20.0% diethyl sebacate by weight of the topical composition, about 1.0% to about 20.0% dimethyl isosorbide by weight of the topical composition, about 1.0% to about 30.0% 2-(2-ethoxyethoxy)ethanol by weight of the topical composition, about 1.0% to about 15.0% hexylene glycol by weight of the topical composition, about 1.0% to about 10.0% polysorbate 80 by weight of the topical composition, and optionally one or more pharmaceutically acceptable topical excipients.

12. A topical composition comprising about 0.1% to about 1.0% 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid by weight of the topical composition, about 0.5% to about 5.0% benzyl alcohol by weight of the topical composition, about 30.0% to about 60.0% PEG 400 by weight of the topical composition, about 1.0% to about 30.0% 2-(2-ethoxyethoxy)ethanol by weight of the topical composition, about 1.0% to about 10.0% polysorbate 80 by weight of the topical composition, and optionally one or more pharmaceutically acceptable topical excipients.

13. The topical composition of claim 12, further comprising diisopropyl adipate in a concentration from about 1.0% to about 25.0% by weight of the topical composition.

14. The topical composition of claim 12, further comprising hexylene glycol in a concentration from about 1.0% to about 20.0% by weight of the topical composition.

15. Use of a topical composition of claim 1 in the manufacture of a medicament for treating skin conditions in a patient in need thereof, wherein the medicament is to be topically applied to the patient.

16. The use of claim 15, wherein the skin condition is selected from the group consisting of inflammatory acne, non-inflammatory acne, acne, comedonal acne, inflammatory acne, papular acne, pustular acne, cystic acne, follicular hyperkeratinization, seborrheic cysts, seborrhea, sebostasis, seborrheic dermatitis, sebaceous adenomas, sebaceous hyperplasia, and excess sebum production, dermatitis, atopic dermatitis, seborrheic dermatitis, alopecia, contact dermatitis, psoriasis, urticaria eczema, burns, sunburn, pancreatitis, hepatitis, lichen planus, scleritis, scleroderma, dermatomyositis, itching associated with any of the preceding conditions, and any combination thereof.

17. Use of a topical composition of claim 6 in the manufacture of medicament for treating skin conditions in a patient in need thereof, wherein the medicament is to be topically applied to the patient.

18. The use of claim 17, wherein the skin condition is selected from the group consisting of inflammatory acne, non-inflammatory acne, acne, comedonal acne, inflammatory acne, papular acne, pustular acne, cystic acne, follicular hyperkeratinization, seborrheic cysts, seborrhea, sebostasis, seborrheic dermatitis, sebaceous adenomas, sebaceous hyperplasia, and excess sebum production, dermatitis, atopic dermatitis, seborrheic dermatitis, alopecia, contact dermatitis, psoriasis, urticaria eczema, burns, sunburn, pancreatitis, hepatitis, lichen planus, scleritis, scleroderma, dermatomyositis, itching associated with any of the preceding conditions, and any combination thereof.

19. Use of a topical composition of claim 7 in the manufacture of a medicament for treating skin conditions in a patient in need thereof, wherein the medicament is to be topically applied to the patient.

20. The use of claim 19, wherein the skin condition is selected from the group consisting of inflammatory acne, non-inflammatory acne, acne, comedonal acne, inflammatory acne, papular acne, pustular acne, cystic acne, follicular hyperkeratinization, seborrheic cysts, seborrhea, sebostasis, seborrheic dermatitis, sebaceous adenomas, sebaceous hyperplasia, and excess sebum production, dermatitis, atopic dermatitis, seborrheic dermatitis, alopecia, contact dermatitis, psoriasis, urticaria eczema, burns, sunburn, pancreatitis, hepatitis, lichen planus, scleritis, scleroderma, dermatomyositis, itching associated with any of the preceding conditions, and any combination thereof.

21. Use of a topical composition of claim 11 in the manufacture of a medicament for treating skin conditions in a patient in need thereof, wherein the medicament is to be topically applied to the patient.

22. The use of claim 21, wherein the skin condition is selected from the group consisting of inflammatory acne, non-inflammatory acne, acne, comedonal acne, inflammatory acne, papular acne, pustular acne, cystic acne, follicular hyperkeratinization, seborrheic cysts, seborrhea, sebostasis, seborrheic dermatitis, sebaceous adenomas, sebaceous hyperplasia, and excess sebum production, dermatitis, atopic dermatitis, seborrheic dermatitis, alopecia, contact dermatitis, psoriasis, urticaria eczema, burns, sunburn, pancreatitis, hepatitis, lichen planus, scleritis, scleroderma, dermatomyositis, itching associated with any of the preceding conditions, and any combination thereof.

23. Use of a topical composition of claim 12 in the manufacture of a medicament for treating skin conditions in a patient in need thereof, wherein the medicament is to be topically applied to the patient.

24. The use of claim 23, wherein the skin condition is selected from the group consisting of inflammatory acne, non-inflammatory acne, acne, comedonal acne, inflammatory acne, papular acne, pustular acne, cystic acne, follicular hyperkeratinization, seborrheic cysts, seborrhea, sebostasis, seborrheic dermatitis, sebaceous adenomas, sebaceous hyperplasia, and excess sebum production, dermatitis, atopic dermatitis, seborrheic dermatitis, alopecia, contact dermatitis, psoriasis, urticaria eczema, burns, sunburn,

pancreatitis, hepatitis, lichen planus, scleritis, scleroderma, dermatomyositis, itching associated with any of the preceding conditions, and any combination thereof.