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(54) Title: POTENT SOFT ANTI-INFLAMMATORY CORTICOSTEROID COMPOUNDS AND USES THEREOF

(57) Abstract: Potent soft corticosteroid pharmaceutical compositions comprising them and method for use as anti-inflammatory agents. Also, a method for softening fluticasone propionate and similar corticosteroids to arrive at potent but safer alternatives. The compound S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrost-1,4-diene-17 β -carbothioate, which is equally potent to but safer than fluticasone, is among those provided. Another compound of particular interest is 2-hydroxyethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 β -methyl-3-oxoandrost-1,4-diene-17 β -carboxylate.



POTENT SOFT ANTI-INFLAMMATORY CORTICOSTEROID COMPOUNDS AND USES THEROF

CROSS-REFERENCE TO RELATED APPLICATIONS

5 **[0001]** This application claims the benefit of United States Provisional Application No. 62/518,922, filed June 13, 2017, United States Provisional Application No. 62/559,201, filed September 15, 2017 and United States Provisional Application No. 62/562,099, filed September 22, 2017, which are all incorporated by reference herein in their entireties and relied upon.

FIELD

[0002] Potent soft corticosteroids, pharmaceutical compositions comprising them and methods for use as anti-inflammatory agents. Also, a method for softening fluticasone propionate and similar corticosteroids to arrive at potent but safer alternatives.

BACKGROUND ART

[0003] Topical or other local application of potent glucocorticoids can produce severe toxic effects such as Cushingoid features, pituitary-adrenal suppression, skin atrophy, immunosuppression and inhibition of wound healing. Other kinds of toxic responses, including allergies and cataracts, have resulted from long term use of drugs of this type.

[0004] Ophthalmic application of glucocorticosteroids presents additional problems. The protective mechanisms built into the eye allow only small amounts of doses applied to the eye to reach the target sites within the eye; generally, over 90 per cent of the total dose will find its way into the general circulation. This in turn leads to serious systemic side effects of the type described above. Moreover, there is a more serious and specific side effect when these drugs are used in the eye,

which is an increase in intraocular pressure (IOP). Corticosteroid-induced chronic or acute glaucoma has in fact been reported since the early 1960's. Generally, the corticosteroid is needed only topically to control the inflammation. However, the absorbed steroid is responsible for the serious side effects noted above. It is
5 believed that the effect of the corticosteroid on the aqueous outflow pathway and adjacent tissue glycosaminoglycans (GAG's) is important in the development of glucocorticoid-induced ocular hypertension.

[0005] There is, therefore, a serious need for potent local anti-inflammatory steroids, which lack systemic activity and consequently do not produce the serious
10 systemic side effects associated with drugs of this class.

[0006] 'Soft' steroids are compounds having potent anti-inflammatory activity, comparable with conventional steroids, but with minimal systemic activity. These compounds include Δ^4 and $\Delta^{1,4}$ 17 α -alkoxy-11 β -hydroxy-3-oxoandrostenes optionally bearing various substituents at the 6, 9 and 16-positions and related 11-
15 substituted compounds, which are esters or thioesters of 17 β -carboxylic acids. These 17 α -ethers are described in Bodor U.S. Pat. No. 4,710,495. Preferred compounds are taught to be the haloalkyl esters of 17 α -alkoxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylic acids.

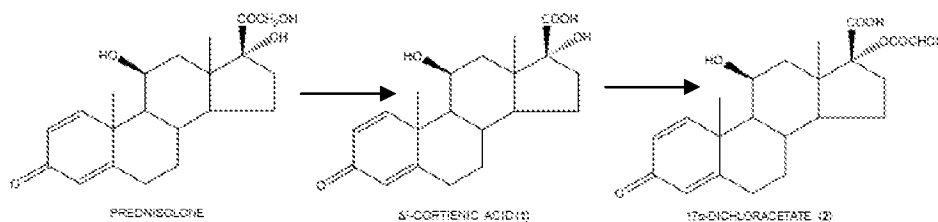
[0007] Another series of 'soft' steroids which are described as having potent
20 anti-inflammatory activity with minimal systemic activity are the 17 α -carbonates of Bodor U.S. Pat. No. 4,996,335. These compounds include as preferred embodiments, haloalkyl 17 α -alkoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylates and the corresponding $\Delta^{1,4}$ compounds, optionally bearing 6 α -and/or 9 α -fluorine and 16 α - or 16 β -methyl substituents. One of these compounds is
25 chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrosta-1,4-dien-3-one-17 β -carboxylate, also known as loteprednol etabonate (LE), approved by the FDA in 1998 and marketed worldwide in five or more products.

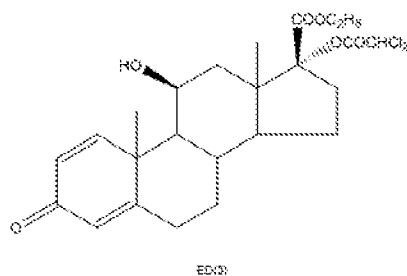
[0008] During the design and development of the first generation of the 'soft' corticosteroids, more than 120 compounds were synthesized and studied,
30 combining the soft pharmacophore center of 17 α -carbonate-17 β -chloromethyl

esters, with the usual modifications of the corticosteroid structure, such as fluorination at 6 α and/or 9 α , methylation at 16 α and 16 β positions and varying the 17 β -ester and 17 α -carbonate functions. QSAR studies indicated that the known activity enhancer groups were very effective in the soft steroids of this type as well.

- 5 The relative receptor binding activity (RRBA) values nicely correlated with presence or absence of the fluoro substituents, the molecular volume (calculated by semi-empirical quantum chemical methods) and calculated partition coefficients. Some of the substituted LE derivatives are extremely potent; for example, the 6 α ,9 α -difluoro-16 α -methyl loteprednol derivative showed the highest RRBA among all known corticosteroids (2100 on a scale where dexamethasone is 100). However, it was found that in this class, the more potent the new steroid, the less 'soft' it is. In other words, these are more like the currently known potent corticosteroids, not being easily hydrolyzed/deactivated, but subject to oxidative metabolism. Thus, the compounds substituted at the 6- and 9- and 16- positions were subsequently found to not be true 'soft' drugs after all.

[0009] Etiprednol dicloacetate (ED; ethyl 17 α -dichloroacetoxy-11 β -hydroxyandrosta-1,4-diene-3-one-17 β -carboxylate) is a second-generation soft corticosteroid designed using retrometabolic principles starting with the inactive metabolite of prednisolone, Δ^1 -cortienic acid (1), which is converted to the 17 α -dichloroacetate (2) and by esterification to the ED (3). See SCHEME 1 below; also see Bodor USP 5,981,517.

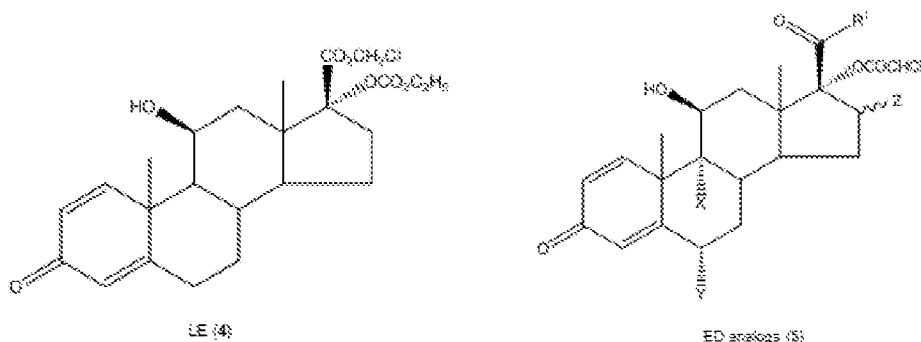




SCHEME 1

[0010] ED is a unique second generation 'soft' corticosteroid, the first to contain halogen substituents in the 17 α -position, which actually serves as the important pharmacophore. It has been shown that the dichloro function is necessary for activity (the monochloro derivative is void of activity, due to the unfavorable position the chlorine is forced into by steric hindrance). The dichloroacetyl functional group is also responsible for the 'soft' nature of ED. Dichloro substituents increase the second order rate constant k_{cat}/k_M of enzymatic hydrolysis in acetate esters by a factor of 20, compared to the unsubstituted ester while one chlorine substituent does not cause any change.

[0011] Contrary to the first generation of 'soft' corticosteroids based on cortienic acid, represented by Loteprednol Etabonate (LE; **4**) which is hydrolytically deactivated by ester cleavage of the 17 β -chloromethyl ester, in ED, the hydrolysis does not cleave at the 17 β -ester, but primarily cleaves at the 17 α -dichloroacetyl function. Nevertheless, the corresponding 17 α -OH- metabolites are inactive, thus fulfilling the soft drug requirement.



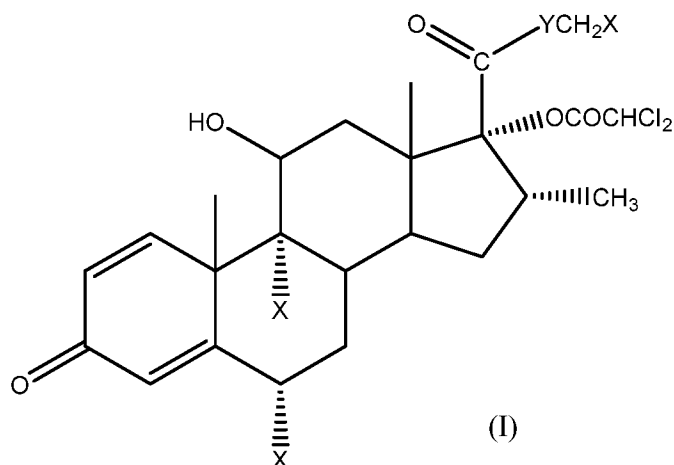
[0012] Nevertheless, there remains a serious need in this art for new anti-inflammatory steroids which have potent local anti-inflammatory activity while having minimal or non-existent systemic activity.

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SUMMARY

[0013] As noted above, the second generation of the soft steroids (etiprednol dicloacetate) based on the Δ^1 -cortienic acid, having a 17 α -dichloroacetyl function appears to be hydrolyzed primarily not at the 17 β - ester, but at the 17 α -dichloroacetate. Depending on the animal species, both ester functions can be hydrolyzed, which has a strong influence on the 'soft' nature of these compounds. On the other hand, ED is somewhat more potent than LE (RRBA ~ 200 vs. 160). Surprisingly, the usual potency-enhancing F or Cl at 6 α and 9 α and 16 α -methyl or β -methyl substitution can yield even more potent, but softer corticosteroids, unlike the situation with the first generation LE family of compounds. Accordingly, the synthesis and investigation of the properties of this new selected class of steroids was undertaken and reported here.

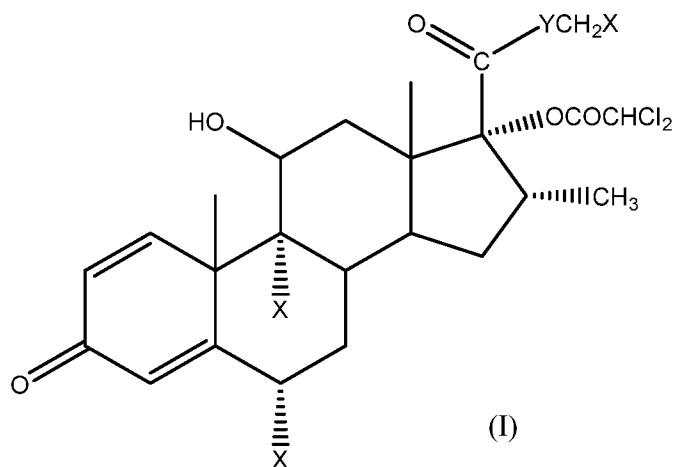
[0014] In a first major exemplary embodiment of this application, there is provided a soft corticosteroid having high local or topical anti-inflammatory activity and an improved therapeutic index compared to fluticasone propionate, where the compound is represented by the formula (I):



wherein each X is independently F or Cl, and Y is O or S.

[0015] In another exemplary embodiment, the soft corticosteroid of formula (I) is: S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (fluticasone dicloacetate); S-chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate; fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate; or chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate. Among the compounds of formula (I), the closest analog of fluticasone propionate, i.e. the S-fluoromethyl compound just named, has remarkable activity and still the desired hydrolytic susceptibility and thus is a potent but safer alternative to fluticasone propionate.

[0016] In another exemplary embodiment, there is provided a pharmaceutical composition comprising an anti-inflammatory effective amount of a compound having the formula (I):



wherein each X is independently selected from the group consisting of F and Cl, and Y is O or S, and a non-toxic pharmaceutically acceptable carrier therefor, suitable for topical or other local application. In further specific embodiments, the compound of formula (I) is S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate; S-chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-

diene-17 β -carbothioate; fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate; or chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

5 **[0017]** In a still further embodiment, there is provided an ophthalmic composition comprising an anti-inflammatory effective amount of a compound of formula (I) above and a non-toxic ophthalmically acceptable carrier therefor. In further specific embodiments, the compound of formula (I) is one of the four specific compounds named above.

10 **[0018]** Another embodiment herein is a method for alleviating inflammation in or on a warm-blooded animal exhibiting a localized inflammatory response, which comprises locally administering to said animal an anti-inflammatory effective amount of a compound of formula (I) as defined above, particularly when the compound is one of the four specific compounds named above, or of a pharmaceutical
15 composition as defined above, particularly when the compound of formula (I) is one of the four specific compounds named above.

[0019] Another embodiment herein is a method for alleviating inflammation in or on a warm-blooded animal exhibiting a topical inflammatory response, which comprises topically administering to said animal an anti-inflammatory effective
20 amount of a compound of formula (I) as defined above, particularly when the compound is one of the four specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (I) is one of the four specific compounds named above.

[0020] Another embodiment herein is a method for alleviating inflammation in
25 the eye or eyes of a warm-blooded animal exhibiting an ophthalmic inflammatory response, which comprises administering to the eye or eyes of said animal an anti-inflammatory effective amount of a compound of formula (I) as defined above, particularly when the compound is one of the four specific compounds named above, or of an ophthalmic composition as defined above, particularly when the
30 compound of formula (I) is one of the four specific compounds named above.

[0021] Another embodiment is a method for alleviating inflammation of the nasal mucosa in a warm-blooded animal exhibiting a nasal inflammatory response, which comprises nasally administering to said animal an anti-inflammatory effective amount of a compound of formula (I) as defined above, particularly when the
5 compound is one of the four specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (I) is one of the four specific compounds named above.

[0022] Yet another embodiment is a method for alleviating asthma or COPD in the lungs or bronchi of a warm-blooded animal exhibiting an inflammatory response
10 in the lungs or bronchi, which comprises administering to said animal by oral inhalation an anti-inflammatory effective amount of a compound of formula (I) as defined above, particularly when the compound is one of the four specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (I) is one of the four specific compounds
15 named above.

[0023] Still another embodiment is a method for alleviating inflammation of the upper or lower intestine in a warm-blooded animal exhibiting an intestinal inflammatory response, which comprises rectally administering to said animal an anti-inflammatory effective amount of a compound of formula (I) as defined above,
20 particularly when the compound is one of the four specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (I) is one of the four specific compounds named above.

[0024] Another embodiment is a method for alleviating inflammation of the upper or lower intestine in a warm-blooded animal exhibiting an intestinal
25 inflammatory response, which comprises orally administering to said animal an anti-inflammatory effective amount of a compound of formula (I) as defined above, particularly when the compound is one of the four specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (I) is one of the four specific compounds named above.

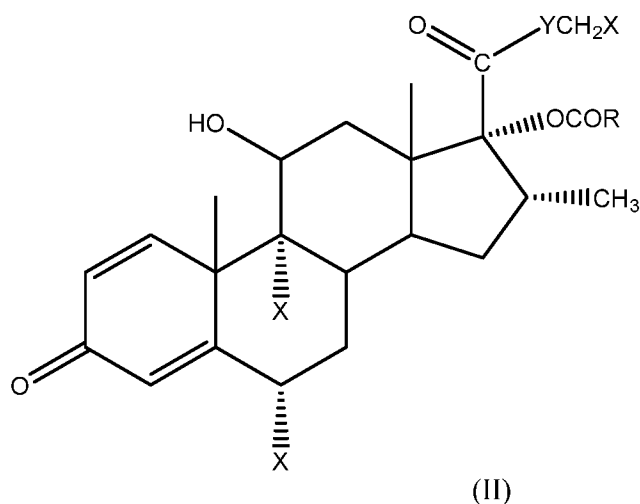
[0025] Yet another embodiment is a method for alleviating inflammation in the ear or ears of a warm-blooded animal exhibiting an otic inflammatory response, which comprises administering to the ear or ears of said animal an anti-inflammatory effective amount of a compound of formula (I) as defined above, particularly when the compound is one of the four specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (I) is one of the four specific compounds named above.

[0026] Another embodiment is a method for alleviating inflammation in a joint or joints of a warm-blooded animal exhibiting an arthritic inflammatory response, which comprises injecting into said joint or joints an anti-inflammatory effective amount of a compound of formula (I) as defined above, particularly when the compound is one of the four specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (I) is one of the four specific compounds named above.

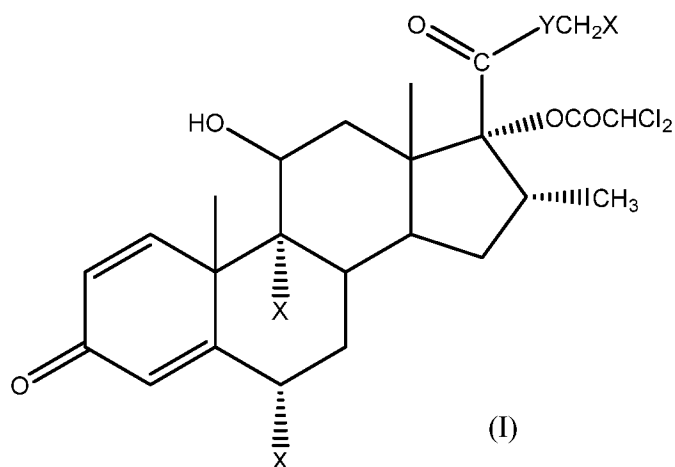
[0027] Still a further embodiment is a method for alleviating inflammation of the skin of a warm-blooded animal exhibiting a dermal inflammatory response, which comprises dermally administering to said animal an anti-inflammatory effective amount of a compound of formula (I) as defined above, particularly when the compound is one of the four specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (I) is one of the four specific compounds named above.

[0028] Yet another embodiment herein is a method for alleviating inflammation of the mouth, gums or throat of a warm-blooded animal exhibiting an oral, gingival or throat inflammatory response, which comprises orally administering to said animal an anti-inflammatory effective amount of a compound of formula (I) as defined above, particularly when the compound is one of the four specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (I) is one of the four specific compounds named above.

[0029] In a still further embodiment, there is provided a process for softening a 17 α -alkylcarbonyloxy-substituted corticosteroid compound of the formula (II):



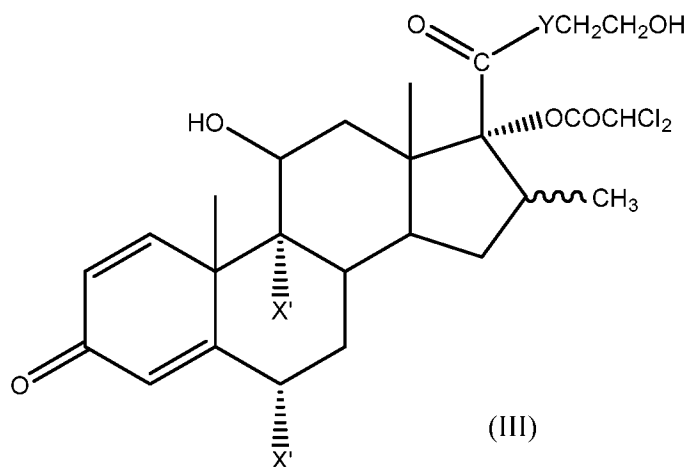
wherein each X is independently F or Cl, Y is O or S and R is C₁-C₃ alkyl, said compound of formula (II) having local or topical as well as systemic corticosteroid activity, said process comprising synthesizing the corresponding corticosteroid compound wherein the 17 α -OCOR group in formula (II) is replaced by a 17 α -dichloroacetoxyl (17 α -OCOCHCl₂) group, to provide the resultant soft corticosteroid compound of formula (I):



wherein X and Y are as defined with formula (II) above, said compound of formula (I) having substantially equivalent local or topical corticosteroid activity as compared to the corresponding compound of formula (II) but having substantially decreased

systemic corticosteroid activity compared to the corresponding compound of formula (II). In specific embodiments of this process, the resultant soft corticosteroid compound of formula (I) is S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate; S-chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate; fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate; or chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

10 **[0030]** In a second major exemplary embodiment of this application, there is provided a soft corticosteroid having high local or topical anti-inflammatory activity and an improved therapeutic index compared to the corresponding 17 α -alkoxycarbonyl (-OCOR) ester, where the compound is represented by the formula (III):



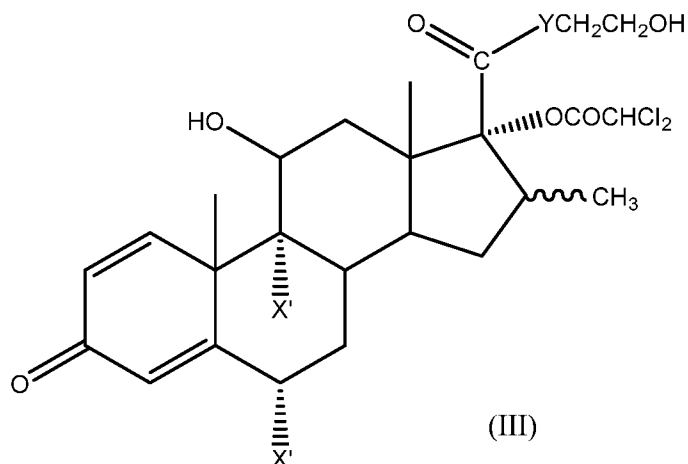
15 wherein each X' is independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S and the wavy line indicates the α - or β -configuration.

[0031] In another exemplary embodiment, the soft corticosteroid of formula (III) is: 2-hydroxyethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate or 2-hydroxyethyl 17 α -dichloroacetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate. The compounds of formula (III) have remarkable activity and still the desired hydrolytic

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susceptivity and are potent but safer alternatives to the corresponding 17 α -alkoxycarbonyl (-OCOR) esters.

[0032] In another exemplary embodiment, there is provided a pharmaceutical composition comprising an anti-inflammatory effective amount of a compound having the formula (III):



wherein each X' is independently selected from the group consisting of H, F and Cl provided that at least one X' is F or Cl, Y is O or S and the wavy line indicates the α - or β -configuration, and a non-toxic pharmaceutically acceptable carrier therefor, suitable for topical or other local application. In further specific embodiments, the compound of formula (III) is 2-hydroxyethyl 17 α -dichloroacetox-6 α ,9 α -difluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate or 2-hydroxyethyl 17 α -dichloroacetox-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

[0033] In a still further embodiment, there is provided an ophthalmic composition comprising an anti-inflammatory effective amount of a compound of formula (III) above and a non-toxic ophthalmically acceptable carrier therefor. In further specific embodiments, the compound of formula (III) is one of the two specific compounds named above.

[0034] Another embodiment herein is a method for alleviating inflammation in or on a warm-blooded animal exhibiting a localized inflammatory response, which comprises locally administering to said animal an anti-inflammatory effective amount

of a compound of formula (III) as defined above, particularly when the compound is one of the two specific compounds of formula (III) named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (III) is one of the two specific compounds named above.

5 **[0035]** Another embodiment herein is a method for alleviating inflammation in or on a warm-blooded animal exhibiting a topical inflammatory response, which comprises topically administering to said animal an anti-inflammatory effective amount of a compound of formula (III) as defined above, particularly when the compound is one of the two specific compounds of formula (III) named above, or of
10 a pharmaceutical composition as defined above, particularly when the compound of formula (III) is one of the two specific compounds named above.

[0036] Another embodiment herein is a method for alleviating inflammation in the eye or eyes of a warm-blooded animal exhibiting an ophthalmic inflammatory response, which comprises administering to the eye or eyes of said animal an anti-
15 inflammatory effective amount of a compound of formula (III) as defined above, particularly when the compound of formula (III) is one of the two specific compounds of formula (III) named above, or of an ophthalmic composition as defined above, particularly when the compound of formula (III) is one of the two specific compounds named above.

20 **[0037]** Another embodiment is a method for alleviating inflammation of the nasal mucosa in a warm-blooded animal exhibiting a nasal inflammatory response, which comprises nasally administering to said animal an anti-inflammatory effective amount of a compound of formula (III) as defined above, particularly when the compound of formula (III) is one of the two specific compounds named above, or of
25 a pharmaceutical composition as defined above, particularly when the compound of formula (III) is one of the two specific compounds named above.

[0038] Yet another embodiment is a method for alleviating asthma or COPD in the lungs or bronchi of a warm-blooded animal exhibiting an inflammatory response in the lungs or bronchi, which comprises administering to said animal by oral
30 inhalation an anti-inflammatory effective amount of a compound of formula (III) as

defined above, particularly when the compound of formula (III) is one of the two specific compounds of formula (III) named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (III) is one of the two specific compounds named above.

5 **[0039]** Still another embodiment is a method for alleviating inflammation of the upper or lower intestine in a warm-blooded animal exhibiting an intestinal inflammatory response, which comprises rectally administering to said animal an anti-inflammatory effective amount of a compound of formula (III) as defined above, particularly when the compound of formula (III) is one of the two specific compounds
10 named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (III) is one of the two specific compounds named above.

[0040] Another embodiment is a method for alleviating inflammation of the upper or lower intestine in a warm-blooded animal exhibiting an intestinal
15 inflammatory response, which comprises orally administering to said animal an anti-inflammatory effective amount of a compound of formula (III) as defined above, particularly when the compound of formula (III) is one of the two specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (III) is one of the two specific compounds named
20 above.

[0041] Yet another embodiment is a method for alleviating inflammation in the ear or ears of a warm-blooded animal exhibiting an otic inflammatory response, which comprises administering to the ear or ears of said animal an anti-inflammatory effective amount of a compound of formula (III) as defined above,
25 particularly when the compound of formula (III) is one of the two specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (III) is one of the two specific compounds named above.

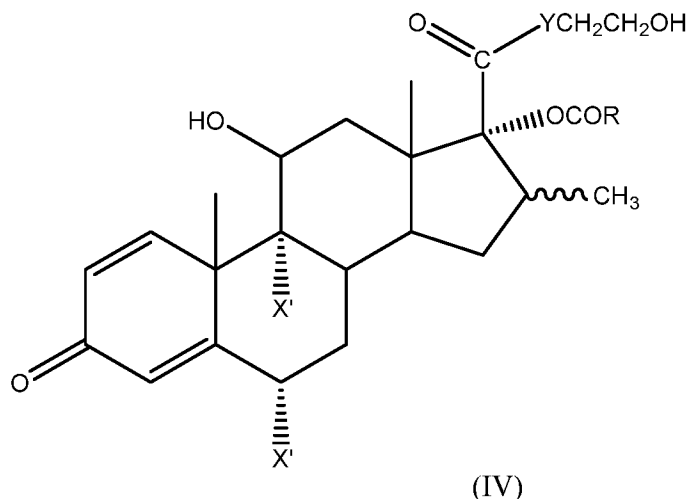
[0042] Another embodiment is a method for alleviating inflammation in a joint
30 or joints of a warm-blooded animal exhibiting an arthritic inflammatory response,

which comprises injecting into said joint or joints an anti-inflammatory effective amount of a compound of formula (III) as defined above, particularly when the compound of formula (III) is one of the two specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of
5 formula (III) is one of the two specific compounds named above.

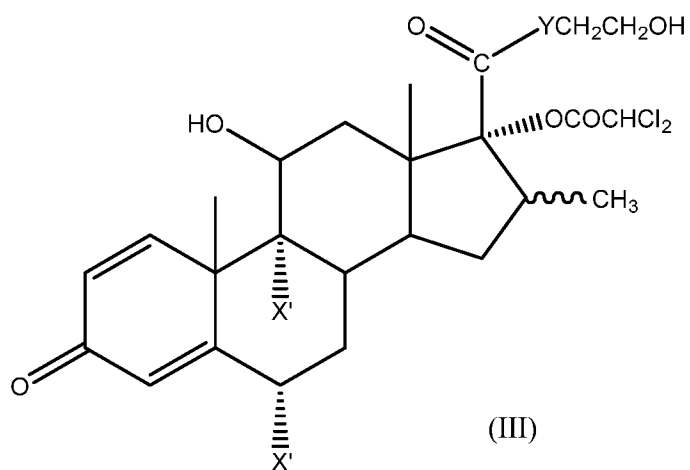
[0043] Still a further embodiment is a method for alleviating inflammation of the skin of a warm-blooded animal exhibiting a dermal inflammatory response, which comprises dermally administering to said animal an anti-inflammatory effective amount of a compound of formula (III) as defined above, particularly when
10 the compound of formula (III) is one of the two specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (III) is one of the two specific compounds named above.

[0044] Yet another embodiment herein is a method for alleviating inflammation of the mouth, gums or throat of a warm-blooded animal exhibiting an oral, gingival
15 or throat inflammatory response, which comprises orally administering to said animal an anti-inflammatory effective amount of a compound of formula (III) as defined above, particularly when the compound of formula (III) is one of the two specific compounds named above, or of a pharmaceutical composition as defined above, particularly when the compound of formula (III) is one of the two specific
20 compounds named above.

[0045] In a still further embodiment, there is provided a process for softening a 17 α -alkylcarbonyloxy-substituted corticosteroid compound of the formula (IV):



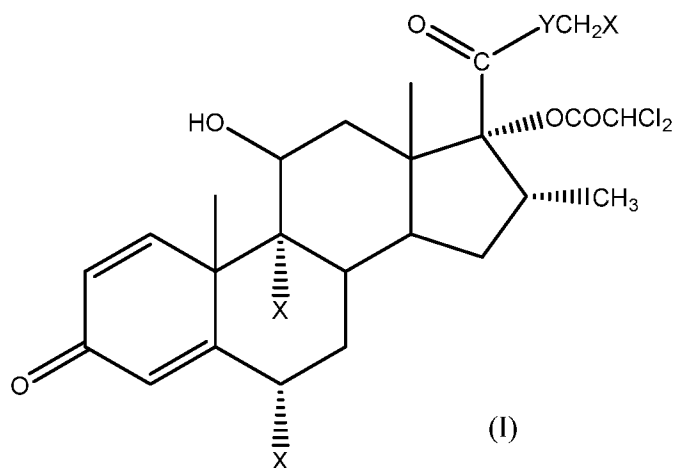
wherein each X' is independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S, R is C_1 - C_3 alkyl and the wavy line indicates the α - or β -configuration, said compound of formula (IV) having local or topical as well as systemic corticosteroid activity, said process comprising synthesizing the corresponding corticosteroid compound wherein the 17α -OCOR group in formula (IV) is replaced by a 17α -dichloroacetoxyl (17α -OCOCHCl₂) group, to provide the resultant soft corticosteroid compound of formula (III):



- 10 wherein X' , Y and the wavy line are as defined with formula (IV) above, said compound of formula (III) having substantially equivalent local or topical corticosteroid activity as compared to the corresponding compound of formula (IV) but having substantially decreased systemic corticosteroid activity compared to the

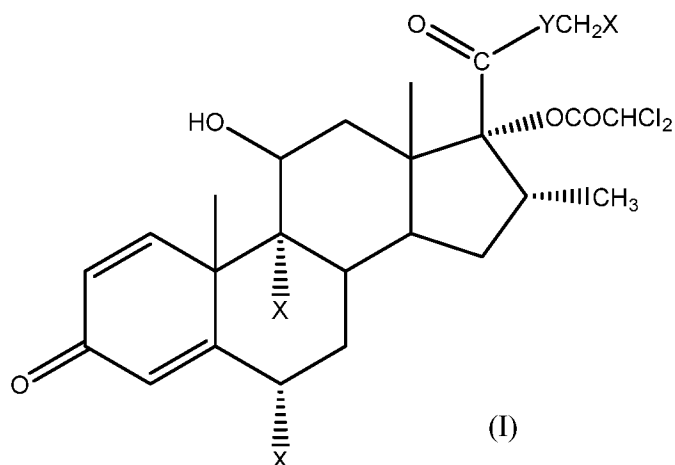
corresponding compound of formula (IV). In specific embodiments of this process, the resultant soft corticosteroid compound of formula (III) is 2-hydroxyethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate; or 2-hydroxyethyl 17 α -dichloroacetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

[0046] In a still further embodiment, there is provided a use of a compound having the formula (I):



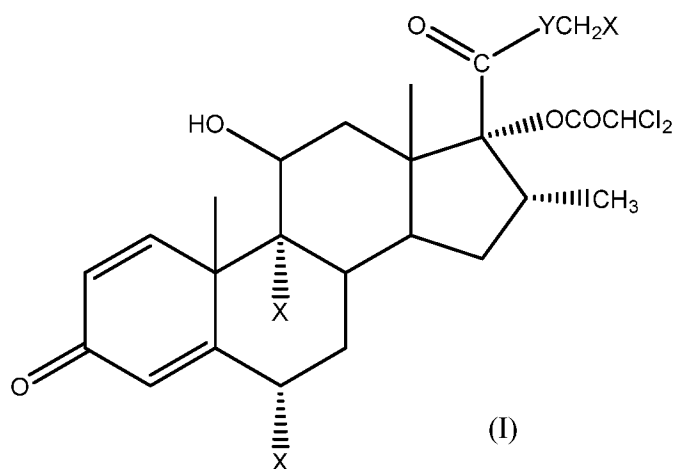
wherein each X is independently F or Cl, and Y is O or S, in the preparation of a pharmaceutical composition suitable for topical or other local application, the pharmaceutical composition comprising an anti-inflammatory effective amount of the compound and a non-toxic pharmaceutically acceptable carrier therefor.

[0047] In yet another exemplary embodiment, there is provided a use of a compound having the formula (I):



wherein each X is independently F or Cl, and Y is O or S, in the preparation of an ophthalmic composition comprising an anti-inflammatory effective amount of the compound and a non-toxic ophthalmically acceptable carrier therefor.

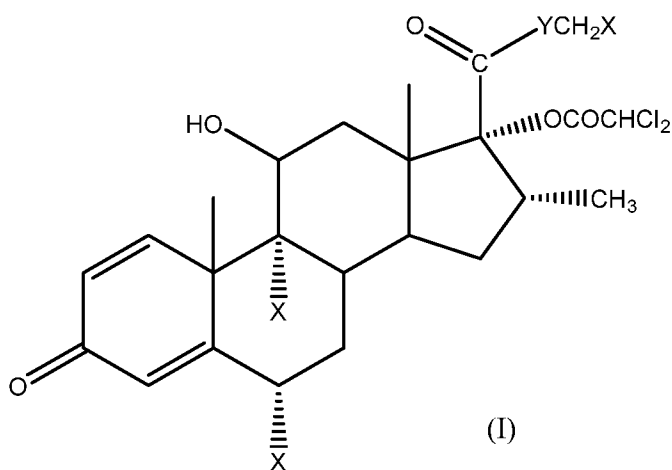
- 5 **[0048]** In a further exemplary embodiment, there is provided a pharmaceutical composition suitable for topical or other local application, the pharmaceutical composition comprising an anti-inflammatory effective amount of a compound having the formula (I):



, wherein each X is

- 10 independently F or Cl, and Y is O or S, and a non-toxic pharmaceutically acceptable carrier therefor, for use in alleviating inflammation in or on a warm-blooded animal exhibiting an inflammatory response, wherein the inflammatory response is localized or topical.

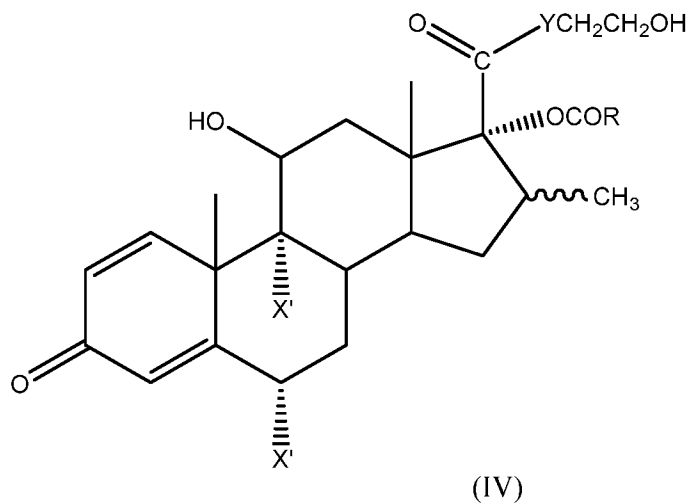
In another exemplary embodiment, there is provided an ophthalmic composition comprising an anti-inflammatory effective amount of a compound having the formula (I):



, wherein each X is

- 5 independently F or Cl, and Y is O or S, and a non-toxic ophthalmically acceptable carrier therefor, for use in alleviating inflammation in the eye or eyes of a warm-blooded animal exhibiting an ophthalmic inflammatory response.

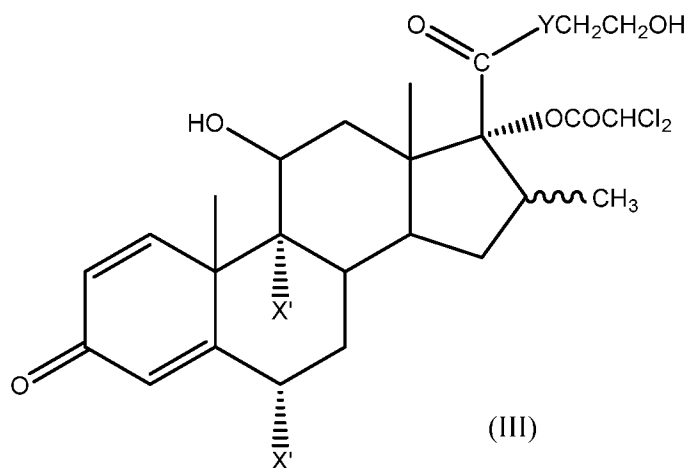
[0049] In yet another exemplary embodiment, there is provided the use of a 17 α -alkylcarbonyloxy-substituted corticosteroid compound of the formula (IV):



, wherein each X' is

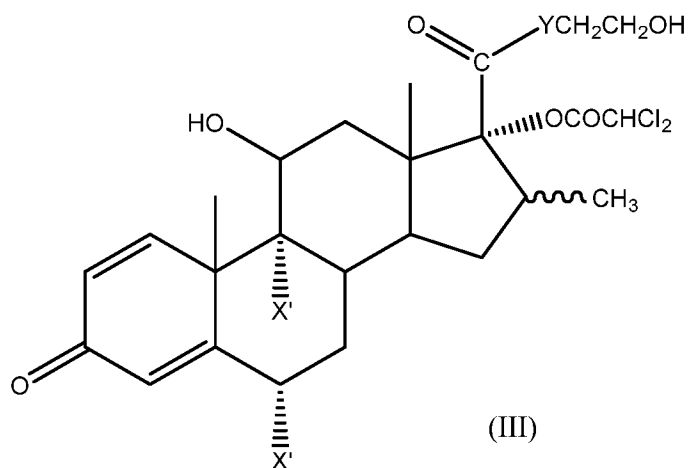
independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S, R is C1-C3 alkyl and the wavy line indicates the α - or β -configuration; said compound of formula (IV) having local or topical as well as systemic corticosteroid activity, to

produce a soft corticosteroid compound of formula (III) by replacing the 17α -OCOR group in formula (IV) with a 17α -dichloroacetoxy (17α -OCOCHCl₂) group:



5 , wherein each X' and Y are as defined with formula (IV) above, said compound of formula (III) having substantially equivalent local or topical corticosteroid activity as compared to the corresponding compound of formula (IV) but having substantially decreased systemic corticosteroid activity as compared to the corresponding compound of formula (IV).

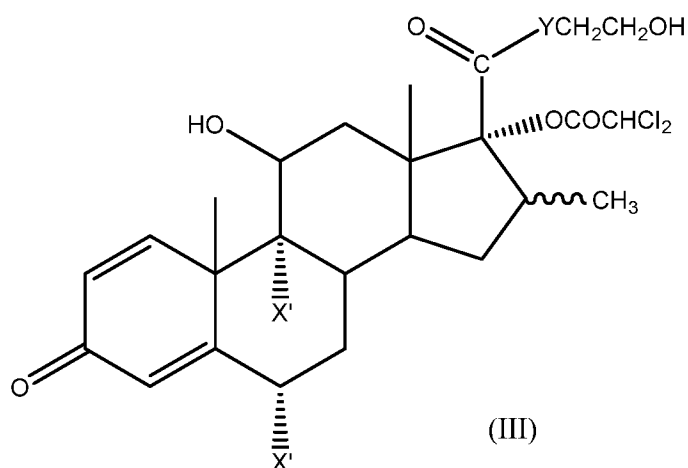
[0050] In another exemplary embodiment, there is provided the use of compound having the formula (III):



10 , wherein each X' is independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S and the wavy line indicates the α - or β -configuration, in the preparation of a pharmaceutical composition suitable for topical or other local application, the pharmaceutical

composition comprising an anti-inflammatory effective amount of the compound and a non-toxic pharmaceutically acceptable carrier therefor.

[0051] In yet another exemplary embodiment, there is provided the use of compound having the formula (III):



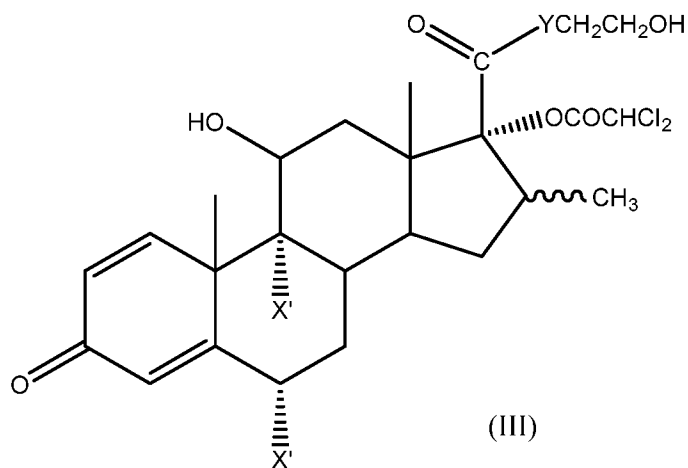
5

, wherein each X' is

independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S and the wavy line indicates the α - or β -configuration, in the preparation of an ophthalmic composition comprising an anti-inflammatory effective amount of the compound and a non-toxic ophthalmically acceptable carrier therefor.

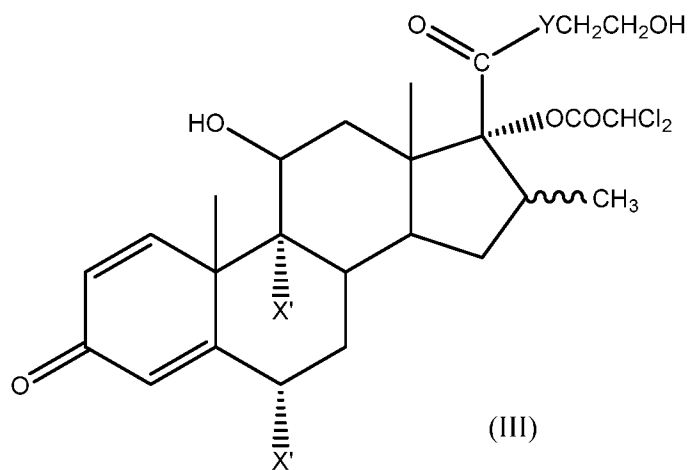
10

[0052] In another exemplary embodiment, there is provided a pharmaceutical composition suitable for topical or other local application, the pharmaceutical composition comprising an anti-inflammatory effective amount of a compound having the formula (III):



, wherein each X' is independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S and the wavy line indicates the α - or β -configuration, and a non-toxic pharmaceutically acceptable carrier therefor, for use in alleviating inflammation in or on a warm-blooded animal exhibiting an inflammatory response, wherein the inflammatory response is localized or topical.

[0053] In yet another exemplary embodiment, there is provided an ophthalmic composition comprising an anti-inflammatory effective amount of a compound having the formula (III):

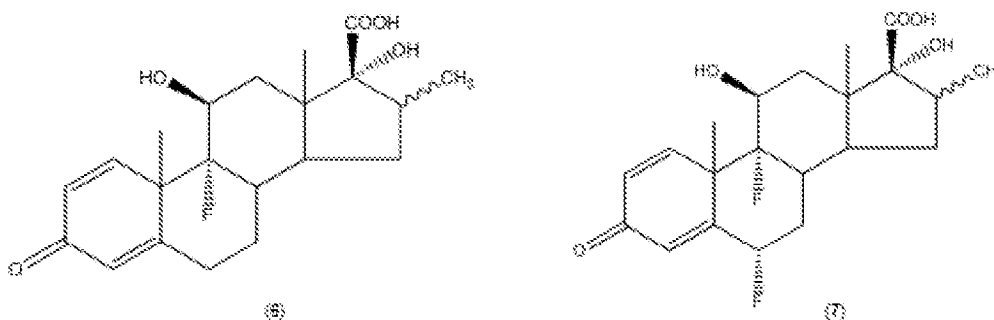


, wherein each X' is independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S and the wavy line indicates the α - or β -configuration, and a non-toxic ophthalmically acceptable carrier therefor, for use in alleviating inflammation in the eye or eyes of a warm-blooded animal exhibiting an ophthalmic inflammatory response.

DETAILED DESCRIPTION

[0054] The expression 'softening' as used herein means decreasing the systemic corticosteroid activity/toxicity (or side-effects) of an anti-inflammatory corticosteroid by replacing an oxidatively metabolizable structural group in said corticosteroid compound [e.g. as in (II)] with a readily hydrolyzable structural group while maintaining high local/topical corticosteroid activity. In particular, the expression 'softening' means synthesizing a corticosteroid compound [(I) or (III) above] which retains potency-increasing substitution at the 6 α , 9 α and 16 α -positions of the compound (II) or (IV) while replacing the 17 α -OCOR group with a 17 α -dichloroacetoxy (17 α -OCOCHCl₂) group to provide the corresponding (I) or (III), respectively.

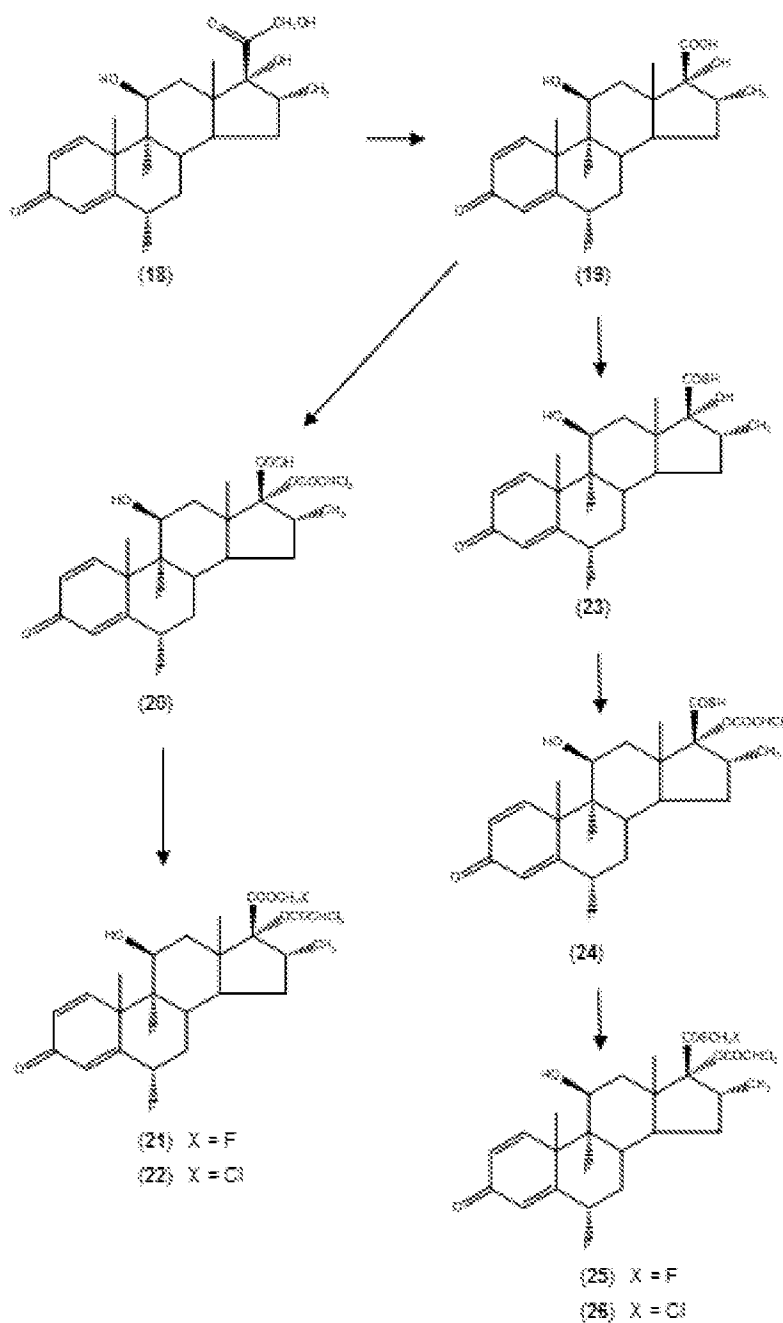
[0055] The synthesis of ED (**3**) is illustrated in SCHEME 1 above. The ED analogs represented by the general formula **5** were synthesized using a process similar to that shown for the compound of formula **3**, but replacing Δ^1 -cortienic acid with the fluorinated analogs **6** and **7** depicted below.



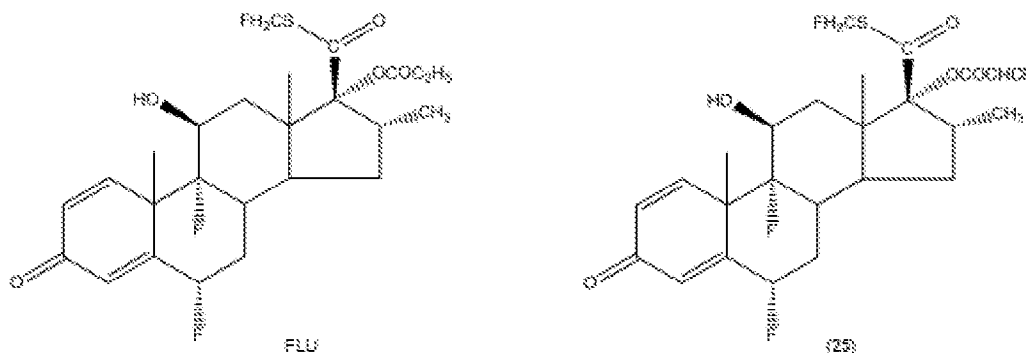
[0056] The cortienic acids **6** and **7** were converted to the corresponding 17 α -dichloroacetyl esters, which were the starting materials for the various 17 β -esters **8-15** listed in following Table 1 and included in the working Examples that follow herewith.

[0057] Finally, the commercially available 6 α ,9 α -difluoro-16 α -methyl prednisolone (**18**), the precursor of fluticasone propionate (**FLU**), one of the most used and highly potent corticosteroids, was oxidized to the corresponding cortienic

acid derivative **19**, and as needed, **19** was converted to the thiocortienic acid **23**. Dichloroacetylation of **19** and **23** to **20** and **24** respectively, and subsequent esterification of the 17 β -carboxy function led to the target halo (Cl or F) 16 α -methyl esters **21**, **22**, **25** and **26**, as illustrated in SCHEME 2 below.



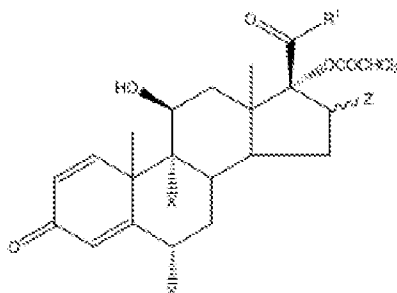
[0058] Compound **25** is a soft analog of fluticasone propionate, where the 17 α -propionyl function is now replaced by the hydrolytically more labile dichloroacetyl function. Compound **25** or some of the other structural analogs are surprisingly superior to fluticasone in terms of high activity but with improved safety, and thus an improved therapeutic index.



[0059] Etiprednol dicloacetate and its analogs significantly inhibited the liberation of IL - 1 β from the human monocyte cell line THP - 1. The *in vitro* anti-inflammatory effect of ED and its analogs was assessed using LPS-induced TNF α -release under various conditions (diluted or undiluted whole human blood, preincubation with sera) to determine the intrinsic anti-inflammatory activity and systemic biological stability of the various compounds. The results are shown in Table 1.

[0060] Two representative analogs of ED were selected for *in vivo* studies in the widely-used ovalbumin-sensitized and challenged Brown Norway rat model. Allergic challenge in this animal causes extensive inflammation in the lung with characteristic increase in the number of eosinophils and mucus-producing goblet cells, and in the exudate of perivascular edema. In addition, airway hypersensitivity also develops, which is a cardinal feature of asthma. ED was then compared in this model to the selected 9 α -fluoro-16 β -methyl analog (**11**). Finally, the fluticasone analog **25** was compared to fluticasone. The results are summarized in Table 2.

[0061] Table 1: *In vitro* anti-inflammatory activity (IC₅₀ values in nM) of selected 17 α -dichloroacetoxy etiprednol analogs represented by structure (5):



ED analogs (5)

Compound	X	Y	Z	R'	TNF α *		Prolif.**	Stability***	
					a	b		c	d
3 (ED)	H	H	H	OCH ₂ CH ₃	27	103	10	73	2700
10	F	H	β -CH ₃	OCH ₃	4 $\pm$ 3	20 $\pm$ 10	< 0.01	1.7	10.2
11	F	H	β -CH ₃	OCH ₂ CH ₃	1.7 $\pm$ 2	7.1 $\pm$ 4	0.012	16	18
12	F	H	β -CH ₃	OCH ₂ Cl	20 $\pm$ 8	35 $\pm$ 12	0.05 $\pm$ 0.12	---	---
13	F	H	β -CH ₃	OCH ₂ CH ₂ OH	4.6 $\pm$ 6.0	5.8 $\pm$ 5.0	0.28 $\pm$ 16	4.5	53.5
14	F	F	β -CH ₃	OCH ₃	0.8 $\pm$ 0.6	1.7 $\pm$ 0.9	< 0.01	---	---
15	F	F	β -CH ₃	OCH ₂ CH ₃	2.0	14.0	< 0.01	---	---
16	F	F	β -CH ₃	OCH ₂ Cl	0.4 $\pm$ 3	5.1 $\pm$ 1.7	26 $\pm$ 26	---	---
17	F	F	β -CH ₃	OCH ₂ CH ₂ OH	< 1	3.7 $\pm$ 2.6	0.13 $\pm$ 0.020	1.9	19.2
21	F	F	α -CH ₃	OCH ₂ F	1.4	4.5	9	1.4	25
22	F	F	α -CH ₃	OCH ₂ Cl	4.0	4.0	0.02	---	---
25	F	F	α -CH ₃	SCH ₂ F	2.0	3.0	0.1	1	87
26	F	F	α -CH ₃	SCH ₂ Cl	6.0	12.0	3	---	---

* Inhibition of TNF α -production of LPS-stimulated blood cells. The variations reflect differences in blood of different individuals (3 - 6 individuals provided blood).

(a) diluted blood 1:5

5 (b) undiluted

**Inhibition of mitogen-induced proliferation of PBMC.

***Inhibition (IC_{50} in nM) of TNF- α production of LPS-stimulated whole blood cells.

(c) non-preincubated in human plasma

10 (d) preincubated overnight

[0062] Table 2: Effect of intratracheally administered (2 hours prior challenge) Etiprednol Dicloacetate (ED), the analog **11**, fluticasone (FLU) and its analog **25** on the airway changes of ovalbumin sensitized and challenged Brown Norway rats (N = 10)

Measured parameter		Effective Doses* (µg/kg)	ED	11	FLU	25
AHR**		<u>ED50</u>	≈ 1.0	19.4	0.14	3.75
		MSED	≈1.0	20.0	0.1	10
BALF*** protein		<u>ED50</u>	ND	ND	11.2	0.64
		MSED			10.0	100
Eosino philia	BALF***	<u>ED50</u>	≤ 0.1	>100	>100	16.1
		MSED	0.1		10.0	1.0
	Peri- bronchial	<u>ED50</u>	0.62	10.3	10.5	
		MSED	0.1	12.0	1.0	
	Peri- vascular	<u>ED50</u>	>100	ND	45.0	83.8
		MSED	1.0		10.0	1.0
Mucus production		<u>ED50</u>	13.8	<1	<1.0	7.42
		MSED	0.1	<1	1.0	100

Edema formation	ED50	2.9	9.3	2.8	<1.0
	MSED	0.1	0.5	1.0	1.0

* ED50= 50% effective dose (Prisma);

MSED= Minimal statistically significantly effective dose (Mann-Whitney U-test)

5 ** Airways hyperreactivity measured as relative response to maximal acetylcholine dose

*** Broncho-alveolar lavage fluid

ND = not determined

[0063] The inventor and co-workers have previously reported the pronounced anti-inflammatory activity of ED (**3**) on the TNF- α production on LPS stimulated human blood. The difference in the activity of **3** in undiluted versus diluted (1:5) blood was also noted. The efficacy of ED decreased in parallel with the increase in the amount of serum proteins present and it was demonstrated by LC/MS/MS that this decline in activity coincided with the rate of disappearance of the original compound and the appearance of a proposed major metabolite. At that time the putative degrading enzyme of ED was not known, and it was assumed to be a carboxylesterase. Surprisingly, the main metabolite identified was the 17 α -hydroxy derivative, that is, the dichloroacetyl function cleaved easier than the highly hindered 17 β -ester.

[0064] Recently, the inventor and co-workers have identified the hydrolyzing enzyme to be Paraoxonase 1, which is associated with HDL in human blood. This fact not only explains the effect of the dilution, but also raises the possibility of identifying highly potent corticosteroids having multiple substitutions and yet also having improved therapeutic indexes. As mentioned before, the substituted loteprednol derivatives (6 α , 9 α , 16- α , β) do not hydrolyze easily, and, thus, are not acceptably 'soft.' Furthermore, fluticasone, an allegedly 'soft' steroid, does not undergo hydrolysis of the 17 β -fluoromethyl thio ester, but is instead dependent on the relatively slow P-450 catalyzed metabolism. This application describes studies of ED substituted analogs, including the dichloroacetyl analog of fluticasone (**25**).

[0065] Table 1 shows the *in vitro* activity results in various conditions. The first column clearly shows the effect of dilution of the blood, with the corresponding IC₅₀ up to ten times lower in the undiluted blood. The other important property studied is the effect of pre-incubation before assessing the TNF- α production. This

is the indicator of the unexpectedly superior stability of these compounds in the general circulatory system. Previous studies showed that ED (3) loses its activity during incubation (by five-fold in two days, 100-fold in five days). Under the same conditions, the comparably effective dexamethasone and budesonide maintain full activity.

[0066] Two of these compounds were selected for further *in vivo* studies. The 9 α -fluoro-16 β -methyl analog (**11**) of ED and the fluticasone analog (**25**) were studied in the ovalbumin sensitized Brown Norway rats model. The various parameters measured, including allergen-induced airway hyperreactivity (AHR), allergen induced cellular infiltration (eosinophils in the broncho-alveolar lavage fluid (BALF) and in the lung tissues), goblet cell hyperplasia, increased mucus secretion and allergen-induced perivascular edema formation, are shown in Table 2.

[0067] The results clearly demonstrate that the 9 α , and the 6 α ,9 α -difluoro and 16-methyl substitution enhance the activity of etiprednol. The most attractive feature, however, is the enhanced soft nature, as reflected by the effect of incubation time with serum/blood on the efficacy. Evidently, the Paraoxonase present hydrolyzes the 17 α -dichloroacetyl function, with little slowing down by the substituents, unlike in the LE series. Interestingly, the 9 α -F-16 β -methyl analog (**11**) of ED (**3**) does not represent significant improvement over ED, except in mucus production. On the other hand, the fluticasone analog **25** is overall superior to FLU, primarily in reducing eosinophilia and edema formation.

[0068] As illustrated by the results included in Tables 1 and 2, selected substituted analogs of the second-generation soft steroid, ED, unexpectedly/surprisingly possess both high overall local/topical anti-inflammatory activity and significantly improved therapeutic indexes when compared with the hard and 17 α -carbonate soft analogs. Particularly, compound **25**, the fluticasone analog, promises to be superior to fluticasone, the most potent, but most toxic corticosteroid with the steepest side effects curve.

[0069] For the following exemplary embodiments, chemicals were purchased from SIGMA (St. Louis, MO, USA), unless indicated otherwise. Etiprednol

dicloacetate (ethyl 17 α -dichloroacetoxy-11 β -hydroxyandrost-1,4-diene-3-one-17 β -carboxylate, BNP-166) was synthesized at the Department of Chemistry, Institute for Drug Research, Budapest, Hungary. Urethane, Primazin (2% xylazine), Ketalar (10% ketamine), and the Unopette kit were purchased from Reanal (Budapest, Hungary), Alfasan International BV (AB Woerden, The Netherlands), Parke Davis (London, UK), and BD Biosciences (Franklin Lakes, NJ, USA), respectively.

EXAMPLE 1: 11 β ,17 α -Dihydroxyandrost-1,4-diene-3-one-17 β -carboxylic acid (**1**)

[0070] To (70 g, 0.194 mol) of prednisolone in a mixture of tetrahydrofuran (600 ml) and methanol (220 ml) at 30 °C was added a solution of sodium metaperiodate (120 g, 0.561 mol) in warm (50 °C) water (550 ml) over 25 min. The reaction mixture was stirred at room temperature for 2 h. The organic solvents were removed *in vacuo*. The precipitate was collected by filtration, washed twice with water and without drying dissolved in 0.25 N aqueous sodium hydroxide solution (880 ml). Insoluble impurities were removed by filtration, the clear solution was washed twice with methylene chloride and acidified with 0.5 N hydrochloric acid (550 ml) to pH = 1. The precipitate was collected by filtration, washed three times with water and dried at 40 °C until constant weight. Yield: 63.7 g (95%), white crystalline powder. Mp 230 °C (decomp.).

[0071] ¹H NMR (250 MHz, DMSO-d₆): δ 0.92 (3 H, s, CH₃-18), 1.40 (3 H, s, CH₃-19), 4.36 (1 H, ms, H α -11), 5.91 (1 H, d, J = 10 Hz, H-2).

EXAMPLE 2: 17 α -Dichloroacetoxy-11 β -hydroxyandrost-1,4-diene-3-one-17 β -carboxylic acid (**2**)

[0072] Dichloroacetyl chloride (62.5 ml, 95.8 g; 0.65 mol) in methylene chloride (1500 ml) was slowly added to a stirred solution of potassium bicarbonate (139.5 g, 1.39 mol) and **1** (45.0 g, 0.13 mol) in water (2000 ml) over 2 h. The obtained reaction mixture was acidified with 5 N hydrochloric acid (135 ml) to pH = 1–2. The layers were separated and the aqueous layer was extracted with

methylene chloride (2 x 210 ml). The combined organic layers were washed with saturated ammonium chloride solution (2 x 360 ml). The organic layer was stirred with the solution of potassium bicarbonate (17.1 g, 172 mmol) in water (1000 ml) for 30 min. The process was repeated with the solution of potassium bicarbonate (8.6 g, 86.0 mmol) in water (600 ml). The combined aqueous solutions were washed with methylene chloride (135 ml) and then slowly acidified with 2 N hydrochloric acid to pH = 1–2 under stirring. The solution was warmed to 45–50 °C then the precipitated white solids were collected by filtration and washed with water. The obtained white powder was dried at 45°C *in vacuo* until constant weight. Yield: 55.4 g (93%), white crystalline powder. Mp 210–214 °C.

[0073] ^1H NMR (250 MHz, DMSO- d_6): δ 1.01 (3 H s, CH₃-18), 1.41 (CH, s, CH₃-19), 5.94 (1 H, s, H-4), 6.18 (1 H, d, J = 10 Hz, H-2), 6.85 (1 H, s, CO₂-CHCl₂), 7.33 (1 H, d, H-1).

EXAMPLE 3: Ethyl 17 α -dichloroacetox-11 β -hydroxyandrosta-1,4-diene-3-one-17 β -carboxylate (**3**) (ED – Etiprednol dicloacetate)

[0074] Method A: By esterification of **2** with ethyl iodide

[0075] To a stirred suspension of **2** (50 g, 0.109 mol) and anhydrous potassium carbonate (16.58 g, 0.120 mol) in anhydrous dimethyl formamide (500 ml) was added ethyl iodide (13.1 ml, 25.5 g; 0.164 mol) at room temperature. After stirring for 1.5 h the reaction mixture was diluted with saturated aqueous sodium chloride solution (1000 ml) and stirred for 1 h. The obtained precipitate was collected by filtration and washed with water (3 x 180 ml). The crude product (53.2 g) was recrystallized from ethyl acetate (400 ml). Yield: 31.9 g (61%), white crystalline powder. Mp 201–202.5 °C.

[0076] ^1H NMR (500 MHz, CDCl₃): δ 1.06 (3H, s, CH₃-18), 1.47 (3H, s, CH₃-19), 1.27 (3H, t, CH₃CH₂O), 4.21 (2H, q, CH₃CH₂O), 2.97 (1H, m, H $_{\beta}$ -16), 4.53 (1H, m, H $_{\alpha}$ -11), 2.36 (1H, m, H $_{\alpha}$ -6), 2.59 (1H, m, H $_{\beta}$ -6), 5.91 (1H, s, CHCl₂), 6.03 (1H, d, H-4), 6.28 (1H, dd, H-2), 7.29 (1H, d, H-1), ^{13}C NMR (125 MHz, CDCl₃): 14.1 (CH₃CH₂O), 16.9 (C-18), 21.0 (C-19), 61.6 (CH₃CH₂O), 64.2 (CHCl₂), 31.9 (C-6),

69.9 (C-11), 93.4 (C-17), 122.5 (C-4), 127.9 (C-2), 156.0 (C-1), 162.8 ($\text{CH}_2\text{-CHCl}_2$), 169.7 (C-5), 168.3 ($\text{CO}_2\text{-CH}_2\text{CH}_3$), 186.5 (C-3). MS: EI: $[\text{M}]^+$: 484/486 (3.92/2.6%), m/z 363/365 (8.5/5.7%), m/z 356 (3%), m/z 283 (21%), m/z 265 (34%), m/z 122 (100%), m/z 121 (41%). CI: $[\text{M} + \text{H}]^+$ 485/487 (93/64%), m/z 122 (100%).

5 **[0077]** Method B: By esterification of **2** with diethyl sulfate

[0078] The procedure described above (Method A) was followed with the difference that diethyl sulfate (21.5 ml, 25.3 g, 0.164 mol) was used instead of ethyl iodide. Yield: 70%.

10 EXAMPLE 4: 9 α -Fluoro-11 β ,17 α -dihydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (**6**)

[0079] Prepared as described for **1** above starting with 9 α -fluoroprednisolone. Yield: 89%, white crystalline powder. Mp 258-259 °C.

15 **[0080]** ^1H NMR (DMSO-d_6): δ 1.07 (3H, s, CH_3 -18), 1.50 (3H, s, CH_3 -19), 1.14 (3H, d, CH_3 -16), 2.05 (1H, m, H_α -16), 5.19 (1H, m, H_α -11), 6.00 (1H, m, H-4), 6.20 (1H, dd, H-2), 7.28 (1H, d, H-1). EI: $[\text{M}]^+$: 378 (2%); $\underline{\text{m/z}}$: 358 (18%), 122 (100%), 121 (66%). CI: $[\text{M}+\text{H}]^+$: 379 (100%), $\underline{\text{m/z}}$: 359 (20%).

20 EXAMPLE 5: 6 α ,9 α -Difluoro-11 β ,17 α -dihydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (**7**)

[0081] Prepared as described for **1** above starting with 6 α ,9 α -difluoroprednisolone. Yield: 97%, white crystalline powder. Mp 265-267 °C.

25 **[0082]** ^1H NMR (CD_3OD): δ 1.17 (3H, s, CH_3 -18), 1.24 (3H, d, CH_3 -16), 1.59 (3H, s, CH_3 -19), 2.60 (1H, m, H-8), 4.25 (1H, ddd, H_α -11), 5.54 (1H, dddd, H_β -6), 6.29 (1H, m, H-4), 6.32 (1H, dd, H-2), 7.34 (1H, dd, H-1).

EXAMPLE 6: 17- α -Dichloroacetoxy-9 α -fluoro-16 β -methyl-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (**8**)

[0083] Dichloroacetyl chloride (3.1 ml, 4.76 g; 32.3 mmol) in dichloromethane (75 ml) was slowly added to a stirred solution of potassium hydrogencarbonate (6.94 g, 69.3 mmol) and **6** (1.75 g, 4.62 mmol) in water (100 ml) over 2 hours. The obtained reaction mixture was acidified with 5 N hydrochloric acid (4.8 ml) to pH=1.2. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 ml). The combined organic layers were washed with saturated ammonium chloride solution (2 x 13 ml). The organic layer was stirred with a solution of potassium hydrogencarbonate (0.608 g, 6.07 mmol) in water (35 ml) for 30 minutes. The process was repeated with a solution of potassium hydrogencarbonate (0.306 g, 3.05 mmol) in water (22 ml). The combined aqueous solutions were washed with dichloromethane (10 ml) and then slowly acidified with 2 N hydrochloric acid to pH = 1-2 under stirring. The solution was warmed to 45-50° C then the precipitated white solids were collected by filtration and washed with water. The obtained white powder was dried at 45°C *in vacuo* until constant weight. Yield: 1.95 g (86%), white crystalline powder. Mp 193-194 °C.

[0084] ¹H NMR (MeOH-d₄): δ 1.13 (3H, s, CH₃-19), 1.43 (3H, d, CH₃-16), 4.29 (1H, m, H_α-11), 6.10 (1H, m, H-4), 6.30 (1H, dd, H-2), 7.40 (1H, d, H-10).

EXAMPLE 7: 17α-Dichloroacetoxy-6α,9α-difloro-16β-methyl-11β-hydroxy-3-oxoandrost-1,4-diene-17β-carboxylic acid (**9**)

[0085] Prepared as described for **8** above starting with **7**. Yield: 78%, white crystalline powder. Mp 186° C.

[0086] ¹H NMR (CDCl₃ + 3 drops of methanol-d₄): δ 1.07 (3H, s, H-18), 1.40 (3H, d, CH₃-16), 1.51 (3H, s, H-19), 2.17 (1H, m, H_α-16), 2.45 (1H, m, H-8), 4.29 (1H, m, H_α-11), 5.37 (1H, dddd, H_β-6), 5.91 (1H, s, CHCl₂), 6.32 (1H, dd, H-2), 6.38 (1H, m, h-4), 7.16 (1H, dd, H-1). ¹³C NMR (CDCl₃ + 3 drops of methanol-d₄): δ 16.7 (18), 20.0 (CH₃-16), 22.9 (19), 32.6 (8), 33.9 (7), 34.8 (15), 36.1 (12), 43.0 (14), 45.1 (16), 47.3 (13), 48.2 (10), 64.3 (CHCl₂), 71.2 (11), 82.6 (6), 92.7 (17), 99.1 (9), 120.7 (4), 129.7 (2), 151.5 (1), 162.3 (5), 163.4 (OC=O), 169.6 (20), 186.1 (3).

EXAMPLE 8: Methyl 17 α -dichloroacetoxy-9 α -fluoro-16 β -methyl-11 β -hydroxy-3-oxoandrost-1,4-diene-17 β -carboxylate (**10**)

[0087] To a stirred suspension of **8** (0.35 g, 0.8 mmol) and anhydrous potassium carbonate (0.122 g, 0.88 mmol) in anhydrous dimethyl formamide (3.5 ml) methyl iodide (0.17 g, 1.2 mmol) was added at room temperature. After stirring for 1.5 hours the reaction mixture was diluted with saturated aqueous sodium chloride solution (8 ml) and stirred for 90 minutes. The obtained precipitate was collected by filtration and washed with water (3 x 5 ml). The crude product (0.32 g) was purified by column chromatography on silica gel eluting with dichloromethane – methanol 95:5 then was recrystallized from ethyl acetate/*n*-hexane. Yield: 90%, off-white crystalline powder. Mp 213-215 °C.

[0088] ¹H NMR (CDCl₃): δ 1.08 (3H, s, CH₃-18), 1.57 (3H, s, CH₃-19), 1.46 (3H, d, CH₃-16), 2.22 (1H, m, H α -16), 4.44 (1H, m, H α -11), 6.14 (1H, m, H-4), 6.35 (1H, dd, H-2), 7.20 (1H, d, H-1), 3.71 (3H, s, CH₃O), 5.91 (1H, s, CHCl₂). ¹³C NMR (CDCl₃): 151.6 (C-1), 130.0 (C-2), 186.3 (C-3), 125.3 (C-4), 166.5 (C-5), 30.9 (C-6), 27.5 (C-7), 33.9 (C-8), 100.0 (C-9), 48.1 (C-10), 72.0 (C-11), 37.3 (C-12), 47.7 (C-13), 43.3 (C-14), 35.0 (C-15), 45.6 (C-16), 20.0 (CH₃-16), 92.8 (C-17), 17.3 (C-18), 23.0 (C-19), 167.8 (C-20), 51.9 (CH₃O), 163.4 (OC=O), 64.3 (CHCl₂).

EXAMPLE 9: Ethyl 17 α -dichloroacetoxy-9 α -fluoro-16 β -methyl-11 β -hydroxy-3-oxoandrost-1,4-diene-17 β -carboxylate (**11**)

[0089] Prepared as described for **10** above starting with **8** and using diethyl sulfate instead of methyl iodide. Yield: ~100%, white crystalline powder. Mp 194-195° C.

[0090] ¹H NMR (CDCl₃): δ 1.08 (3H, s, CH₃-18), 1.57 (3H, s, CH₃-19), 1.45 (3H, d, CH₃-16), 2.21 (1H, m, H α -16), 4.43 (1H, m, H α -11), 6.13 (1H, m, H-4), 6.34 (1H, dd, H-2), 7.23 (1H, d, H-1), 1.25 (3H, t, CH₃CH₂O), 4.17 (2H, q, CH₃CH₂O), 5.91 (1H, s, CHCl₂). ¹³C NMR (CDCl₃): 152.1 (C-1), 129.8 (C-2), 186.5 (C-3), 125.1 (C-4), 166.0 (C-5), 31.0 (C-6), 27.5 (C-7), 33.9 (C-8), 100.2 (C-9), 48.1 (C-10), 71.9 (C-11), 37.1 (C-12), 47.7 (C-13), 43.3 (C-14), 35.0 (C-15), 45.5 (C-16),

20.0 (CH₃-16), 92.6 (C-17), 17.2 (C-18), 23.0 (C-19), 167.2 (C-20), 14.1 (CH₃CH₂O), 61.0 (CH₃CH₂O), 163.3 OC=O), 64.3 CHCl₂).

EXAMPLE 10: Chloromethyl 17 α -dichloroacetoxy-9 α -fluoro-16 β -methyl-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate (**12**)

[0091] Prepared as described for **11** above starting with **8** and using a 4 molar excess of chloriodomethane instead of methyl iodide. After stirring for 8.5 hours the reaction mixture was diluted with saturated aqueous sodium chloride solution. The crude product was isolated by extraction with diethyl ether and purified by column chromatography on silica gel eluting ethyl acetate – *n*-hexane 1:1. The product was then recrystallized from ethyl acetate/*n*-hexane. Yield: 48%, white crystalline powder. Mp 177-180 °C.

[0092] ¹H NMR (CDCl₃): δ 1.13 (3H, s, CH₃-18), 1.57 (3H, s, CH₃-19), 1.48 (3H, d, CH₃-16), 2.23 (1H, m, H α -16), 4.46 (1H, m, H α -11), 6.15 (1H, m, H-4), 6.36 (1H, dd, H-2), 7.18 (1H, d, H-1), 3.50/5.94 (2H, d, CH₂O), 5.92 (1H, s, CHCl₂). ¹³C NMR (CDCl₃): 151.3 (C-1), 130.1 (C-2), 186.2 (C-3), 125.4 (C-4), 166.3 (C-5), 30.9 (C-6), 27.5 (C-7), 33.9 (C-8), 99.7 (C-9), 48.0 (C-10), 71.9 (C-11), 37.3 (C-12), 48.0 (C-13), 43.5 (C-14), 34.9 (C-15), 45.8 (C-16), 19.9 (CH₃-16), 91.9 (C-17), 16.9 (C-18), 23.0 (C-19), 165.3 (C-20), 68.9 (CH₂O), 163.4 OC=O), 64.1 (CHCl₂).

EXAMPLE 11: 2-Hydroxyethyl 17 α -dichloroacetoxy-9 α -fluoro-16 β -methyl-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate (**13**)

[0093] Prepared as described for **11** above starting with **8** using a 6 molar excess of 2-bromoethanol instead of methyl iodide and a catalytic amount of potassium iodide. After stirring the reaction mixture for 24 hours and diluting it with water the crude product was isolated by extraction with diethyl ether and was purified by column chromatography on silica gel eluting dichloromethane – methanol 95:5. The product was then crystallized by triturating with *n*-hexane. Yield: 50%, white crystalline powder. Mp 193 °C.

[0094] ^1H NMR (CDCl_3): δ 1.11 (3H, s, CH_3 -18), 1.57 (3H, s, CH_3 -19), 1.46 (3H, d, CH_3 -16), 2.23 (1H, m, H_α -16), 4.41 (1H, m, H_α -11), 6.15 (1H, m, H-4), 6.35 (1H, dd, H-2), 7.21 (1H, d, H-1), 4.28 (2H, m, CH_2O), 3.82 (2H, m, CH_2OH), 5.93 (1H, s, CHCl_2). ^{13}C NMR (CDCl_3): 151.9 (C-1), 129.9 (C-2), 186.5 (C-3), 125.2 (C-4), 166.9 (C-5), 30.9 (C-6), 27.6 (C-7), 33.9 (C-8), 100.0 (C-9), 48.1 (C-10), 72.0 (C-11), 37.0 (C-12), 47.8 (C-13), 43.4 (C-14), 35.0 (C-15), 45.7 (C-16), 20.0 (CH_3 -16), 92.8 (C-17), 17.2 (C-18), 22.9 (C-19), 167.2 (C-20), 66.5 (CH_2O), 60.9 (CH_2OH), 163.7 ($\text{OC}=\text{O}$), 64.3 (CHCl_2).

10 EXAMPLE 12: Methyl 6 α ,9 α -difluoro-17 α -dichloroacetox-16 β -methyl-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate (**14**)

[0095] Prepared as described for **10** above starting with **9**. Yield: 51%, white crystalline powder. Mp 216-217 °C.

[0096] ^1H NMR (CDCl_3): δ 1.08 (3H, s, H-18), 1.46 (3H, d, CH_3 -16), 1.55 (3H, s, H-19), 2.50 (1H, m, H-8), 3.72 (3H, s, CH_3O), 4.44 (1H, m, H_α -11), 5.38 (1H, dddd, H_β -6), 5.92 (1H, s, CHCl_2), 6.38 (1H, dd, H-2), 6.45 (1H, m, H-4), 7.12 (1H, dd, H-1). ^{13}C NMR (CDCl_3): δ 17.2 (18), 20.0 (CH_3 -16), 23.1 (19), 32.6 (8), 33.9 (7), 34.9 (15), 37.1 (12), 43.0 (14), 45.5 (16), 47.7 (13), 47.9 (10), 51.9 (CH_3O), 64.3 (CHCl_2), 71.8 (11), 86.3 (6), 92.5 (17), 98.6 (9), 121.3 (4), 130.4 (2), 150.2 (1), 161.0 (5), 163.3 ($\text{OC}=\text{O}$), 171.7 (20), 185.4 (3).

EXAMPLE 13: Ethyl 6 α ,9 α -difluoro-17 α -dichloroacetox-16 β -methyl-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate (**15**)

[0097] Prepared as described for **11** above starting with **9**. The crude product was recrystallized from ethyl acetate/*n*-hexane. Yield: 57%, white crystalline powder. Mp 155-156 °C.

[0098] ^1H NMR (CDCl_3): δ 1.09 (3H, s, H-18), 1.27 (3H, t, $\text{CH}_3\text{CH}_2\text{O}$), 1.47 (3H, d, CH_3 -16), 1.55 (3H, s, H-19), 2.50 (1H, m, H-8), 4.19 (2H, q, $\text{CH}_3\text{CH}_2\text{O}$), 4.45 (1H, m, H_α -11), 5.91 (1H, s, CHCl_2), 5.41 (1H, dddd, H_β -6), 6.38 (1H, dd, H-2), 6.45

(1H, m, H-4), 7.11 (1H, dd, H-1). ¹³C NMR (CDCl₃): δ 14.1 (CH₃CH₂O), 17.2 (18), 20.0 (CH₃-16), 23.1 (19), 32.6 (8), 33.9 (7), 34.8 (15), 37.2 (12), 43.0 (14), 45.5 (16), 46.7 (13), 48.0 (10), 61.2 (CH₃CH₂O), 64.3 (CHCl₂), 71.8 (11), 86.5 (6), 92.3 (17), 98.7 (9), 121.3 (4), 130.3 (2), 150.2 (1), 161.0 (5), 163.2 (OC=O), 167.1 (20), 185.4 (3).

EXAMPLE 14: Chloromethyl 6α,9α-difluoro-17α-dichloroacetoxy-16β-methyl-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate (**16**)

[0099] Prepared as described for **12** above starting with **9** using a 4 molar excess of chloriodomethane instead of methyl iodide. The reaction mixture was stirred for 26.5 hours, then diluted with water. The crude product was isolated by extraction with diethyl ether and purified by column chromatography on silica gel eluting dichloromethane – methanol 95:5. The obtained product was recrystallized from ethyl acetate/*n*-hexane. Yield: 28%, white crystalline powder. Mp 142-144°C.

[00100] ¹H NMR (CDCl₃): δ 1.13 (3H, s, H-18), 1.49 (3H, d, CH₃-16), 1.55 (3H, s, H-19), 2.51 (1H, m, H-8), 4.46 (1H, m, H_α-11), 5.41 (1H, dddd, H_β-6), 5.50/5.97 (1H + 1H, d, CH₂Cl), 5.93 (1H, s, CHCl₂), 6.39 (1H, dd, H-2), 6.45 (1H, m, H-4), 7.11 (1H, dd, H-1).

EXAMPLE 15: 2-Hydroxyethyl 6α,9α-difluoro-17α-dichloroacetoxy-16β-methyl-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate (**17**)

[00101] Prepared as described for **13** above starting with **9** using a 6 molar excess of 2-bromoethanol instead of methyl iodide and a catalytic amount of potassium iodide. After stirring of the reaction mixture for 5.5 hours and dilution with water the crude product was isolated by extraction with diethyl ether and purified by column chromatography on silica gel eluting dichloromethane – methanol 95:5. The product was then recrystallized from ethyl acetate/*n*-hexane. Yield: 45%, white crystalline powder. Mp 205-207 °C.

[00102] ^1H NMR (CDCl_3 + 2 drops of methanol- d_4): δ 1.05 (3H, s, H-18), 1.44 (3H, d, CH_3 -16), 1.53 (3H, s, H-19), 2.48 (1H, m, H-8), 3.75 (2H, m, $\text{OCH}_2\text{CH}_2\text{OH}$), 3.98/4.44 (1H + 1H, m, $\text{OCH}_2\text{CH}_2\text{OH}$), 4.31 (1H, m, H_{α} -11), 5.39 (1H, dddd, H_{β} -6), 5.93 (1H, s, CHCl_2), 6.34 (1H, dd, H-2), 6.40 (1H, m, H-4), 7.18 (1H, dd, H-1).

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EXAMPLE 16: Fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrost-1,4-diene-17 β -carboxylate (**21**)

[00103] Step 1: Preparation of 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrost-1,4-diene-17 β -carboxylic acid (**20**)

10 **[00104]** 11 β ,17 α -Dihydroxy-6 α ,9 α -difluoro-16 α -methyl-3-oxoandrost-1,4-diene-17 β -carboxylic acid **19** (2.55 g, 6.5 mmol) was added successively to a solution of KHCO_3 (7.0 g) in water (100 ml). To this stirred solution dichloroacetylchloride (3.12 ml, 32.48 mmol) dissolved in dichloromethane (75 ml) was added dropwise at r.t. over 2 h. Stirring was continued 1 h more. Then the
15 reaction mixture was acidified with 1 N HCl and the phases were separated. The organic phase was washed with water, dried and evaporated to give one part of the title product (1.06 g). The watery phase was extracted with ethyl acetate and this extract gave after drying and evaporation another fraction (1.73 g) of the title product. The united product was recrystallized from methanol (25 ml) to give the
20 pure product **20** (2.21 g, 67%). Mp: 206 °C (dec), $[\alpha]_D$: +8.9° (c=0.5, EtOH).

[00105] ^1H NMR (500 MHz, DMSO): δ 0.89 (3H, d, CH_3 -16), 1.04 (3H, s, H-18), 1.49 (3H, s, H-19), 3.23 (1H, m, H_{β} -16), 4.16 (1H, m, H_{α} -11), 5.47 (1H, d, HOCH_{α} -11), 5.62 (1H, dddd, H_{β} -6), 6.11 (1H, d, H-4), 6.28 (1H, dd, H-2), 6.98 (1H, s, CHCl_2), 7.24 (1H, d, H-1), 13.02 (1H, COOH).

25 **[00106]** Anal. Calcd. For $\text{C}_{23}\text{H}_{26}\text{Cl}_2\text{F}_2\text{O}_6$ (507.35): C 54.44; H 5.17; Found: C 53.72; H 5.02.

[00107] Step 2: The carboxylic acid derivative **20** of the previous Step 1 (0.51 g, 1.0 mmol) was dissolved in DMF (7 ml), KHCO_3 (0.15 g, 1.5 mmol) was added and after 0.5 h stirring at 0° C bromofluoromethane gas was introduced by a

capillary tube for 1 min. The absorbed amount of gas was ca. 1.7 g. After 2 h stirring at 0° C the mixture was left to stand overnight. To reach full conversion another amount of gas (ca. 0.5 g) was then absorbed and stirring was continued 4 h more. The reaction mixture was poured onto ice water and the separated product (0.5 g) was isolated by filtration. The crude title product was recrystallized from methanol (50 ml) using charcoal and the solution was concentrated to a volume of ca. 10 ml. Yield: 0.34 g of **21**, mp: 241 °C; $[\alpha]_D$: +7.3° (c=0.5, ethyl acetate).

[00108] ^1H NMR (500 MHz, DMSO): δ 0.91 (3H, d, CH₃-16), 1.04 (3H, s, H-18), 1.49 (3H, s, H -19), 3.30 (1H, m, H _{β} -16), 4.19 (1H, m, H _{α} -11), 5.63 (1H, dddd, H _{β} -6), 5.58 (1H, d, HO-CH _{α} -11), 5.75/5.85 (1H+1H, dd, OCH₂F), 6.12 (1H, d, H-4), 6.29 (1H, dd, H-2), 7.06 (1H, s, CHCl₂), 7.25 (1H, d, H-1). ^{13}C NMR (125 MHz, DMSO): δ 15.4 (CH₃-16), 16.0 (18), 22.6 (19), 64.6 (CHCl₂), 69.9 (11), 86.7 (6), 93.7 (17), 94.5 (OCH₂F), 99.8 (9), 119.4 (4), 129.1 (2), 151.6 (1), 162.6 (5), 163.3 (O=CCHCl₂), 166.5 (O=CO), 184.3 (3). Ei-MS: $[\text{M}]^+$: 538/540/542 (3/2/1); m/z: 140 (100), 44 (92), 139 (90), 134 (88); Ci-MS: $[\text{M}+\text{H}]^+$: 539/541/543 (100/71/11).

EXAMPLE 17: Chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate (**22**)

[00109] 17 α -Dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylic acid **20** (1.0 g, 2.0 mmol, Example 5, Step 1) was dissolved in DMF (15.0 ml) and while stirring KHCO₃ (0.30 g, 3.0 mmol) was added. After 0.5 h stirring chloriodomethane (0.58 ml, 8.0 mmol) was added and stirring at r.t. was continued overnight. The mixture was then poured onto ice water and the crude product was isolated by filtration. Recrystallization from ethanol by using charcoal for decolorization gave 0.42 g of the title product **22**, mp: 226 °C, $[\alpha]_D$: +15.1° (c=0.5, ethyl acetate).

[00110] ^1H NMR (500 MHz, DMSO): δ 0.91 (3H, d, CH₃-16), 1.05 (3H, s, H-18), 1.49 (3H, s, H -19), 3.29 (1H, m, H _{β} -16), 4.19 (1H, m, H _{α} -11), 5.63 (1H, dddd, H _{β} -6), 5.63 (1H, dddd, H _{β} -6), 5.63 (1H, d, HOCH _{α} -11), 5.87/5.96 (1H+1H, d, OCH₂F), 6.11 (1H, d, H-4), 6.29 (1H, dd, H-2), 7.06 (1H, s, CHCl₂), 7.24 (1H, d, H-

1). Ei-MS: $[M]^+$: 554/556/558 (3/3/1); m/z : 140 (100), 139 (94), 134 (77); Ci-MS: $[M+H]^+$: 555/557/559 (96/100/36).

EXAMPLE 18: S-Fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-
5 16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (**25**)

[00111] Step 1: Preparation of 17 α -Dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioic acid (**24**)

[00112] 11 β ,17 α -Dihydroxy-6 α ,9 α -difluoro-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioic acid **23** (7.6 g, 18.4 mmol) was transformed into the 17 α -
10 dichloroacetate derivative according to the procedure as described for **20**, Step 1. However, the oily residue that was produced by the evaporation of the last ethyl acetate solution was triturated with diisopropyl ether to give the solid title compound **24** (9.40 g, 97%). This crude substance was purified by recrystallization from chloroform. Yield: 6.67 g (69%), mp: 170 °(dec).

15 **[00113]** Anal. Calcd. For C₂₃H₂₆Cl₂F₂O₅S (523.42): S 6.13; Found: S 6.19.

[00114] Step 2: The carbothioic acid derivative (1.05 g, 2.0 mmol) of the previous Step 1, was dissolved in ethyl acetate (12 ml), water (3.5 ml), triethylamine (0.31 ml, 2.2 mmol) and benzyltributylammonium chloride (90 mg) was added and the stirred heterogenous mixture was cooled to 0 °C, then bromofluoromethane gas
20 was introduced by a capillary tube for c. 1 min. The absorbed amount was ca. 1.5 g. Stirring was continued and temperature was let to warm to r.t. during 2 h. TLC investigation (silicagel, eluent: c.hexane-ethyl acetate-acetic acid (5:4:1)) showed complete conversion. The mixture was diluted with ethyl acetate (10 ml), the phases were separated and the organic phase was washed successively with 0.5 N
25 HCl, saturated NaHCO₃ solution and brine. The solution was then filtered through a pad of neutral alumina and evaporated to give a solid. Column chromatography on silicagel by using an eluent: N.hexane-ethyl acetate (1:1) gave the title compound **25** (0.80 g, 72%). A sample was recrystallized from ethanol, mp: 267 °C, $[\alpha]_D$: +40.0° (c=0.3, ethanol).

[00115] ^1H NMR (500 MHz, pyridine- d_5): δ 1.16 (3H, d, CH_3 -16), 1.44 (3H, s, H-18), 1.73 (3H, s, H -19), 3.61 (1H, m, H_β -16), 4.68 (1H, m, H_α -11), 5.68 (1H, dddd, H_β -6), 6.07/6.12 (1H+1H, d, OCH_2F), 6.60 (1H, dd, H-2), 6.80 (1H, d, H-4), 7.26 (1H, d, H-1), 7.44 (1H, s, CHCl_2). Ei-MS: $[\text{M}]^+$: 554/556 (2/1); m/z: 139 (100), 333 (89), 140 (73); Ci-MS: $[\text{M}+\text{H}]^+$: 555/557 (100/69). Anal. Calcd. For $\text{C}_{24}\text{H}_{27}\text{Cl}_2\text{F}_3\text{O}_5\text{S}$ (555.44): S 5.77; Found: S 5.75.

EXAMPLE 19: S-Chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (**26**)

[00116] 17 α -Dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioic acid **24** (1.04 g, 2.0 mmol, Step 1) was dissolved in DMF (12 ml) and the solution was cooled to 0° C. NaHCO_3 (0.26 g, 3.0 mmol) was added and after 10 min stirring chloriodomethane (0.22 ml, 3.0 mmol) was added dropwise. The temperature was raised over 1 h to r.t. and stirring was continued for 3 h. The mixture was then poured onto water (240 ml) and the product was extracted with ethyl acetate. The extract was washed with brine, dried and evaporated to dryness. The partially solid residue was purified by column chromatography on silicagel with the eluent chloroform-ethyl acetate (4:1). The main fraction (0.81 g) was triturated with hot methanol and after cooling pure title compound **26** (0.35 g) was collected. Mp: 272 °C, $[\alpha]_D$: +59.8° (c=0.5, ethanol).

[00117] ^1H NMR (500 MHz, DMSO): δ 0.94 (3H, d, CH_3 -16), 1.05 (3H, s, H-18), 1.48 (3H, s, H -19), 3.35 (1H, m, H_β -16), 4.20 (1H, m, H_α -11), 5.19/5.22 (1H+1H, d, OCH_2Cl), 5.60 (1H, d, HOCH_α -11), 5.63 (1H, dddd, H_β -6), 6.11 (1H, d, H-4), 6.28 (1H, dd, H-2), 7.06 (1H, s, CHCl_2), 7.24 (1H, d, H-1). Ei-MS: $[\text{M}]^+$: 577/572 (0.7/0.7); m/z: 333 (100), 139 (62); Ci-MS: $[\text{M}+\text{H}]^+$: 571/573/575 (94/100/33); m/z: 489/491 (74/56).

PHARMACOLOGICAL STUDIES

[00118] *Animals*

[00119] Male Brown Norway rats, weighing 140 to 170 g at the beginning of the experiments, were purchased from Charles River Hungary LTD (Budapest, Hungary). Upon arrival, the animals were inspected for overt signs of ill health then quarantined for a week before use. They were kept in standard animal cages (five to a cage) on a constant 12-h light/dark cycle. The animals had free access to tap water and standard laboratory chow, also purchased from Charles River. Animals were treated according to the European Communities Council Directive (86/609/EEC), and all the experimental procedures were approved by the Institutional Animal Care Committee (Institute for Drug Research, Budapest, Hungary).

[00120] *Sensitization, Treatment, and Challenge of Animals*

[00121] Animals were randomly assigned into various treatment groups (4-5 animals/group), weighed, and numbered. They were sensitized with ovalbumin precipitated on alum (25 µg of ovalbumin + 20 mg of Al(OH)₃ in 0.5 ml of saline/animal) administered subcutaneously on the back on days 0, 14, and 21. Simultaneously, on each occasion, 0.25 ml (10⁹ cells/ml) of heat-inactivated *Bordetella pertussis* vaccine was injected intraperitoneally. On the 28th day, different doses (0.1, 1.0, 10.0, and 100.0 µg/kg) of the glucocorticoids tested were administered intratracheally 2 h before the challenge. Intratracheal drug application was performed under short-lasting general anesthesia plus muscle relaxation produced by intramuscularly given xylazine (10 mg/kg) and ketamine (10 mg/kg). Animals were kept in supine position, and a special cannula (Vasocan Braunüle) was led through the larynx and was advanced into the midportion of the trachea. Powdered solid substance (10 mg) [vehicle (lactose monohydrate) and active drug] was puffed into the lung by a 5-ml syringe. Control animals were treated with vehicle only. Antigen challenge was carried out by exposing the animals for 1 h to vaporized 1% aqueous solution (saline) of ovalbumin administered via the “nose

only inhalation system” (Nose Only Exposure System for Rodents; Technical and Scientific Equipment GmbH, Bad Homburg Germany).

[00122] *Bronchoalveolar Lavage*

[00123] Forty-eight hours after challenge, animals were sacrificed by an overdose of urethane, and then bronchoalveolar lavage fluid (BALF) was obtained. After a tracheotomy, a polyethylene catheter was inserted and advanced to the bifurcation of the trachea. The airways were then washed by 3 ml of Hank’s balanced salt solution prewarmed to 37 °C. Washing was repeated three times with the same volume of buffer, and the washouts were collected into a centrifuge tube containing sodium citrate. Total eosinophil number was counted in the collected BALF after phloxine B staining (Unopette kit).

[00124] *Measurement of Airway Hyperreactivity Ex Vivo*

[00125] Tracheae were removed from the animals, and after careful cleaning from the adhesive tissues, they were cut into single rings. Ring preparations were suspended into organ bath chambers containing Krebs’ buffer and were maintained at 37 °C with continuous aeration. For the recording of isometric tension changes, rings were placed under 1.0 g of tension, and after an equilibration period of 30 min, cumulative concentration response to acetylcholine was determined. Maximal response of control (sensitized, unchallenged, and nontreated) tracheal rings was obtained at 10^{-3} M acetylcholine. The magnitude of this response was defined as 100%. All other contractions were expressed as a percentage and related to the control response. Concentrations of acetylcholine necessary to cause contraction equal to 50% to that of the control were determined for each preparation using linear regression. Two to three rings were investigated from each animal.

[00126] *Histochemistry*

[00127] Lung specimens of all lobules from each animal were collected after the bronchoalveolar lavage. Samples were fixed in phosphate-buffered 8% formalin for 2 weeks, and then were routinely processed for histochemistry. Thick sections (5 µm) were cut and mounted on surface-treated slides. Perivascular and peribronchial eosinophilia were determined on modified May-Grünwald-Giemsa-

stained sections, by counting all eosinophils within visual fields in all peribronchial and perivascular lung tissue at a magnification of 630X. Perivascular edematous areas were determined on periodic acid-Schiff-stained (PAS) specimens that were counterstained with hematoxylin. Fifty randomly chosen microvessels of each experimental group were digitally exposed (Zeiss Axiocam; Axiovert 200 system) at a magnification of 400X. Measurement of the area of perivascular edema was Performed by Zeiss Axiovision 3.1 software (Carl Zeiss Vision GmbH, Jena, Germany). Extension of the perivascular edema is expressed as a percentage of the area of the respective microvessel. Mucus production and goblet cell hyperplasia were determined on similarly prepared (PAS + hematoxylin) lung tissue sections counting all epithelial cells of each airway segment in the whole preparations at a magnification of 400X. Changes in the number of mucus producing cells are expressed as the ratio of PAS positive goblet cells to all epithelial cells counted in all lobules of tissue sections.

[00128] *Assay for cytokines*

[00129] Commercially available human cytokine ELISA sets were used. TNF- α and GM-CSF sets were purchased from BD Pharmingen, San Diego, CA, USA) and the IL-1 β set was obtained from R&D Systems (Minneapolis, MN, USA). ELISA was performed according to the manufacturer's protocol. Cell-free supernatants were tested in duplicate. Detection limits were 7.8 pg/ml for TNF- α , 4.7 pg/ml for GM-CSF, and 3.9 pg/ml for IL-1 β . Results were expressed as the mean percentage of inhibition. IC₅₀ values for test compounds were calculated by linear regression.

[00130] *IL-1 β production of stimulated THP.1 cells*

[00131] THP.1 cells (human monocytic cell line: American Type Culture Collection, Rockville, MD, USA) were maintained in RPMI-1640 medium, supplemented with 10% FCS, 5 x 10⁻⁵ M 2-merkapto-ethanol, 2 mM glutamine and antibiotics, and were split in every 3rd days. To examine the effect of test compounds 2 x 10⁶ cells/well (24 well plates in 1 ml/well volume) were stimulated with 1 μ g/ml LPS and 25 μ g/ml silica for IL-1 β production as described previously (Németh et al. 1995). The test compounds were dissolved in RPMI-1640 medium

or the medium containing 0.01% DMSO. Two parallel cell cultures per treatment groups were run in three independent experiments. IL-1 β levels in cell-free supernatants were determined by ELISA.

[00132] *TNF- α production of lipopolysaccharide-stimulated human blood*

5 **[00133]** Peripheral blood from healthy donors was collected aseptically into sterile heparinized (Vacutainer™) tubes. Whole blood samples from each individual were parallel used both undiluted and after 5-fold dilution with RPMI-1640 medium in every experiment. Blood samples were distributed into 24-well plates and incubated with serial concentrations of the test compounds and 1 μ g/ml
10 lipopolysaccharide for 24 h at 37 °C in a CO₂ thermostat. Controls were treated with lipopolysaccharide and the vehicle (PBS or 0.01% dimethyl sulfoxide in PBS). After incubation, cell-free supernatants were separated by centrifugation (1000 g for 10 minutes) and stored at -20 °C until determination of the amount of TNF- α . Test compounds were examined in blood samples from five different individuals. Two
15 parallel cultures per treatments were run.

[00134] *Preincubation of the experimental compounds with serum and measurement of their effect on TNF- α production of lipopolysaccharides-stimulated human peripheral blood mononuclear cells*

[00135] Mononuclear cells from peripheral blood of healthy donors were
20 isolated on Ficoll-gradient. One million cells in 0.9 ml of RPMI 1640 medium were distributed into 24-well plates and serial concentrations of the test compounds, made in fresh human serum either instantly or 18 h previously, were added (0.05 ml) together with the lipopolysaccharide (0.05 ml; 1 μ g/ml final concentration). Preincubation of the compounds with serum was carried out at 37 °C. Processing
25 of the cultures was done as described above.

[00136] *ED₅₀ calculation, statistical evaluation*

[00137] ED₅₀ values were calculated with GraphPad Prism software (GraphPad Software, Inc., San Diego CA, USA). Statistical analysis between groups was done with Mann-Whitney *U* test or with Student's *t* test; differences between treatments
30 (e.g., etiprednol dicloacetate versus budesonide) was analyzed by two-way ANOVA.

All the calculations were done with a Statistica for Windows software version 5.1 (StatSoft Inc., Tulsa, OK, USA).

[00138] *Proliferation of lectin-stimulated peripheral mononuclear cells*

[00139] Mononuclear cells from heparinized peripheral blood of healthy donors were isolated on suitable gradient (Optiprep solution, 1.077 g/ml). Serial dilutions of the test compounds (ranging from 2×10^{-5} to 2×10^{-8} M) were made in 100 μ l of medium per well of sterile round-bottomed 96-well microtiter plate. Control wells contained culture medium only. 100 μ l of cell suspension (10^6 cells/ml), containing concanavalin A (2 μ g/ml) was added to each well. Proliferation background control cell suspension did not contain the lectin. All cultures were done in triplicate. Microtiter plates were incubated for 72 h at 37 °C, in 5% CO₂ containing humidified atmosphere. For the last 18 h of incubation, [³H]thymidine was added to the cells cultures, at 0.1 μ Ci/well final concentration. At the end of the incubation, cells were harvested to glass microfiber filter (Whatman G/F) and associated radioactivity was determined by liquid scintillation.

[00140] *Stability of etiprednol dicloacetate in the presence of human plasma*

[00141] Etiprednol dicloacetate (BNP-166) was added to freshly prepared human plasma of healthy donors at a concentration of 5 ng/ml, and were incubated at 37 °C for different intervals. After incubation the amount of the original compound (ethyl-17 α -dichloroacetoxy-11 β -hydroxyandost-1,4-diene-3-one-17 β -carboxylate), and one of its main metabolite, M-OH (17 α ,11 β -dihydroxyandost-1,4-diene-3-one-17 β -carboxylate) were determined using an HPLC/MS/MS method. In brief: Fluocinolone acetonide served as internal standard (20ng/ml), samples were extracted with a liquid-liquid extraction on Extrelut[®] columns, and were separated on a Purospher STAR 30 x 2 mm (3 μ m) reversed phase column at a flow rate of 0.3 ml/min, using a linear gradient with a mobile phase system containing acetonitrile, water and acetic acid. Determination were performed on a triple quadrupole mass spectrometer (Perkin-Elmer SCIEX API 2000) supplied with an electrospray interface operated in the positive ionization mode. The multiple ion monitoring, parent $\rightarrow$ daughter ion transitions of 485.2 $\rightarrow$ 265.2, 375.2 $\rightarrow$ 265.2 and 495.2 $\rightarrow$

337.2 were used for the quantification of etiprednol dicloacetate, its M–OH metabolite and for the internal standard respectively. Results are expressed as peak areas normalized to the internal control. Stability of the selected ED analogs (**10**, **11**, **13**, **17**, **21**, **25**) were determined as described above for ED (**3**).

- 5 Compounds **13**, **17**, **21** and **25** were particularly stable. It is also noted that compounds **13** and **17** are more potent but softer than the corresponding 17β-C(O)CH₂CH₃ compounds **11** and **15**, respectively. See Table 1 above.

- [00142] The compounds of formula (I) or (III) can be combined with suitable non-toxic pharmaceutically acceptable carriers to provide pharmaceutical compositions for use in the treatment of topical or other localized inflammation. Obviously, in view of their lack of systemic activity, the compounds of formula (I) and (III) are not intended for treatment of conditions where systemic adrenocortical therapy is indicated, e.g., adrenocortical insufficiency. As examples of inflammatory conditions which can be treated with pharmaceutical compositions comprising at least one compound of formula (I) or (III) and one or more pharmaceutical carriers, the following can be mentioned: dermatological disorders such as atopic dermatitis, acne, psoriasis or contact dermatitis; allergic states such as bronchial asthma; respiratory diseases such as COPD; ophthalmic and optic diseases involving acute and chronic allergic and inflammatory reactions (for example, ophthalmic inflammatory conditions such as blepharitis, conjunctivitis, episcleritis, scleritis, keratitis, anterior uveitis and sympathetic ophthalmia); inflammations of the mouth, gums and/or throat, such as gingivitis or oral aphtha; inflammations of the nasal mucosa, for example, those caused by allergies; inflammations of the upper and lower intestines, such as ulcerative colitis; inflammations associated with arthritis; and anorectal inflammation, pruritus and pain associated with hemorrhoids, proctitis, cryptitis, fissures, postoperative pain and pruritus ani. Such compositions can also be applied locally as a prophylactic measure against the inflammation and tissue rejection which arise in connection with transplants.

[00143] Obviously, the choice of carrier(s) and dosage forms will vary with the particular condition for which the composition is to be administered and the route of administration.

[00144] Examples of various types of preparations for topical/local administration include ointments, lotions, creams, powders, drops (e.g., eye or ear or nose drops), sprays (e.g., for the nose or throat), suppositories, retention enemas, chewable or suckable tablets or pellets (e.g., for the treatment of aphthous ulcers) and aerosols. Ointments and creams can, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or glycols. Such base can thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a glycolic solvent such as propylene glycol or 1,3-butanediol. Thickening agents which can be used according to the nature of the base include soft paraffin, aluminum stearate, cetostearyl alcohol, polyethylene glycols, woolfat, hydrogenated lanolin and beeswax and/or glyceryl monostearate and/or non-ionic emulsifying agents.

[00145] The solubility of the steroid in the ointment or cream can be enhanced by incorporation of an aromatic alcohol such as benzyl alcohol, phenylethyl alcohol or phenoxyethyl alcohol.

[00146] Lotions can be formulated with an aqueous or oily base and will in general also include one or more of the following, namely, emulsifying agents, dispersing agents, suspending agents, thickening agents, solvents, coloring agents and perfumes. Powders can be formed with the aid of any suitable powder base e.g., talc, lactose or starch. Drops can be formulated with an aqueous base also comprising one or more dispersing agents, suspending agents or solubilizing agents, etc. Spray compositions can, for example, be formulated as aerosols with the use of a suitable propellant, e.g., dichlorodifluoromethane or trichlorofluoromethane.

[00147] Nebulized or powdered formulations can be prepared for oral inhalation in the treatment of asthma, COPD or the like, as is well-known in the art. Solutions and suspensions can be prepared for oral or rectal administration for use in the

treatment of inflammations of the intestines, for example, as described in more detail in the examples hereinafter. Parenteral/injectable formulations can be prepared for direct injection into the joints in the treatment of arthritis in accord with methods well-known to those skilled in the art of parenteral formulations.

5 **[00148]** The proportion of active ingredient in the compositions will vary with the precise compound used, the type of formulation prepared and the particular condition for which the composition is to be administered. The formulation will generally contain from about 0.0001 to about 5.0% by weight of the compound of formula (I) or (III). Topical preparations will generally contain 0.0001 to 2.5%,
10 preferably 0.01 to 0.5%, and will be administered once daily, or as needed. Also, generally speaking, the compounds of formula (I) or (III) can be incorporated into topical and other local compositions formulated substantially as are such presently available types of compositions containing known glucocorticosteroids, at approximately the same (or in the case of the most potent compounds of the
15 invention, at proportionately lower) dosage levels as compared to known highly active agents such as methyl prednisolone acetate and beclomethasone dipropionate or at considerably lower dosage levels as compared to less active known agents such as hydrocortisone.

[00149] Thus, for example, an inhalation formulation suitable for use in the
20 treatment of asthma can be prepared as a metered-dose aerosol unit containing a representative species such as S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate or 2-hydroxyethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate, according to procedures well-known to
25 those skilled in the art of pharmaceutical formulations. Such an aerosol unit may contain a microcrystalline suspension of one of the aforementioned compounds in suitable propellants (e.g., trichlorofluoromethane and dichlorodifluoromethane), with oleic acid or other suitable dispersing agent. Each unit typically contains 1-10 milligrams of the aforesaid active ingredient, approximately 5-50 micrograms of
30 which are released at each actuation.

[00150] Another example of a pharmaceutical composition is a foam suitable for treatment of a wide variety of inflammatory anorectal disorders, to be applied anally or perianally, comprising 0.05% to 0.1% of a compound of formula (I) or (III), such as the aforementioned S-fluoromethyl or 2-hydroxyethyl compound, and 1% of a local anesthetic such as pramoxine hydrochloride, in a mucoadhesive foam base of propylene glycol, ethoxylated stearyl alcohol, polyoxyethylene-10-stearyl ether, cetyl alcohol, methyl paraben, propyl paraben, triethanolamine, and water, with inert propellants.

[00151] Yet another pharmaceutical formulation is a solution or suspension suitable for use as a retention enema, a single dose of which typically contains 20-40 milligrams of a compound of formula (I) or (III) such as the aforementioned S-fluoromethyl or 2-hydroxyethyl compound, together with sodium chloride, polysorbate 80 and from 1 to 6 ounces of water (the water being added shortly before use). The suspension can be administered as a retention enema or by continuous drip several times weekly in the treatment of ulcerative colitis.

[00152] Other pharmaceutical formulations according to the application are illustrated in the Example which follows.

FORMULATION EXAMPLE

<u>Ointment</u>		
Compound of formula (I) or (III), e.g. S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro- 11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β - carbothioate or 2-hydroxyethyl 17 α -dichloroacetoxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta- 1,4-diene-17 β -carboxylate	0.2%	w/w
Liquid paraffin	10.0%	w/w
White soft paraffin	89.8%	w/w

<u>Aphthous Ulcer Pellet</u>		
Compound of formula (I) or (III), as above	0.25	mg
Lactose	69.90	mg
Acacia	3.00	mg
Magnesium stearate	0.75	mg
<u>Retention Enema</u>		
Compound of formula (I) or (III), as above	0.001%	w/v
Tween 80	0.05%	w/v
Ethanol	0.015%	w/v
Propylparaben	0.02%	w/v
Methylparaben	0.08%	w/v
Distilled water	q.s. 100 volumes	
<u>Eye Drops</u>		
Compound of formula (I) or (III), as above	0.1%	w/v
Tween 80	2.5%	w/v
Ethanol	0.75%	w/v
Benzalkonium chloride	0.02%	w/v
Phenyl ethanol	0.25%	w/v
Sodium chloride	0.60%	w/v
Water for injection	q.s. 100 volumes	

[00153] Another example of a suitable nasal spray for treating seasonal or perennial allergic and non-allergic rhinitis is formulated analogously to FLONASE® nasal spray, 50 mcg. Fluticasone propionate, the active component of FLONASE® nasal spray, is replaced in the formulation with a representative compound of formula (I) or (III) herein, preferably S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -

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difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate or 2-hydroxyethyl 17 α -dichlororacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate. The nasal spray delivers 50 mcg of the microfine compound of formula (I) or (III) by means of a metering, atomizing spray pump. The composition also contains microcrystalline cellulose, sodium carboxymethylcellulose, dextrose, benzalkonium chloride (0.02% w/w), polysorbate 80, phenylethylalcohol (0.25% w/w) and has a pH between 5 and 7. An exemplary dosage is 200 mcg daily (two 50 mcg sprays in each nostril once daily or one 50 mcg spray in each nostril twice daily).

[00154] For oral inhalation to treat asthma, for example, the fluticasone propionate present in FLOVENT® HFA 44 mcg oral inhalation aerosol, FLOVENT® HFA 110 mcg oral inhalation aerosol or FLOVENT® HFA 220 mcg oral inhalation aerosol can be replaced with an equivalent quantity of a compound of formula (I) or (III) herein, preferably S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate or 2-hydroxyethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate. In addition to the micronized corticosteroid, each inhaler contains the propellant HFA-134a (1,1,1,2-tetrafluoroethane). In the case of the S-fluoromethyl compound, each activation of the propellant delivers the equivalent of 44, 110 or 220 mcg of the corticosteroid fluticasone propionate.

[00155] All US patents and all literature articles identified hereinabove and herebelow are incorporated by reference in their entireties and relied upon.

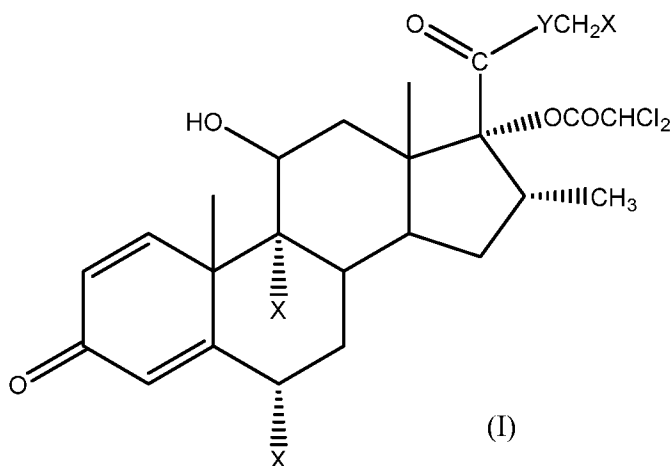
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WHAT IS CLAIMED IS:

1. A compound having the formula (I):



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wherein each X is independently F or Cl, and Y is O or S.

2. The compound of claim 1, selected from the group consisting of S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, S-chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate, and chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

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3. A pharmaceutical composition comprising an anti-inflammatory effective amount of the compound of any one of claims 1 and 2, and a non-toxic pharmaceutically acceptable carrier therefor, suitable for topical or other local application.

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4. An ophthalmic composition comprising an anti-inflammatory effective amount of the compound of any one of claims 1 and 2, and a non-toxic ophthalmically acceptable carrier therefor.

5 5. A method for alleviating inflammation in or on a warm-blooded animal exhibiting an inflammatory response, which comprises administering to said animal an anti-inflammatory effective amount of the compound of any one of claims 1 and 2 or of the composition of claim 3, wherein the administration is local when inflammatory response is localized or the administration is topical when the
10 inflammatory response is topical.

6. A method for alleviating inflammation in the eye or eyes of a warm-blooded animal exhibiting an ophthalmic inflammatory response, which comprises administering to the eye or eyes of said animal an anti-inflammatory effective amount
15 of the compound of any one of claims 1 and 2 or of the composition of claim 4.

7. A method for alleviating inflammation of the nasal mucosa in a warm-blooded animal exhibiting a nasal inflammatory response, which comprises nasally administering to said animal an anti-inflammatory effective amount of the compound
20 of any one of claims 1 and 2 or of the composition of claim 3.

8. A method for alleviating asthma or COPD in a warm-blooded animal exhibiting an inflammatory response in the lungs or bronchi, which comprises administering to said animal by oral inhalation an anti-inflammatory effective amount of the compound
25 of any one of claims 1 and 2 or of the composition of claim 3.

9. A method for alleviating inflammation of the upper or lower intestine in a warm-blooded animal exhibiting an intestinal inflammatory response, which comprises administering to said animal an anti-inflammatory effective amount of the

compound of any one of claims 1 and 2 or of the composition of claim 3, wherein the administration is rectal or oral.

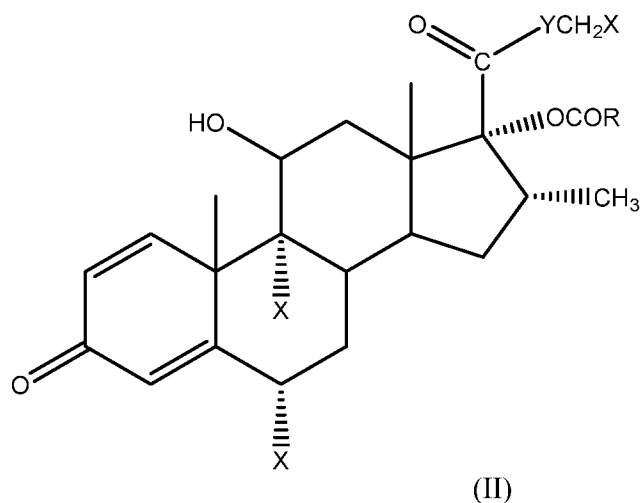
10. A method for alleviating inflammation in the ear or ears of a warm-blooded
5 animal exhibiting an otic inflammatory response, which comprises administering to the ear or ears of said animal an anti-inflammatory effective amount of the compound of any one of claims 1 and 2 or of the composition of claim 3.

11. A method for alleviating inflammation in a joint or joints of a warm-blooded
10 animal exhibiting an arthritic inflammatory response, which comprises injecting into said joint or joints an anti-inflammatory effective amount of the compound of any one of claims 1 and 2 or of the composition of claim 3.

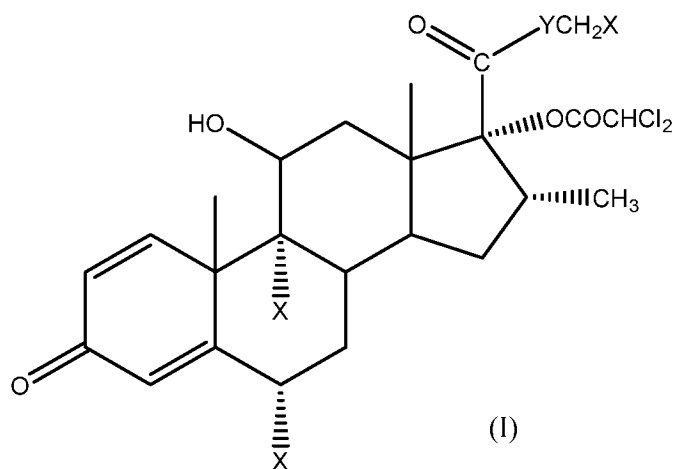
12. A method for alleviating inflammation of the skin of a warm-blooded animal
15 exhibiting a dermal inflammatory response, which comprises dermally administering to said animal an anti-inflammatory effective amount of the compound of any one of claims 1 and 2 or of the composition of claim 3.

13. A method for alleviating inflammation of the mouth, gums or throat of a warm-
20 blooded animal exhibiting an oral, gingival or throat inflammatory response, which comprises orally administering to said animal an anti-inflammatory effective amount of the compound of any one of claims 1 and 2 or of the composition of claim 3.

14. A process for softening a 17α -alkylcarbonyloxy-substituted corticosteroid
25 compound of the formula (II)



wherein each X is independently F or Cl, Y is O or S and R is C₁-C₃ alkyl, said compound of formula (II) having local or topical as well as systemic corticosteroid activity, said process comprising synthesizing the corresponding corticosteroid compound wherein the 17 α -OCOR group in formula (II) is replaced by a 17 α -dichloroacetoxy (17 α -OCOCHCl₂) group, to provide the resultant soft corticosteroid compound of formula (I)

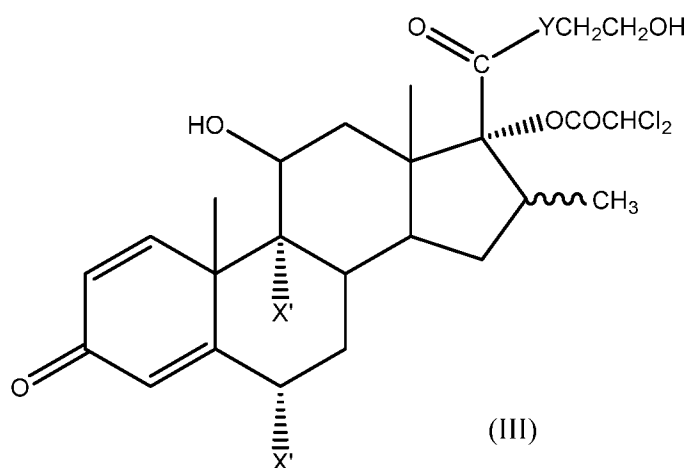


wherein each X and Y are as defined with formula (II) above, said compound of formula (I) having substantially equivalent local or topical corticosteroid activity as compared to the corresponding compound of formula (II) but having substantially

decreased systemic corticosteroid activity as compared to the corresponding compound of formula (II).

15. The process according to claim 14, wherein the resultant soft corticosteroid compound of formula (I) is selected from the group consisting of S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, S-chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate, and chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

16. A compound having the formula (III):



wherein each X' is independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S and the wavy line indicates the α - or β -configuration.

17. The compound of claim 16, selected from the group consisting of 2-hydroxyethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate and 2-hydroxyethyl 17 α -dichloroacetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

18. A pharmaceutical composition comprising an anti-inflammatory effective amount of the compound of any one of claims 16 and 17, and a non-toxic pharmaceutically acceptable carrier therefor, suitable for topical or other local application.

19. An ophthalmic composition comprising an anti-inflammatory effective amount of the compound of any one of claims 16 and 17, and a non-toxic ophthalmically acceptable carrier therefor.

10

20. A method for alleviating inflammation in or on a warm-blooded animal exhibiting an inflammatory response, which comprises administering to said animal an anti-inflammatory effective amount of the compound of any one of claims 16 and 17 or of the composition of claim 18, wherein the administration is local when the inflammatory response is localized or the administration is topical when the inflammatory response is topical.

21. A method for alleviating inflammation in the eye or eyes of a warm-blooded animal exhibiting an ophthalmic inflammatory response, which comprises administering to the eye or eyes of said animal an anti-inflammatory effective amount of the compound of any one of claims 16 and 17 or of the composition of claim 19.

22. A method for alleviating inflammation of the nasal mucosa in a warm-blooded animal exhibiting a nasal inflammatory response, which comprises nasally administering to said animal an anti-inflammatory effective amount of the compound of any one of claims 16 and 17 or of the composition of claim 18.

23. A method for alleviating asthma or COPD in a warm-blooded animal exhibiting an inflammatory response in the lungs or bronchi, which comprises administering to said animal by oral inhalation an anti-inflammatory effective amount of the compound of any one of claims 16 and 17 or of the composition of claim 18.

5

24. A method for alleviating inflammation of the upper or lower intestine in a warm-blooded animal exhibiting an intestinal inflammatory response, which comprises administering to said animal an anti-inflammatory effective amount of the compound of any one of claims 16 and 17 or of the composition of claim 18, wherein
10 the administration is rectal or oral.

25. A method for alleviating inflammation in the ear or ears of a warm-blooded animal exhibiting an otic inflammatory response, which comprises administering to the ear or ears of said animal an anti-inflammatory effective amount of the
15 compound of any one of claims 16 and 17 or of the composition of claim 18.

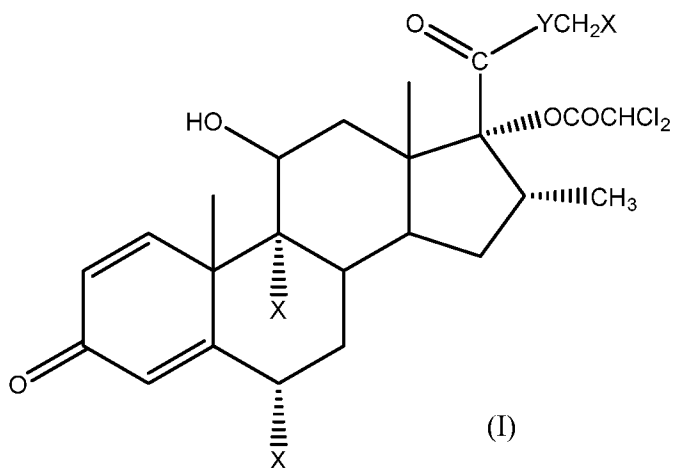
26. A method for alleviating inflammation in a joint or joints of a warm-blooded animal exhibiting an arthritic inflammatory response, which comprises injecting into said joint or joints an anti-inflammatory effective amount of the compound of any one
20 of claims 16 and 17 or of the composition of claim 18.

27. A method for alleviating inflammation of the skin of a warm-blooded animal exhibiting a dermal inflammatory response, which comprises dermally administering to said animal an anti-inflammatory effective amount of the compound of any one of
25 claims 16 and 17 or of the composition of claim 18.

28. A method for alleviating inflammation of the mouth, gums or throat of a warm-blooded animal exhibiting an oral, gingival or throat inflammatory response, which

comprises orally administering to said animal an anti-inflammatory effective amount of the compound of any one of claims 16 and 17 or of the composition of claim 18.

29. Use of a compound having the formula (I):



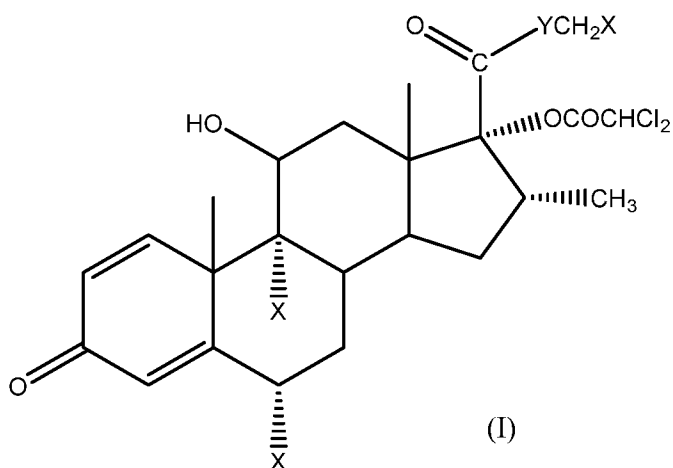
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wherein each X is independently F or Cl, and Y is O or S,

in the preparation of a pharmaceutical composition suitable for topical or other local application, the pharmaceutical composition comprising an anti-inflammatory effective amount of the compound and a non-toxic pharmaceutically acceptable carrier therefor.

10

30. Use of a compound having the formula (I):



wherein each X is independently F or Cl, and Y is O or S,

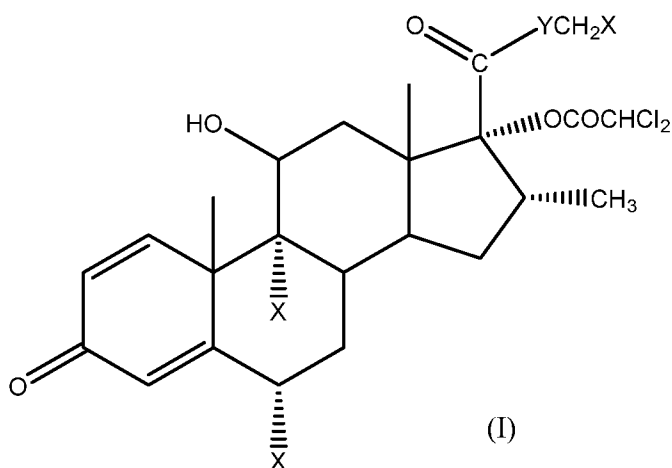
in the preparation of an ophthalmic composition comprising an anti-inflammatory effective amount of the compound and a non-toxic ophthalmically acceptable carrier therefor.

5

31. Use according to any of claims 29 and 30, wherein the compound is selected from the group consisting of S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, S-chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate, and chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

10

15 32. A pharmaceutical composition suitable for topical or other local application, the pharmaceutical composition comprising an anti-inflammatory effective amount of a compound having the formula (I):



, wherein each X is

independently F or Cl, and Y is O or S, and a non-toxic pharmaceutically acceptable carrier therefor, for use in alleviating inflammation in or on a warm-blooded animal

20

exhibiting an inflammatory response, wherein the inflammatory response is localized or topical.

33. The pharmaceutical composition according to claim 32, wherein the inflammatory response is selected from the group consisting of:

a nasal inflammatory response;

an inflammatory response in the lungs or bronchi;

an intestinal inflammatory response;

an otic inflammatory response;

an arthritic inflammatory response;

a dermal inflammatory response; and

an oral, gingival or throat inflammatory response.

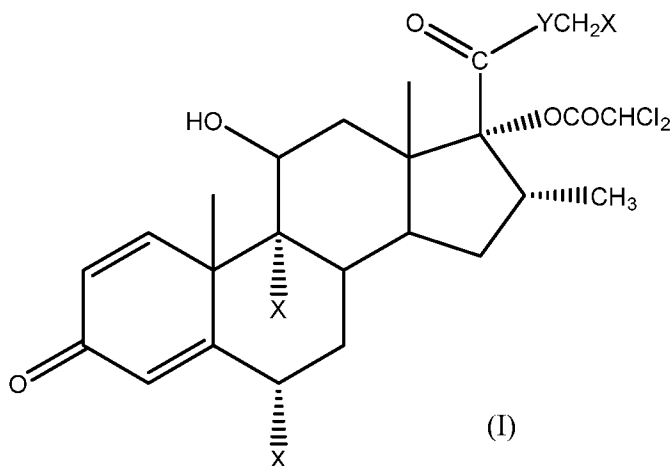
34. The pharmaceutical composition according to any of claims 32 and 33,

wherein the compound is selected from the group consisting of S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, S-chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-

16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-

17 β -carboxylate, and chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

35. An ophthalmic composition comprising an anti-inflammatory effective amount of a compound having the formula (I):



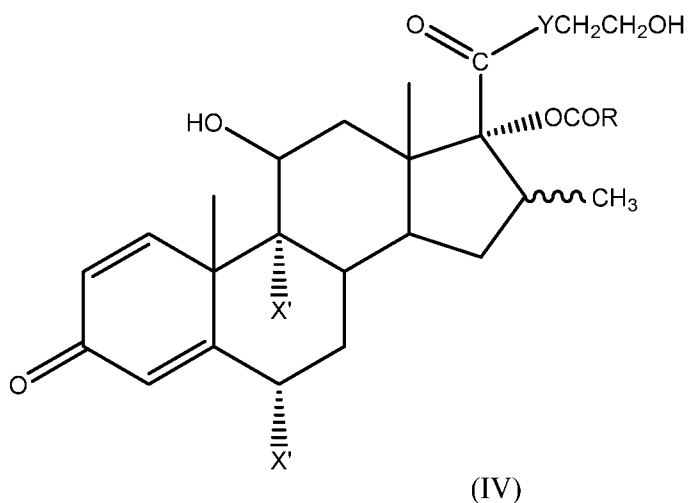
, wherein each X is

independently F or Cl, and Y is O or S, and a non-toxic ophthalmically acceptable carrier therefor, for use in alleviating inflammation in the eye or eyes of a warm-blooded animal exhibiting an ophthalmic inflammatory response.

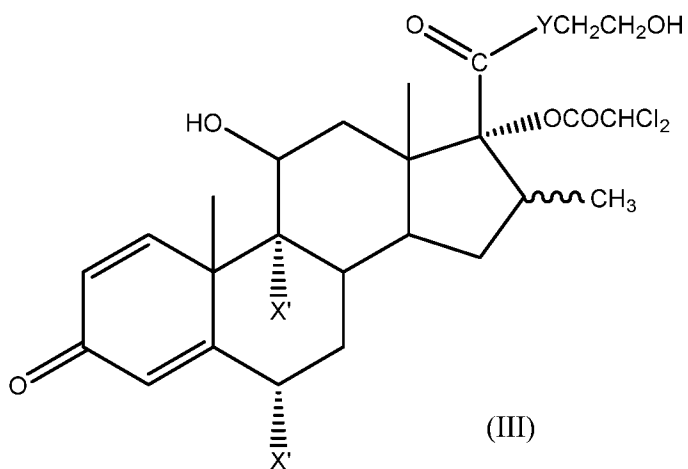
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36. The ophthalmic composition according to claim 35, wherein the compound is selected from the group consisting of S-fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, S-chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, fluoromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate, and chloromethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

15 37. Use of a 17 α -alkylcarbonyloxy-substituted corticosteroid compound of the formula (IV):



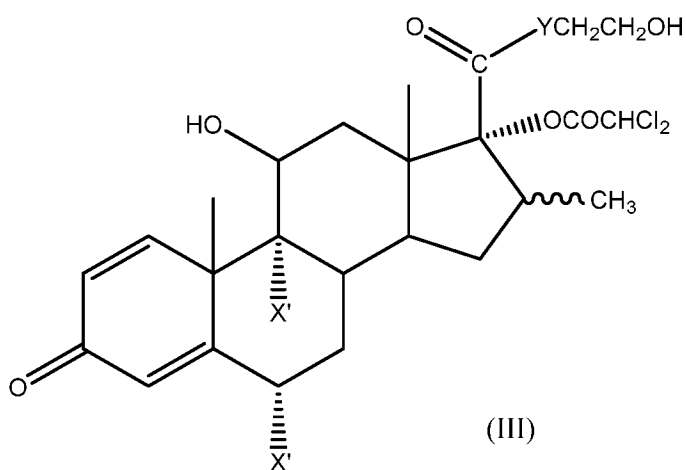
wherein each X' is independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S, R is C₁-C₃ alkyl and the wavy line indicates the α- or β-configuration; said compound of formula (IV) having local or topical as well as systemic corticosteroid activity, to produce a soft corticosteroid compound of formula (III) by replacing the 17α-OCOR group in formula (IV) with a 17α-dichloroacetoxyl (17α-OCOCHCl₂) group:



wherein each X' and Y are as defined with formula (IV) above, said compound of formula (III) having substantially equivalent local or topical corticosteroid activity as compared to the corresponding compound of formula (IV) but having substantially decreased systemic corticosteroid activity as compared to the corresponding compound of formula (IV).

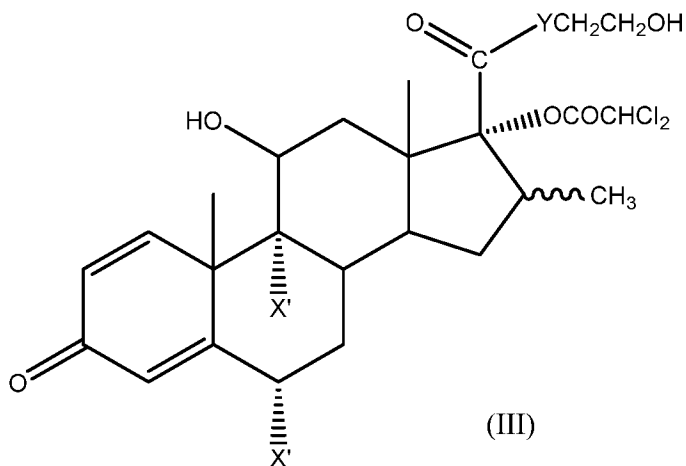
38. Use according to claim 37, wherein the soft corticosteroid compound of formula (III) is selected from the group consisting of 2-hydroxyethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate and 2-hydroxyethyl 17 α -dichloroacetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

39. Use of compound having the formula (III):



- 10 wherein each X' is independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S and the wavy line indicates the α - or β -configuration, in the preparation of a pharmaceutical composition suitable for topical or other local application, the pharmaceutical composition comprising an anti-inflammatory effective amount of the compound and a non-toxic pharmaceutically acceptable carrier therefor.
- 15

40. Use of compound having the formula (III):

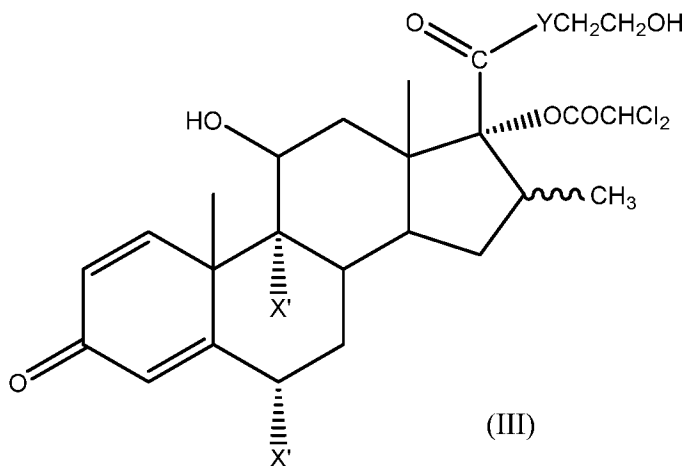


wherein each X' is independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S and the wavy line indicates the α - or β -configuration,

in the preparation of an ophthalmic composition comprising an anti-inflammatory
 5 effective amount of the compound and a non-toxic ophthalmically acceptable carrier therefor.

41. Use according to any of claims 39 and 40, wherein the compound is selected from the group consisting of 2-hydroxyethyl 17 α -dichloroacetox-6 α ,9 α -difluoro-11 β -
 10 hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate and 2-hydroxyethyl 17 α -dichloroacetox-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

42. A pharmaceutical composition suitable for topical or other local application,
 15 the pharmaceutical composition comprising an anti-inflammatory effective amount of a compound having the formula (III):



wherein each X' is independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S and the wavy line indicates the α - or β -configuration,

and a non-toxic pharmaceutically acceptable carrier therefor, for use in alleviating
 5 inflammation in or on a warm-blooded animal exhibiting an inflammatory response, wherein the inflammatory response is localized or topical.

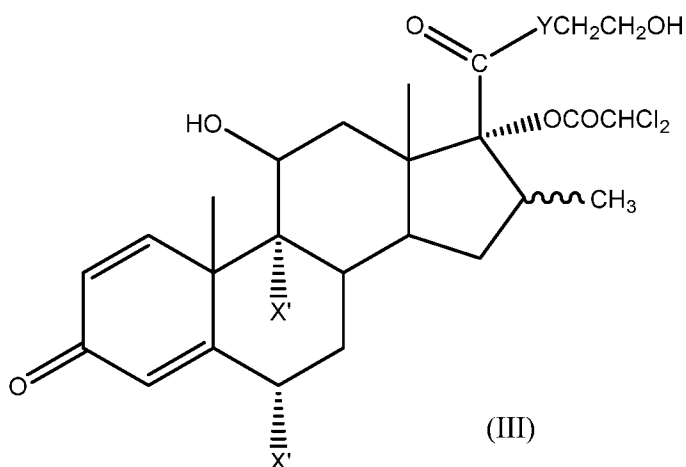
43. The pharmaceutical composition according to claim 42, wherein the inflammatory response is selected from the group consisting of

- 10 a nasal inflammatory response;
 an inflammatory response in the lungs or bronchi;
 an intestinal inflammatory response;
 an otic inflammatory response;
 an arthritic inflammatory response;
 15 a dermal inflammatory response; and
 an oral, gingival or throat inflammatory response.

44. The pharmaceutical composition according to any of claims 42 and 43, wherein compound is selected from the group consisting of 2-hydroxyethyl 17 α -

dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate and 2-hydroxyethyl 17 α -dichloroacetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

- 5 45. An ophthalmic composition comprising an anti-inflammatory effective amount of a compound having the formula (III):



wherein each X' is independently H, F or Cl provided that at least one X' is F or Cl, Y is O or S and the wavy line indicates the α - or β -configuration, and a non-toxic ophthalmically acceptable carrier therefor, for use in alleviating inflammation in the eye or eyes of a warm-blooded animal exhibiting an ophthalmic inflammatory response.

46. The ophthalmic composition according to claim 45, wherein the compound is selected from the group consisting of 2-hydroxyethyl 17 α -dichloroacetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate and 2-hydroxyethyl 17 α -dichloroacetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/037366

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/56 A61K31/569 C07J3/00 A61P29/00 ADD.		
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 C07J A61P		
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, WPI Data, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE, INSPEC		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/42214 A1 (SOFT DRUGS INC [US]) 13 November 1997 (1997-11-13) cited in the application pages 43-44, paragraph bridging; claims 1,7,15; compounds 13-19,13-67,20-3 -----	1-46
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 29 August 2018		Date of mailing of the international search report 04/09/2018
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		Authorized officer Bareyt, Sébastien

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2018/037366

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