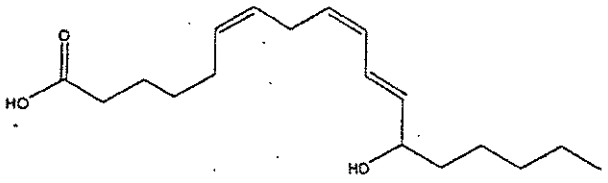
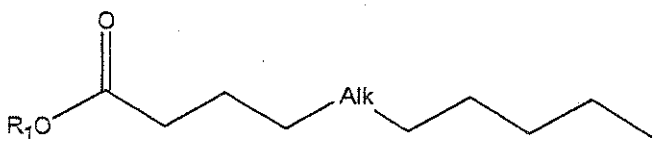
13-Hydroxy-octadeca-6Z, 9Z, 11E-γ-trienoic acid (13-HOTrE(γ)) is a commercially available PUFA derivative derived from gamma-linolenic acid (GLA). 13-HOTrE(γ) has the structure shown below.



It has now been surprisingly found that DGLA, 5-HETrE, 8-HETrE, 15-HETrE, 13-HOTrE(γ) and their derivatives are clinically useful in treating skin inflammation, in particular skin inflammation caused by atopic eczema, contact dermatitis, psoriasis or uremic pruritis, by topical administration in mammals. A particular finding of the present invention is that these compounds reduce the level of COX-2 enzymes in the skin when applied topically. The COX-2 family of enzymes have been strongly linked to inflammation and have been found to be present in increased amounts in inflamed tissue.

Summary of the Invention

In one aspect, there is provided a compound which is a polyunsaturated fatty acid (PUFA) derivative of formula (I),



I

or a pharmaceutically acceptable salt, or solvate thereof, wherein

- -Alk- is -CH(OR_2)-[*trans*]CH=CH-[*cis*]CH=CH-CH_2-[*cis*]CH=CH-C_3H_6-, -$(CH_2)_3$-CH(OR_2)-[*trans*]CH=CH-[*cis*]CH=CH-CH_2-[*cis*]CH=CH-, -$(CH_2)_3$-[*cis*]CH=CH-CH_2-[*cis*]CH=CH-[*trans*]CH=CH-CH(OR_2)-, or -$(CH_2)_3$-[*cis*]CH=CH-CH_2-[*cis*]-CH=CH-CH_2-[*cis*]CH=CH-;
- R_1 is a hydrogen atom; or

  R_1 is a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 carbocyclyl or 5- to 10-membered heterocyclyl group; or

  R_1 is a group of formula -CH_2-CH(OR_3)-CH_2-(OR_4), wherein R_3 and R_4 are each independently hydrogen atoms or -(C=O)-R_6, wherein R_6 is an aliphatic group having from 3 to 29 carbon atoms; or

  R_1 is a group of formula -$(CH_2OCH_2)_m$OH, wherein m is an integer of from 1 to 200;
- R_2 is a hydrogen atom; or

  R_2 is a group -(C=O)-R_5, wherein R_5 is a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 carbocyclyl or 5- to 10-membered heterocyclyl group, or R_5 is an aliphatic group having from 3 to 29 carbon atoms; or

  R_2 is a group of formula -$(CH_2OCH_2)_n$OH, wherein n is an integer of from 1 to 200;

and wherein

- said alkyl, alkenyl, alkynyl and aliphatic groups are the same or different and are each unsubstituted or substituted with 1, 2 or 3 unsubstituted substituents which are the same or different and are selected from halogen atoms and C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, C_1-C_4 haloalkyl, C_2-C_4 haloalkenyl, C_1-C_4 haloalkoxy, C_2-C_4 haloalkenyloxy, hydroxyl, -SR′, and -NR′R′′ groups where R′ and R′′ are the same or different and represent hydrogen or unsubstituted C_1-C_2 alkyl;
- said aryl, heteroaryl, carbocyclyl and heterocyclyl groups are the same or different and are each unsubstituted or substituted by 1, 2, 3 or 4 unsubstituted substituents which are the same or different and are selected from halogen atoms, and cyano, nitro, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_4 alkenyl, C_2-C_4 alkenyloxy, C_1-C_4 haloalkyl, C_2-C_4 haloalkenyl, C_1-C_4 haloalkoxy, C_2-C_4 haloalkenyloxy, hydroxyl, C_1-C_4 hydroxyalkyl, -SR′ and -NR′R′′ groups wherein each R′ and R′′ is the same or different and represents hydrogen or unsubstituted C_1-C_4 alkyl;

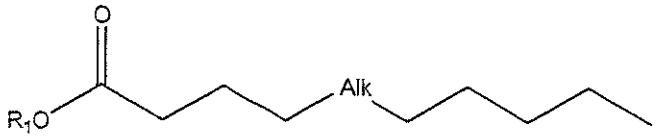
and wherein the PUFA derivative is in the form of a racemate, a stereoisomer or a mixture of stereoisomers,

which compound is for use in treating skin inflammation in a mammal, by topical administration.

In another aspect, there is provided the use of a composition comprising a PUFA derivative, as defined above, or a pharmaceutically acceptable salt, or solvate thereof, and a pharmaceutically acceptable diluent or carrier in the manufacture of a medicament for treating skin inflammation, as defined above, in a mammal, as defined above, wherein the medicament is suitable for topical administration.

In yet another aspect, there is provided the use of a therapeutically effective amount of a compound which is a PUFA derivative of formula (I) as defined above or a pharmaceutically acceptable salt, or solvate thereof in the manufacture of a medicament for treating skin inflammation, as defined above, in a mammal, as defined above.

In yet another aspect, there is provided the use of a composition comprising a polyunsaturated fatty acid (PUFA) derivative of formula (II),



II

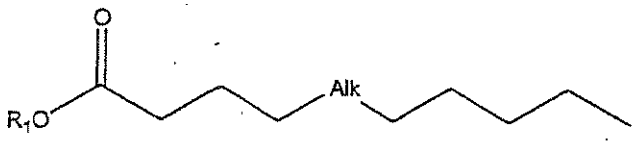
or a pharmaceutically acceptable salt, or solvate thereof, wherein

- -Alk- is -$(CH_2)_3$ -[*cis*]CH=CH-CH_2-[*cis*]CH=CH-CH_2-[*cis*]CH=CH-; and
- R_1 is as defined above;

in the manufacture of a medicament for treating skin inflammation in a mammal by topical administration, wherein the composition is substantially free of lithium salts and glucocorticoids.

In yet another aspect, there is provided a pharmaceutical composition as defined above which contains the polyunsaturated fatty acid (PUFA) derivative of formula (II) as sole active ingredient.

The present disclosure~~invention therefore~~ provides a compound which is a polyunsaturated fatty acid (PUFA) derivative of formula (I),



I

or a pharmaceutically acceptable salt, or solvate thereof, wherein

-Alk- is -$CH(OR_2)$-[*trans*]CH=CH-[*cis*]CH=CH-CH_2-[*cis*]CH=CH-C_3H_6-, -$(CH_2)_3$-$CH(OR_2)$-[*trans*]CH=CH-[*cis*]CH=CH-CH_2-[*cis*]CH=CH-, -$(CH_2)_3$-[*cis*]CH=CH-CH_2-[*cis*]CH=CH-[*trans*]CH=CH-$CH(OR_2)$- or -CH_2-[*cis*]CH=CH-CH_2-[*cis*]CH=CH-[*trans*]CH=CH-$CH(OR_2)$-;