

(43) International Publication Date
11 December 2014 (11.12.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/197184 A1

(51) International Patent Classification:

A61K 8/34 (2006.01) **A61K 47/26** (2006.01)
A61K 8/49 (2006.01) **A61K 9/08** (2006.01)
A61K 8/60 (2006.01) **A61K 31/045** (2006.01)
A61Q 19/10 (2006.01) **A61K 31/357** (2006.01)
A61K 9/00 (2006.01) **A61K 31/55** (2006.01)
A61K 47/02 (2006.01) **A61P 17/00** (2006.01)
A61K 47/20 (2006.01)

(21) International Application Number:

PCT/US2014/038295

(22) International Filing Date:

16 May 2014 (16.05.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

13/911,492 6 June 2013 (06.06.2013) US
 14/278,007 15 May 2014 (15.05.2014) US

(71) Applicant: **JOHNSON & JOHNSON CONSUMER COMPANIES, INC.** [US/US]; 199 Grandview Road, Skillman, New Jersey 08558 (US).

(72) Inventors: **CEBULSKI, Salwomir**; 403 Village Commons, Flemington, New Jersey 08822 (US). **GARAY, Michelle**; 100 Sky Manor Road, Pittstown, New Jersey 08867 (US). **RODRIGUEZ, Karien J.**; 5505 Perimeter Lofts Circle, Dunwoody, Georgia 30346 (US). **SOUTHALL, Michael D.**; 7 Walking Purchase Drive, Pennington, New Jersey 08534 (US). **KAUR, Simarna**; 220 Johns Lane, Neshanic Station, NJ 08853 (US).

(74) Agents: **PLANTZ, Bernard F.** et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933 (US).

(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, BN, 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, IR, IS, JP, KE, KG, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, 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, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

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

(54) Title: COMPOSITIONS COMPRISING AN AROMATIC ALCOHOL AND A TRPV-1 ANTAGONIST, AND USES THEREOF

(57) Abstract: A topical composition providing reduced irritation that contains aromatic alcohols such as phenoxyethanol and a TRPV-1 antagonist such as 4-tertiary butyl cyclohexanol is described. The composition is substantially free of parabens. The composition may be used for example for cleansing the skin.

COMPOSITIONS COMPRISING AN AROMATIC ALCOHOL AND A TRPV-1 ANTAGONIST, AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

5 This application is a continuation-in-part of US Application Serial No. 13/911,492 filed June 6, 2013, the disclosure of which is hereby incorporated by reference.

FIELD OF THE INVENTION

10 The present invention relates to a composition comprising an aromatic alcohol and a TRPV-1 antagonist, and methods of use thereof.

BACKGROUND OF THE INVENTION

15 Phenoxyethanol is a common ingredient used to preserve cosmetic and pharmaceutical formulations for topical administration. Phenoxyethanol, sometimes known as 2-phenoxy-1-ethanol or ethylene glycol monophenyl ether, is a preservative used to provide biocidal activity against various microorganisms. Unfortunately, phenoxyethanol is also an irritant to the skin (see, for example, Lee E et al., *Contact Dermatitis*. 2007 Mar;56(3):131-6.). Similarly, benzyl alcohol is also known to induce skin irritation *in vivo* (Bagley, D. M. et al. (1996) *Toxicol In Vitro* 10(1): 1-6).

20 TRPV-1 (transient receptor potential vanilloid, subfamily V, receptor 1) is a protein encoded by the TRPV-1 gene. TRPV-1 is a non-selective, ligand-gated cation channel that is activated in response to increased temperature and mechanical or chemical stimulus. This receptor is found in the central nervous system as well as in non-neuronal cells, such as keratinocytes. Activation of TRPV-1 allows the transient
25 flux of cations, especially Ca^{2+} , into the cell. This Ca^{2+} influx stimulates the sensation of pain and has been associated with the onset of various cellular events such as inflammation. Activation of TRPV-1 is known to induce the release of pro-inflammatory mediators in human keratinocytes (Southall, M. D. et al. (2003) "*J Pharmacol Exp Ther* 304(1): 217-222).

30 TRPV-1 is known to be activated by capsaicin, a compound found in chili peppers, and capsazepine is reported to be a TRPV-1 antagonist (Bevan, S. et al., *Br J Pharmacol* 107(2): 544-552). Other compounds known to be TRPV-1 antagonists are

(E)-3-(4-*t*-butylphenyl)-N-(2,3-dihydrobenzo[*b*][1,4] dioxin-6-yl)acrylamide (Gavva, N. R. et al. (2005) *J Pharmacol Exp Ther* 313(1): 474-484), commercially available as AMG9810 from Tocris Bioscience, Bristol, United Kingdom, and 4-tertiary butyl cyclohexane (Kueper, T. et al. (2010) *Exp Dermatol* 19(11): 980-986), commercially
5 available as SYMSITIVE 1609 from Symrise GmbH of Holzminden, Germany.

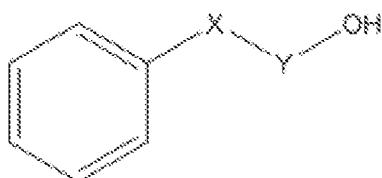
Applicants have now discovered that certain aromatic alcohols including phenoxyethanol activate TRPV-1. This is surprising in that applicants have also found that not all skin irritants activate TRPV-1 and not all topical anti-inflammatory compounds or analgesics inhibit the activation of TRPV-1. Thus, the discovery of the
10 association between aromatic alcohols, their irritating properties, and TRPV-1 is unexpected.

Low irritation, aromatic alcohol-containing topical compositions are provided herein. Advantageously, they also do not require the presence of parabens (esters of para-hydroxybenzoic acid), the effects of which many consumers are concerned about.
15 Further provided are methods of use thereof.

SUMMARY OF THE INVENTION

The invention provides a composition comprising an aromatic alcohol having the formula:

20

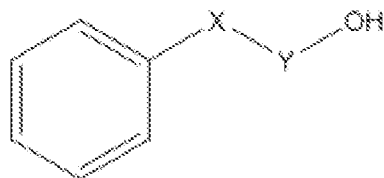


Formula 1

wherein X is an oxygen atom or absent and Y is C1 - C2 alkyl; and a TRPV-1 antagonist, wherein said composition is substantially free of esters of para-
25 hydroxybenzoic acid.

The invention also provides a method of cleansing the skin, comprising applying the above composition to the skin and rinsing the composition off of the skin.

The invention further provides a method of reducing irritation induced by topical application of an aromatic alcohol having the formula:



Formula 1

wherein X is an oxygen atom or absent and Y is C1 - C2 alkyl; said method comprising
5 topically applying said aromatic alcohol with a TRPV-1 antagonist.

DETAILED DESCRIPTION OF THE INVENTION

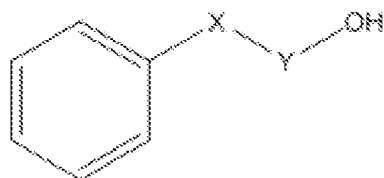
Unless defined otherwise, all technical and scientific terms used herein have the
meaning commonly understood by one of ordinary skill in the art to which the invention
10 pertains. Also, all publications, patent applications, patents, and other references
mentioned herein are incorporated by reference. Unless otherwise indicated, a
percentage refers to a percentage by weight (i.e., %(W/W)).

As used herein, "substantially free" of an ingredient means containing less than
about 1% by weight, such as less than about 0.5% by weight, such as less than about
15 0.25% by weight, such as less than about 0.1% by weight of such ingredient. In one
embodiment, "substantially free" means completely free of such ingredient.

It is believed that one skilled in the art can, based upon the description herein,
utilize the present invention to its fullest extent. The following specific embodiments
are to be construed as merely illustrative, and not limiting of the remainder of the
20 disclosure in any way whatsoever.

Aromatic Alcohol

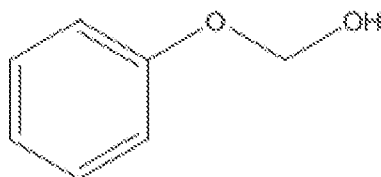
The composition of the invention comprises an aromatic alcohol of Formula 1:



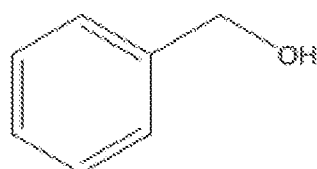
Formula 1

wherein X is an oxygen atom or absent and Y is C1 - C2 alkyl.

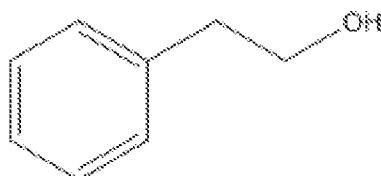
In one embodiment, the aromatic alcohol is selected from the group consisting of phenoxyethanol, benzyl alcohol, phenethyl alcohol, and mixtures thereof:



Phenoxyethanol



Benzyl Alcohol



Phenethyl alcohol

The amount of aromatic alcohol in the composition may be varied depending upon factors such as its particular biocidal requirements or whether the composition is “ready-to use,” requires dilution with water, or is in the form of a concentrate that will be added to a separate formulation.

Broadly, the composition may contain an amount of aromatic alcohol ranging from about 0.1% to about 80%, or 0.1% to about 66%, such as 0.1% to about 50%, by weight of the composition.

TRPV-1 Antagonist

The composition also includes a TRPV-1 antagonist.

In one embodiment, the TRPV-1 antagonist inhibits the calcium flux of the aromatic alcohol by at least about 12%, or at least about 20%, preferably at least about 50%, such as from about 50% to about 80%, as measured by Calcium Flux Test.

The Calcium Flux Test is performed in the following manner: Recombinant HEK293 cells expressing human vanilloid receptor-1 (TRPV-1; accession number AF196175, EMD Millipore, Billerica, MA) are grown in D-MEM/F-12 media (Life Technologies, Grand Island, NY) supplemented with 10% fetal bovine serum, 1% non essential amino acids and 400µg/mL Geneticin (Gibco, Life Technologies). Cells are plated at a concentration of 15,000 cells per well on poly-D-lysine-coated 384 well plates and incubated overnight at 5% CO₂ and 37 °C. After incubation, culture media is removed from the wells and replaced with 50µL per well of Fluo-8 No Wash dye solution (# 36315, AAT Bioquest, Sunnyvale, CA). The Fluo-8 dye solution is prepared by mixing 20uL of Fluo-8 NW with 30mL of 0.33X Pluronic® F127 Plus (BASF of Ludwigshafen, Germany) in assay buffer (1X HBSS + 2% of HEPES). Fluo-8 dye is incubated for 30 minutes at room temperature. Intracellular calcium (Ca²⁺) flux is monitored upon exposure to aromatic alcohol in DMSO vehicle by measuring fluorescence intensity at Ex/Em 490/525 on a Functional Drug Screening System (FDSS; Hamamatsu, Germany). Measurements are taken every second for a period of 4 minutes. Results are presented as mean ± standard deviation of maximum relative fluorescence units (RFU) during the 4 minute period. Statistical differences are obtained using One Way ANOVA with Tukey Post-hoc test; statistical significance is defined as P ≤ 0.05.

The Maximum RFU obtained with a given concentration of aromatic alcohol is compared with the Maximum RFU obtained using the same concentration of aromatic alcohol but pretreated with the TRPV-1 antagonist for 5 minutes after dye incubation. Percent inhibition achieved with the TRPV-1 antagonist is calculated as: 100 * ((Maximum RFU of aromatic alcohol – Maximum RFU of aromatic alcohol pretreated with TRPV-1 antagonist) / Maximum RFU of aromatic alcohol).

Examples of TRPV-1 antagonists include capsazepine, (E)-3-(4-t-butylphenyl)-N-(2,3-dihydrobenzo[b][1,4] dioxin-6-yl)acrylamide (commercially available for

example as AMG9810 from Tocris Bioscience, Bristol, United Kingdom), and 4-tertiary butyl cyclohexane (commercially available as SYMSITIVE 1609 from Symrise GmbH of Holzminden, Germany).

Preferably, the TRPV-1 antagonist is 4-tertiary butyl cyclohexane.

5 The amount of TRPV-1 antagonist in the composition may vary. According to certain embodiments, the amount of TRPV-1 antagonist is from about 0.05% to about 5%, such as from about 0.1% to about 2%, such as from about 0.2% to about 1%, such as from about 0.2% to about 0.5%, by weight of the composition.

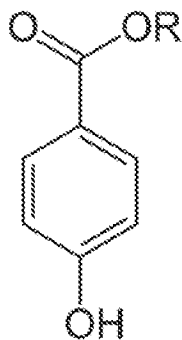
10 The inventors have surprisingly found that TRPV-1 antagonists such as 4-tertiary butyl cyclohexanol are particularly effective at decreasing calcium flux due to aromatic alcohols of Formula 1. Accordingly, small amounts of TRPV-1 antagonist may be used in the composition relative to the amount of aromatic alcohol in the composition.

15 For instance, in certain embodiments when using phenoxyethanol, the mass ratio of TRPV-1 antagonist to aromatic alcohol in the composition may be from about 1:24 to about 1:2.7, such as from about 1:6 to about 1:2.7, such as from about 1:5.4 to about 1:2.7. When using benzyl alcohol, the mass ratio of TRPV-1 antagonist to aromatic alcohol in the composition may be from about 1:0.08 to about 1:0.9. When using phenethyl alcohol, the mass ratio of TRPV-1 antagonist to aromatic alcohol in the composition may be from about 1:0.09 to about 1:3.

20 Since the amount of 4-tertiary butyl cyclohexanol in SYMSITIVE 1609 is believed to be from about 40% to about 60% (diluted in propylene glycol), when using SYMSITIVE 1609 and phenoxyethanol for example, the mass ratio of 4-tertiary butyl cyclohexanol to aromatic alcohol should be 0.4 to 0.6 times the mass ratios above (i.e., 25 0.4:24 to 0.6:24, instead of 1:24; 0.4:2.7 to 0.6:2.7, instead of 1:2.7; etc.).

Substantially Free of Parabens

30 According to certain embodiments, the compositions of the present invention are substantially free of esters of parahydroxybenzoic acid (parabens). Examples of esters of parahydroxybenzoic acid include those having the structure below, wherein R is an alkyl group:



Examples of esters of parahydroxybenzoic acid include methylparaben,
5 ethylparaben, butylparaben, propylparaben, isobutylparaben, heptylparaben, and salts thereof.

Topical Compositions

The compositions of the present invention may include a cosmetically-
10 acceptable topical carrier. The cosmetically-acceptable topical carrier may contain ingredients commonly used, such as water, monoalcohols (such as ethanol and isopropanol); glycols and polyols (such as glycerin, propylene glycol, propanediol, 1,4-butanediol, 1,3-butanediol, 1,2-butanediol, hydroxyethyl urea, sorbitol, sorbitan, xylitol and polyglycerols); glycerin, and combinations thereof. According to certain
15 embodiments, the carrier includes water.

The amount of cosmetically-acceptable topical carrier in the composition may range from about 30% to about 99%, such as from about 40% to about 95%, such as from about 50% to about 95%, such as from about 60% to about 90% by weight of the composition.

20 In embodiments in which the composition includes a cosmetically-acceptable topical carrier, the amount of aromatic alcohol in such composition may be from about 0.1% to about 5%, such as from about 0.2% to about 2.5%, such as from about 0.3% to about 2%, by weight of the composition.

According to other embodiments the composition is in the form of a concentrate.
25 As such, the composition may consist essentially of aromatic alcohol of Formula 1 and a TRPV-1 antagonist. For example, the amount of aromatic alcohol in the composition

may be from about 55% to about 90%, such as from about 60% to about 85%, such as about 70% to about 85%, by weight of the composition, remainder being TRPV-1 antagonist and optionally up to about 20% of a diluent such as water, a monoalcohol, a glycol/polyol, or combinations thereof.

5 The compositions of the present invention may include additional ingredients commonly used in topical compositions. Examples of additional ingredients include but are not limited to surfactants/emulsifiers (cationic, anionic, non-ionic, and zwitterionic), humectants, emollients and hydrophobic compounds, conditioning agents, opacifying agents, chelating agents, conditioning agents, additional preservatives, skin benefit
10 agents, fragrances, water-soluble or dispersible polymers, and active ingredients (e.g., sunscreens, anti-aging actives, anti-acne actives, and the like).

According to certain embodiments, the composition is aqueous and the pH of the composition is about 6.5 or greater, such as from about 6.5 to about 8.5, such as from about 7.5 to about 8.5.

15 Compositions of the present invention are particularly suitable for topically applying to skin or mucosa. According to certain embodiments, the composition is used to cleanse the skin or mucosa and may be rinsed therefrom. The composition may be contained within or be in fluid communication with an applicator that is suitable for dispensing it.

20 According to other embodiments, the invention also provides a method of reducing irritation induced by topical application of an aromatic alcohol of Formula 1, said method comprising topically applying said aromatic alcohol with a TRPV-1 antagonist as described above.

25 **Example 1: Phenoxyethanol Induces Calcium Flux via TRPV-1 Receptor**

Phenoxyethanol was tested at a series of concentrations in DMSO for activity as a TRPV-1 agonist according to the Calcium Flux Test described above. Capsaicin was used as a positive control.

Maximum RFU values for treatment with phenoxyethanol or capsaicin were
30 compared to the Maximum RFU for a DMSO vehicle alone. The results for phenoxyethanol are shown in Table 1. The results for capsaicin are shown in Table 2.

Concentrations of phenoxyethanol and capsaicin are reported in milimolar (mM) and nanomolar (nM), respectively.

Both capsaicin and phenoxyethanol showed dose dependent increases in intracellular calcium flux in TRPV-1-transfected HEK cells. For phenoxyethanol, the increase in Maximum RFU values versus the control vehicle was statistically significant across a wide range of amounts, and increased thirty to forty-fold compared to the vehicle alone. These findings demonstrate activation of the TRPV-1 receptor by phenoxyethanol.

10 **Table 1**

Phenoxyethanol (mM)	Maximum RFU (mean $\pm$ SD)	** P<0.05 Compared to Vehicle
4	453.25 $\pm$ 34.18	**
3.5	404.21 $\pm$ 42.32	**
3	401.68 $\pm$ 26.58	**
2.5	363.73 $\pm$ 44.11	**
2	357.37 $\pm$ 44.88	**
1.5	304.41 $\pm$ 70.10	**
1	200.28 $\pm$ 76.93	**
0.75	124.81 $\pm$ 37.58	n/s
0.5	96.96 $\pm$ 61.20	n/s
Vehicle	13.88 $\pm$ 2.95	-

n/s: Not statistically significant

*** Statistically significant*

Table 2

Capsaicin Concentration (nM)	Maximum RFU (mean $\pm$ SD)	** P<0.05 Compared to Vehicle
10000	698.83 $\pm$ 30.57	**
2500	617.87 $\pm$ 34.14	**
625	604.13 $\pm$ 32.46	**
156	491.07 $\pm$ 21.10	**
39	405.53 $\pm$ 11.25	**
10	348.17 $\pm$ 5.56	**
2	253.47 $\pm$ 24.63	**
0.6104	121.32 $\pm$ 46.41	**
0.1526	29.34 $\pm$ 8.18	n/s
0.0381	10.19 $\pm$ 2.94	n/s
Vehicle	16.23 $\pm$ 2.95	-

n/s: not statistically significant

*** statistically significant*

5 Example 2: TRPV-1 Antagonists Reduce Ca²⁺ Flux Induced By Phenoxyethanol or Capsaicin

Capsazepine and AMG9810 were tested for activity as TRPV-1 antagonists using the Calcium Flux Test using two different concentrations of phenoxyethanol in DMSO. They were also tested using the Calcium Flux Test in which phenoxyethanol was replaced with capsaicin.

The results are shown in Tables 3-6. Concentrations of capsazepine and AMG9810 are reported in nanomolar (nM).

The results demonstrate that treatment with TRPV-1 antagonists reduces phenoxyethanol-induced calcium flux and capsaicin-induced calcium flux.

Table 3

Capsazepine [nM]	Phenoxyethanol 3mM		Phenoxyethanol 2mM	
	Maximum RFU (mean $\pm$ SD)	% of Inhibition	Maximum RFU (mean $\pm$ SD)	% of Inhibition
10000	106.49 $\pm$ 4.15	75.89	79.39 $\pm$ 2.79	72.34
2500	99.71 $\pm$ 6.08	77.43	84.79 $\pm$ 2.68	70.46
625	75.71 $\pm$ 3.39	82.86	57.76 $\pm$ 2.15	79.88
156	101.59 $\pm$ 2.44	77.00	87.54 $\pm$ 8.38	69.50
39	176.52 $\pm$ 75.37	60.04	75.06 $\pm$ 6.64	73.85
10	340.96 $\pm$ 12.96	22.82	154.95 $\pm$ 19.56	46.01
2	486.75 $\pm$ 153.02	-	236.10 $\pm$ 8.91	17.73
0.6104	351.36 $\pm$ 32.21	20.46	210.03 $\pm$ 46.34	26.82
0.1526	508.45 $\pm$ 81.79	-	319.33 $\pm$ 77.43	-
0	441.76 $\pm$ 36.68	-	287.00 $\pm$ 25.75	-

Table 4

Capsazepine (nM)	Capsaicin 300nM		Capsaicin 100nM	
	Maximum RFU (Mean $\pm$ SD)	% of Inhibition	Maximum RFU (Mean $\pm$ SD)	% of Inhibition
10000	58.73 $\pm$ 4.40	93.18	45.31 $\pm$ 14.17	93.00
2500	31.08 $\pm$ 3.44	96.39	27.61 $\pm$ 4.95	95.73
625	28.36 $\pm$ 3.16	96.71	24.39 $\pm$ 5.19	96.23
156	51.20 $\pm$ 14.34	94.05	29.36 $\pm$ 6.46	95.46
39	557.38 $\pm$ 79.48	35.26	187.95 $\pm$ 177.88	70.95
10	771.64 $\pm$ 25.92	10.37	461.29 $\pm$ 221.27	28.71
2	850.93 $\pm$ 28.65	1.16	665.83 $\pm$ 90.25	-
0	860.95 $\pm$ 33.14	-	647.05 $\pm$ 33.18	-

Table 5

AMG9810 (nM)	Phenoxyethanol 3mM		Phenoxyethanol 2mM	
	Maximum RFU (mean ± SD)	% of Inhibition	Maximum RFU (mean ± SD)	% of Inhibition
10000	65.74 ± 4.33	70.69	59.78 ± 3.84	72.37
2500	68.59 ± 4.15	69.42	58.00 ± 5.34	73.19
625	58.16 ± 1.97	74.07	55.53 ± 8.48	74.34
156	75.59 ± 10.97	66.29	58.21 ± 5.97	73.10
39	98.74 ± 23.34	55.97	165.37 ± 162.35	23.57
10	315.60 ± 125.77	-	110.26 ± 27.80	49.05
2	265.02 ± 52.11	-	202.96 ± 18.01	6.20
0.6104	405.29 ± 152.93	-	189.72 ± 34.94	12.32
0.1526	412.30 ± 110.68	-	261.54 ± 114.76	-
0	224.26 ± 42.60	-	216.39 ± 45.19	-

Table 6

AMG9810 (nM)	Capsaicin 300nM		Capsaicin 100nM	
	Maximum RFU (mean ± SD)	% of Inhibition	Maximum RFU (mean ± SD)	% of Inhibition
10000	44.15 ± 2.20	94.95	47.00 ± 11.29	94.47
2500	78.33 ± 46.56	91.05	85.41 ± 20.60	89.95
625	747.36 ± 77.35	14.59	735.36 ± 114.75	13.45
156	958.56 ± 16.66	-	916.79 ± 31.53	-
39	975.35 ± 32.01	-	942.69 ± 88.43	-
0	875.05 ± 55.11	-	849.62 ± 7.02	-

5 Example 3: SYMSITIVE 1609 Reduces Ca²⁺ Flux Induced By Phenoxyethanol or Capsaicin

SYMSITIVE1609 was tested for activity as a TRPV-1 antagonist using the Calcium Flux Test using two different concentrations of phenoxyethanol in DMSO. It

was also tested using the Calcium Flux Test in which phenoxyethanol was replaced with capsaicin. The results are shown in Tables 7 and 8, respectively. Concentrations of phenoxyethanol and capsaicin are reported in milimolar (mM) and nanomolar (nM), respectively, but concentrations of SYMSITIVE1609 are reported in % v/v. In Table 7, mass ratios of SYMSITIVE1609 to phenoxyethanol are also reported (molecular weight of phenoxyethanol of 138.16 g/mol, a density of phenoxyethanol of 1.1 g/mL, and a density of SYMSITIVE1609 of 0.95 g/mL).

These results demonstrate that treatment with SYMSITIVE1609 not only reduces phenoxyethanol-induced calcium flux, but is capable of reducing this flux at low ratios of SYMSITIVE1609 to phenoxyethanol.

Table 7

SYMSITIVE 1609 (% v/v)	Phenoxyethanol 3mM			Phenoxyethanol 2mM		
	Max RFU (mean $\pm$ SD)	% of Inhibition	Ratio (m/m) SYMSITIVE : Phenoxyethanol	Max RFU (mean $\pm$ SD)	% of Inhibition	Mass Ratio SYMSITIVE: Phenoxyethanol
0.04839	52.56 $\pm$ 6.41	79.62	1:0.9	48.89 $\pm$ 4.25	72.44	1:0.6
0.01613	49.86 $\pm$ 5.59	80.67	1:2.7	52.45 $\pm$ 2.42	70.44	1:1.8
0.00538	73.49 $\pm$ 11.30	71.51	1:8	55.66 $\pm$ 2.52	68.63	1:5.4
0.00179	200.63 $\pm$ 15.30	22.22	1:24	137.07 $\pm$ 9.64	22.75	1:16
0.00060	263.43 $\pm$ 3.66	-	1:73	190.00 $\pm$ 48.44	-	1:48.7
0	257.93 $\pm$ 39.06	-	-	177.43 $\pm$ 19.36	-	-

Table 8

	Capsaicin 100nM	
SYMSITIVE1609 (% v/v)	Maximum RFU (mean $\pm$ SD)	% of Inhibition
0.04839	707.54 $\pm$ 269.73	29.73
0.01613	713.35 $\pm$ 621.33	29.15
0.00538	1119.65 $\pm$ 140.29	-
0.00179	1293.49 $\pm$ 40.06	-
0.00060	1305.23 $\pm$ 33.35	-
0	1006.91 $\pm$ 74.51	-

Example 4: Preparation of Formulated Cleansing Compositions

A comparative cleansing composition (Comparative Example C1) was prepared
 5 using the ingredients listed in Table 9:

TABLE 9: Comparative Example, C1

Trade name	INCI Name	% wt
Deionized Water	Water	79.9
Texapon N70A	Sodium Lauryl Sulfate	3.7
Tween 28-LQ	PEG-80 Sorbitan Laurate	5.0
Miranol HMD	Sodium Lauroamphoacetate	2.0
TegoBetain L7V	Cocamidopropyl Betain	6.4
Phenoxetol	Phenoxyethanol	2.0
Hydrolite CG	Caprylyl Glycol	1.0
Citric Acid (50% solution)	Citric Acid	q.s

10 The composition shown in Table 9 above was prepared as follows. Water was added to a glass beaker and heated to 60°C. Texapon N70A was mixed in until fully dissolved. While mixing, Tween 28-LQ, Miranol HMD and TegoBetain L7V were

added and mixing was continued until the mixture was clear. Hydrolite CG and Phenoxetol were added at the same time and mixing was continued while slowly lowering the temperature to room temperature. pH was adjusted to a target of 5.6 using citric acid.

- 5 Another comparative cleansing composition, Comparative Example C2, was prepared using the ingredients listed in Table 10:

TABLE 10: Comparative Example, C2

Trade name	INCI Name	% wt
Deionized Water	Water	80.9
Texapon N70A	Sodium Lauryl Sulfate	3.7
Tween 28-LQ	PEG-80 Sorbitan Laurate	5.0
Miranol HMD	Sodium Lauroamphoacetate	2.0
TegoBetain L7V	Cocamidopropyl Betain	6.4
Phenoxetol	Phenoxyethanol	2.0
Citric Acid (50% solution)	Citric Acid	q.s – pH adjuster

- 10 The composition shown in Table 10 was prepared as follows. Water was added to a glass beaker and heated to 60°C. Texapon N70A was mixed in until fully dissolved. While mixing, Tween 28-LQ, Miranol HMD and TegoBetain L7V were added and mixing was continued until the mixture was clear. Phenoxetol was added at the same time and mixing was continued while slowly lowering the temperature to
- 15 room temperature. pH was adjusted to a target of 5.6 using citric acid.

A composition according the invention, Composition E1, was prepared using the ingredients shown in Table 11.

TABLE 11: Inventive Example, E1

Trade Name	INCI Name	%wt
Deionized Water	Water	81.9
Texapon N70A	Sodium Lauryl Sulfate	3.7
Tween 28-LQ	PEG-80 Sorbitan Laurate	5.0
Miranol HMD	Sodium Lauroamphoacetate	2.0
TegoBetain L7V	Cocamidopropyl Betain	6.4
Phenoxetol	Phenoxyethanol	2.0
Hydrolite CG	Caprylyl Glycol	1.0
SymSitive 1609	trans-4-tert-butylcyclohexanol	1.0
Citric Acid (50% solution)	Citric Acid	q.s

The composition shown in Table 11 was prepared as follows. Water was added to a glass beaker and heated to 60°C. Texapon N70A was mixed in until fully dissolved. While mixing, Tween 28-LQ, Miranol HMD and TegoBetain L7V were added and the mixing was continued until the mixture was clear. Hydrolite CG, Phenoxetol, and SYMSITIVE1609 were then added at the same time and mixing was continued while slowly lowering the temperature to room temperature. pH was adjusted to the target of 5.6 using citric acid.

10

Example 5: Inventive Example, E1 Reduces Ca²⁺ Flux compared with Comparative Example, C1

The compositions of Comparative Examples C1 and C2 were tested for calcium flux levels using the Calcium Flux Test. The results are shown in Table 12, and demonstrate that formulated cleansing compositions including phenoxyethanol (with or without additional preservative caprylyl glycol) induce calcium flux.

15

Table 12

	Comparative Example, C1		Comparative Example, C2	
Cleanser (%v/v)	Maximum RFU (mean $\pm$ SD)	** P<0.05 Compared to Vehicle	Maximum RFU (mean $\pm$ SD)	** P<0.05 Compared to Vehicle
0.125	129.62 $\pm$ 29.43	**	146.97 $\pm$ 23.41	**
0.0625	80.34 $\pm$ 14.75	**	72.05 $\pm$ 8.81	**
0.0313	40.66 $\pm$ 7.89	n/s	33.42 $\pm$ 8.32	n/s
0.0156	27.36 $\pm$ 4.73	n/s	18.51 $\pm$ 1.09	n/s
Vehicle (Cleanser with no phenoxyethanol)	34.60 $\pm$ 5.58	-	-	-

n/s: Not statistically significant

*** Statistically significant*

5

Inventive Example, E1 was also tested using the Calcium Flux Test. The results are shown in Table 13 and compared against the results for Comparative Example C1, reproduced from Table 12.

10 These results demonstrate that inclusion of SYMSITIVE1609 in a cleansing formulation with phenoxyethanol inhibits calcium flux caused by the phenoxyethanol in a manner that increases with the amount of the cleansing formulation.

Table 13

	Comparative Example, C1	Inventive Example, E1	
Cleanser (%v/v)	Maximum RFU (mean $\pm$ SD)	Maximum RFU (mean $\pm$ SD)	% of Inhibition
0.0625	80.34 $\pm$ 14.75	29.23 $\pm$ 5.77	63.62
0.03125	40.66 $\pm$ 7.89	17.67 $\pm$ 4.68	56.54
0.01563	27.36 $\pm$ 4.73	12.44 $\pm$ 2.63	54.54
0.00781	19.04 $\pm$ 11.59	13.72 $\pm$ 2.29	27.94
0.00391	22.35 $\pm$ 3.21	13.85 $\pm$ 2.96	38.04
0.00195	34.38 $\pm$ 4.23	31.02 $\pm$ 4.57	9.76
0.00098	39.83 $\pm$ 1.83	45.16 $\pm$ 1.95	-

Example 6: Hydrocortisone, diphenhydramine or lidocaine do not reduce phenoxyethanol –induced calcium flux in TRPV-1 expressing cells

- 5 The analgesics hydrocortisone, diphenhydramine and lidocaine, all of which have been shown to be effective at reducing neurosensory responses, such as itch and sting (see Lin, T. K. et al. (2013) *J Invest Dermatol* 133(2): 469-478; Yosipovitch, G. et al. (2003) *Lancet* 361(9358): 690-694; and Walling, H. W. et al. (2010) *Clin Cosmet Investig Dermatol* 3: 99-117) were tested using the Calcium Flux Test. The results are
- 10 shown in Table 14.

Table 14

	Phenoxyethanol 3mM	Phenoxyethanol 2mM	Capsaicin 300nM
Compound	Maximum RFU (Mean $\pm$ SD)	Maximum RFU (Mean $\pm$ SD)	Maximum RFU (Mean $\pm$ SD)
Hydrocortisone 100 μ M	225.19 $\pm$ 38.09	160.66 $\pm$ 30.14	963.83 $\pm$ 65.21
Hydrocortisone 25 μ M	309.90 $\pm$ 40.00	171.65 $\pm$ 83.27	950.97 $\pm$ 49.52
Diphenhydramine 100 μ M	195.47 $\pm$ 53.34	141.61 $\pm$ 33.91	825.37 $\pm$ 9.95
Diphenhydramine 25 μ M	312.62 $\pm$ 67.77	158.25 $\pm$ 0.69	899.35 $\pm$ 10.60
Lidocaine 100 μ M	205.92 $\pm$ 16.97	116.25 $\pm$ 25.92	n/d
Lidocaine 25 μ M	197.45 $\pm$ 41.14	124.96 $\pm$ 22.24	n/d
Vehicle	216.86 $\pm$ 36.93	155.87 $\pm$ 46.55	896.85 $\pm$ 16.71

n/d= not determined

5

The results show that none of hydrocortisone, diphenhydramine or lidocaine were effective at reducing phenoxyethanol-induced calcium flux in TRPV-1-expressing HEK293 cells. Thus, not all analgesic agents are TRPV-1 antagonists.

10 **Example 7: Irritants such as sodium bicarbonate do not induce calcium flux in TRPV-1 expressing cells**

Benzyl alcohol and sodium bicarbonate were tested using the Calcium Flux Test. Both of these compounds are known to induce skin irritation in vivo (Bagley, D. M. et al. (1996) *Toxicol In Vitro* 10(1): 1-6.) The results are shown in Table 15.

15

Table 15

Benzyl Alcohol (mM)	Maximum RFU (mean $\pm$ SD)	** P<0.05 Compared to Vehicle	Sodium Bicarbonate (mM)	Maximum RFU (mean $\pm$ SD)	** P<0.05 Compared to Vehicle
4	362.51 $\pm$ 126.09	**	0.5	3.39 $\pm$ 2.66	n/s
2	135.45 $\pm$ 12.15	n/s	0.25	124.90 $\pm$ 8.41	**
1	113.51 $\pm$ 4.70	n/s	0.125	114.34 $\pm$ 6.46	n/s
0.5	104.45 $\pm$ 12.50	n/s	0.0625	102.15 $\pm$ 4.19	n/s
0.25	64.45 $\pm$ 28.15	n/s	0.03125	109.99 $\pm$ 1.37	n/s
Vehicle	101.19 $\pm$ 2.56	-	Vehicle	98.80 $\pm$ 12.93	-

n/s: Not statistically significant

*** Statistically significant*

5

In this test, benzyl alcohol did not show statistically significant activity for TRPV-1 activation at doses of 2mM and below. However, as shown in Example 9, benzyl alcohol does exhibit such activity at lower doses as well. The difference in results may arise from optimization of the test method to lower the background readings (the vehicle alone was approximately 9 RFU in Example 9, Table 19, versus approximately 101 RFU in Table 15 above), resulting in higher sensitivity of the assay showing statistically significant changes for the lower doses of benzyl alcohol.

10

These results also demonstrate that not all skin irritants, i.e., sodium bicarbonate, activate TRPV-1.

15

Example 8: Additional Inventive Examples

A composition according to the invention, Composition E2, is prepared by blending the ingredients listed in Table 16:

TABLE 16: Inventive Example E2

Trade Name	INCI Name	%wt
Deionized Water	Water	82.8
Texapon N70A	Sodium Lauryl Sulfate	3.7
Tween 28-LQ	PEG-80 Sorbitan Laurate	5.0
Miranol HMD	Sodium Lauroamphoacetate	2.0
TegoBetain L7V	Cocamidopropyl Betain	6.4
Phenoxetol	Phenoxyethanol	2.0
Hydrolite CG	Caprylyl Glycol	1.0
SymSitive 1609	trans-4-tert-butylcyclohexanol	0.1
Citric Acid (50% solution)	Citric Acid	q.s

The composition shown in Table 16 above is prepared as follows. Water is
5 added to a glass beaker and heated to 60°C. Texapon N70A is mixed in until fully
dissolved. While mixing, Tween 28-LQ, Miranol HMD and TegoBetain L7V are added
and mixing is continued until the mixture is clear. Hydrolite CG, Phenoxetol, and
SYMSITIVE1609 are then added at the same time and mixing is continued while
slowly lowering the temperature to room temperature. pH is adjusted to the target of
10 5.6 using citric acid.

A composition according to the invention, Composition E3, is prepared by
blending the ingredients listed in Table 17:

Table 17: Inventive Example, E3

Trade Name	INCI Name	%wt
Purified Water	Water	86.95
Carbomer	Cross-linked polyacrylic acid	0.60
VERSENE NA	Disodium EDTA	0.20
Dimethicone	Dow Corning Q7-9120 Silicone	5.0
Brij 72	Steareth-2	0.75
Brij 721	Steareth-21	1.50
Finsolv TN	C12-15 Alkyl Benzoate	2.0
Phenoxetol	Phenoxyethanol	2.0
SymSitive 1609	trans-4-tert-butylcyclohexanol	1.0

The composition shown in Table 17 is prepared as follows. An oil phase is prepared by adding C 12-15 alkyl benzoate to a clean glass beaker. Agitation is begun and the vessel is heated to 55-60° C. When the oil phase reaches 55° C or higher, Brij 72, Brij 721 and SYMSITIVE1609 are added. When the oil phase reaches 55-60° C, it is held at that temperature and mixed for 15 min (or until uniform). The temperature is then held at 55-60° C. with mixing until addition to water phase.

A water phase is prepared by adding water to a clean glass beaker. Agitation is begun and the vessel is heated to 55-60° C. Disodium EDTA is added. At 55-60° C., the ingredients are mixed for 15 min or until homogeneous. The temperature is then held at 55-60° C. with mixing for phasing. The oil phase is added to the water phase with increased agitation and then mixed at high speed for 10-20 min. At 50° C. or lower, dimethicone is added. At 40° C. or lower, Phenoxetol is added. The phases are then mixed for 10 min or until uniform. Sodium hydroxide is added (target pH was

5.4). The composition is then mixed for 10 min or until uniform. This is mixed until uniform. Water is then added to QS and the composition was then mixed for 10 minutes.

A composition according to the invention is prepared by blending the
5 ingredients listed in Table 18:

TABLE 18: Inventive Example, E4

Trade Name	INCI Name	wt%
Deionized Water	Water	69.04
Sodium Chloride	Sodium Chloride	0.01
Hydrolite CG	Caprylyl Glycol	1.0
SymSitive 1609	trans-4-tert-butylcyclohexanol	1.0
Snow White Petrolatum	Petrolatum	4.00
Isofol 28	Dodecylhexadecanol	2.50
Dow Corning Q7-9120 (20 CS)	Dimethicone	1.25
Kessco IPP	Isopropyl Palmitate	3.00
Varisoft TA-100	Distearyldimonium Chloride	5.00
Glycerin	Glycerin	12.00
Phenoxetol	Phenoxyethanol	1.0

The composition shown in Table 8 is prepared as follows. Water is added to a process vessel. Mixing is begun and salt is added and mixed until dissolved. Heat is applied and mixing continued until to 85° C. is reached. Varisoft TA 100 is added, as is petrolatum and Isofol 28, DC Q7-9120 20 cs., and isopropyl palmitate. The
10 composition is mixed at 85° C for another 10-15 minutes. The composition is then removed from heat, mixed again and cooled. At 40° C, Phenoxetol and SYMSITIVE 1609 are added, and then the sample is q.s. with water and continued to mix and cool to 30-35° C.

Example 9: Benzyl Alcohol and Phenethyl Alcohol Induce Calcium Flux via TRPV-1 Receptor

Benzyl alcohol and phenethyl alcohol were tested at a series of concentrations in DMSO for activity as a TRPV-1 agonist as described in Example 1. The results are shown in Table 19. Concentrations of benzyl alcohol and phenethyl alcohol are reported in units of % w/v.

Both benzyl alcohol and phenethyl alcohol showed dose dependent increases in intracellular calcium flux in TRPV-1-transfected HEK cells. For both compounds, the increase in Maximum RFU values versus the control vehicle was statistically significant across a wide range of amounts. These findings demonstrate activation of the TRPV-1 receptor by benzyl alcohol and phenethyl alcohol.

Table 19

Benzyl Alcohol (%w/v)	Maximum RFU (mean $\pm$ SD)
0.04	608.23 $\pm$ 10.21
0.013072	160.8 $\pm$ 12.61
0.004357	43.91 $\pm$ 3.74
0.001452	19.94 $\pm$ 3.08
0.000484	15.75 $\pm$ 1.8
0.000161	10.95 $\pm$ 0.23
5.38E-05	13.23 $\pm$ 6.33
1.79E-05	10.17 $\pm$ 1.19
5.98E-06	7.25 $\pm$ 0.71
1.99E-06	9.36 $\pm$ 0.52
6.64E-07	9.37 $\pm$ 1.66
0	9.54 $\pm$ 1.6

Table 20

Phenethyl Alcohol (%w/v)	Maximum RFU (mean $\pm$ SD)
0.12	755.2 $\pm$ 12.89
0.04	548.5 $\pm$ 37.22
0.013	185.92 $\pm$ 28.6
0.0044	70.4 $\pm$ 31.61
0.0015	25.95 $\pm$ 0.85
0.00048	14.41 $\pm$ 3.06
0.00016	10.14 $\pm$ 4.39
0.000054	8.66 $\pm$ 0.82
0.000018	10.71 $\pm$ 2.34
0.000006	7.99 $\pm$ 1.93
0.000002	12.8 $\pm$ 1.35
0	12.89 $\pm$ 1.79

5 **Example 10: Capsazepine Reduces Ca²⁺ Flux Induced By Benzyl Alcohol**

Capsazepine was tested for activity as a TRPV-1 antagonist with different concentrations of benzyl alcohol in DMSO as described in Example 2.

The results are shown in Tables 21 and 22.

The results demonstrate that treatment with a TRPV-1 antagonist reduces benzyl
10 alcohol-induced calcium flux.

Table 21

	10uM Capsazepine	without Capsazepine	
Benzyl Alcohol (%w/v)	Max RFU	Max RFU	% Inhibition
0.04	18.82	410.41	95.41%
0.013072	10.48	93.35	88.78%
0.004357	8.14	31.54	74.18%
0.001452	11.63	14.03	-
0.000484	8.17	11.38	-
0.000161	7.95	8.44	-
0.0000538	10.90	5.38	-
0.0000179	8.92	4.38	-
0.00000598	9.46	4.25	-
0.00000199	11.32	3.07	-
6.64E-07	11.79	7.66	-
0	13.30	3.65	-

Table 22

	10uM Capsazepine	without Capsazepine	
Benzyl Alcohol (%w/v)	Maximum RFU (mean ± SD)	Maximum RFU (mean ± SD)	% Inhibition
0.04	28.72 ± 1.5	424.01 ± 2.92	93.23%
0.013072	21.7 ± 0.2	124.54 ± 13.18	82.58%
0.004357	15.33 ± 1	55.75 ± 2.68	72.51%
0.001452	15.7 ± 2.1	30.81 ± 0.98	-
0.000484	17.15 ± 1.46	25.83 ± 5.34	-
0.000161	19.83 ± 3.44	16.17 ± 1.16	-
0.0000538	18.44 ± 0.07	17.1 ± 3.42	-
0.0000179	18.21 ± 2.76	17.05 ± 0.19	-
0.00000598	16.77 ± 1.48	17.82 ± 0.88	-
0.00000199	18.74 ± 2.18	18 ± 3.24	-
6.64E-07	18.24 ± 2.53	13.85 ± 1.83	-
0	18.24 ± 1.3	16.68 ± 0.16	-

Example 11: Capsazepine Reduces Ca²⁺ Flux Induced By Phenethyl Alcohol

5 Capsazepine was tested for activity as a TRPV-1 antagonist with different concentrations of phenethyl alcohol in DMSO as described in Example 2.

The results are shown in Tables 23 and 24.

The results demonstrate that treatment with a TRPV-1 antagonist reduces phenethyl alcohol-induced calcium flux.

Table 23

	10uM Capsazepine	without Capsazepine	
Phenethyl Alcohol (%w/v)	Max RFU	Max RFU	
0.12	345.95	605.31	42.85%
0.04	26.42	441.18	94.01%
0.013	4.56	123.10	96.30%
0.0044	11.56	26.36	56.15%
0.0015	11.68	8.68	-
0.00048	11.71	10.59	-
0.00016	11.64	7.21	-
0.000054	6.90	7.70	-
0.000018	13.60	5.43	-
0.000006	13.70	5.48	-
0.000002	12.76	6.43	-
0	13.44	11.50	-

Table 24

	10uM Capsazepine	without Capsazepine	
Phenethyl Alcohol (%w/v)	Maximum RFU (mean $\pm$ SD)	Maximum RFU (mean $\pm$ SD)	
0.12	364.66 $\pm$ 13.76	580.44 $\pm$ 3.06	37.18%
0.04	39.89 $\pm$ 5.81	470.23 $\pm$ 7.11	91.52%
0.013	12.32 $\pm$ 3.27	200.02 $\pm$ 6.15	93.84%
0.0044	15.66 $\pm$ 0.4	79.18 $\pm$ 0.23	80.22%
0.0015	18.5 $\pm$ 0.5	40.5 $\pm$ 0.05	54.32%
0.00048	20.58 $\pm$ 0.6	31.36 $\pm$ 3.52	-
0.00016	19.48 $\pm$ 0.51	22.15 $\pm$ 0.76	-
0.000054	21.47 $\pm$ 3.93	21.75 $\pm$ 4.01	-
0.000018	18.18 $\pm$ 0.59	17.58 $\pm$ 0.7	-
0.000006	18 $\pm$ 0.75	17.74 $\pm$ 1.46	-
0.000002	18.03 $\pm$ 3.35	12.28 $\pm$ 3.52	-
0	17.46 $\pm$ 0.4	17.98 $\pm$ 0.83	-

Example 12: SYMSITIVE 1609 Reduces Ca²⁺ Flux Induced By Benzyl Alcohol

5 SYMSITIVE1609 was tested for activity as a TRPV-1 antagonist as described in Example 3 with different concentrations of benzyl alcohol in DMSO. The results are shown in Table 25. Concentrations of benzyl alcohol are reported in % w/v but concentrations of SYMSITIVE1609 are reported in % v/v.

Table 25

	0.05% v/v Symsitive	without Symsitive	
Benzyl Alcohol (%w/v)	Maximum RFU (mean $\pm$ SD)	Maximum RFU (mean $\pm$ SD)	% Inhibition
0.04	76.89 $\pm$ 8.55	608.23 $\pm$ 10.21	87.36%
0.013072	33.14 $\pm$ 3.51	160.8 $\pm$ 12.61	79.39%
0.004357	29.71 $\pm$ 0.46	43.91 $\pm$ 3.74	32.33%
0.001452	24.12 $\pm$ 2.33	19.94 $\pm$ 3.08	-
0.000484	25.7 $\pm$ 1.62	15.75 $\pm$ 1.8	-
0.000161	30.72 $\pm$ 1.65	10.95 $\pm$ 0.23	-
0.0000538	27.91 $\pm$ 0.47	13.23 $\pm$ 6.33	-
0.0000179	25.07 $\pm$ 1.14	10.17 $\pm$ 1.19	-
5.98E-06	25.56 $\pm$ 1.86	7.25 $\pm$ 0.71	-
1.99E-06	20.27 $\pm$ 6.14	9.36 $\pm$ 0.52	-
6.64E-07	24.22 $\pm$ 2.38	9.37 $\pm$ 1.66	-
0	23.1 $\pm$ 1.61	9.54 $\pm$ 1.6	-

Example 13: SYMSITIVE 1609 Reduces Ca^{2+} Flux Induced By Phenethyl Alcohol

SYMSITIVE1609 was tested for activity as a TRPV-1 antagonist as described in Example 3 with different concentrations of phenethyl alcohol in DMSO. The results are shown in Table 26. Concentrations of phenethyl alcohol are reported in %w/v but

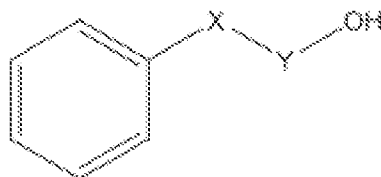
5 concentrations of SYMSITIVE1609 are reported in % v/v.

Table 26

	0.05% v/v Symsitive	without Symsitive	
Phenethyl Alcohol (%w/v)	Maximum RFU (mean $\pm$ SD)	Maximum RFU (mean $\pm$ SD)	% Inhibition
0.12	464.85 $\pm$ 56.24	755.2 $\pm$ 12.89	38.45%
0.04	92.46 $\pm$ 21.67	548.5 $\pm$ 37.22	83.14%
0.013	19 $\pm$ 2.48	185.92 $\pm$ 28.6	89.78%
0.0044	25.22 $\pm$ 2.31	70.4 $\pm$ 31.61	64.17%
0.0015	27.46 $\pm$ 5.12	25.95 $\pm$ 0.85	-
0.00048	27.05 $\pm$ 1.28	14.41 $\pm$ 3.06	-
0.00016	25.21 $\pm$ 1.56	10.14 $\pm$ 4.39	-
0.000054	26.05 $\pm$ 0.64	8.66 $\pm$ 0.82	-
0.000018	21.02 $\pm$ 0.79	10.71 $\pm$ 2.34	-
0.000006	17.15 $\pm$ 5.43	7.99 $\pm$ 1.93	-
0.000002	18.15 $\pm$ 2.97	12.8 $\pm$ 1.35	-
0	21.77 $\pm$ 1.8	12.89 $\pm$ 1.79	-

What is claimed is:

1. A composition comprising an aromatic alcohol having the formula:



wherein X is an oxygen atom or absent and Y is C1 - C2 alkyl; and a TRPV-1 antagonist, wherein said composition is substantially free of esters of para-hydroxybenzoic acid.

10

2. The composition of claim 1, wherein said TRPV-1 antagonist inhibits the calcium flux of the aromatic alcohol by at least about 12% as measured by the Calcium Flux Test.

15

3. The composition of claim 1, wherein said TRPV-1 antagonist is 4-tertiary butyl cyclohexanol.

4. The composition of claim 1 further comprising caprylyl glycol.

20

5. The composition of claim 1 further comprising pentylene glycol.

6. The composition of claim 1 further comprising a cosmetically-acceptable topical carrier.

25

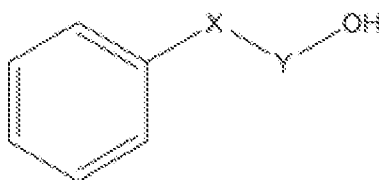
7. The composition of claim 1 further comprising about 70% to about 99% water.

8. The composition of claim 1, wherein said aromatic alcohol is selected from the group consisting of phenoxyethanol, benzyl alcohol, phenethyl alcohol, and mixtures thereof.

9. The composition of claim 1, wherein the aromatic alcohol is phenoxyethanol.

10. A method of cleansing the skin, comprising applying the composition of claim 1
5 to said skin and rinsing the composition off of said skin.

11. A method of reducing irritation induced by topical application of an aromatic alcohol having the formula:



10

wherein X is an oxygen atom or absent and Y is C1 - C2 alkyl; said method comprising topically applying said aromatic alcohol with a TRPV-1 antagonist.

15 12. The method of claim 11, wherein said aromatic alcohol is selected from the group consisting of phenoxyethanol, benzyl alcohol, phenethyl alcohol, and mixtures thereof.

13. The composition of claim 11, wherein the aromatic alcohol is phenoxyethanol.
20

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/038295

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K8/34 A61K8/49 A61K8/60 A61Q19/10 A61K9/00
A61K47/02 A61K47/20 A61K47/26 A61K9/08 A61K31/045
A61K31/357 A61K31/55 A61P17/00

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)

A61K A61Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/087242 A2 (SYMRISE GMBH & CO KG [DE]; VIELHABER GABRIELE [DE]; OERTLING HEIKO [DE]) 16 July 2009 (2009-07-16) formulation examples 1-10; page 52 - page 67 claims -----	1-13
X	US 2012/201902 A1 (MODAK SHANTA M [US] ET AL) 9 August 2012 (2012-08-09) page 12 - page 13; tables 13,14 page 34; tables 84,85 -----	1-3,5,6, 8,11,12
X	WO 2011/131474 A2 (HENKEL AG & CO KGAA [DE]; KLEEN ASTRID [DE]; HAGENOW SUSANNE [DE]) 27 October 2011 (2011-10-27) page 40 - page 41; examples 8.1, 8.2, 9.1 ----- -/--	1-9, 11-13

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

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

22 July 2014

Date of mailing of the international search report

31/07/2014

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

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Kollmannsberger, M

INTERNATIONAL SEARCH REPORT

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PCT/US2014/038295

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Information on patent family members

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