CYCLOSPORINE A-STEROID CONJUGATES

RELATED APPLICATIONS

This application claims the benefit of United States Provisional Patent Application Serial No. 61/775,216 filed March 08, 2013, the disclosure of which is hereby incorporated in its entirety herein by reference.

FIELD OF THE INVENTION

The present invention describes Cyclosporine A/steroid hybrid analogs. These single drug entities are formed by connecting a steroid with Cyclosporine A. Upon topical application to the eye, the conjugate hybrid would undergo enzymatic and/or hydrolytic cleavage to release the individual drugs.

SUMMARY OF THE INVENTION

The steroid moiety and Cyclosporine A, of the compounds disclosed herein, are each separately connected via a covalent bond to a linker such that said compound degrades *in vivo* to yield the respective steroid and Cyclosporine A. Each bond is an amide bond or an ester bond depending on the nature of the compound. In other words, the single drug entity has one amide bond connecting to the steroid and/or one ester bond connecting to the Cyclosporine A.

Hybrid drugs may incorporate at least two drugs joined together by a linker moiety such as an ester, a carboxylate, a carbonyl, a carbonate, an amido, a carbamate, a ketone, an amino, an oxo, an ethylene glycol, an alkylene, a polyethylene glycol, which is cleaved enzymatically or hydrolytically *in vivo* to release the active drugs.

By appropriate structural design of these linkers, it may be possible to control the release of each individual drug. When the drugs are chemically combined, the resulting hybrid drug will usually have different physicochemical properties compared to the individual parent drugs, which may provide superior properties for delivery when compared to delivery of a physical mixture of the drugs. The Cyclosporine A

moiety and the steroid moiety, of the compounds disclosed herein are connected each separately via a covalent bond to a linker such that said compound degrades *in vivo* to yield the individual Cyclosporine A and steroid.

Degradation of the ester or amide bonds generally, but not necessarily, yields the corresponding acid or alcohol by hydrolysis or a related reaction. A compound which degrades *in vivo* to yield the steroid and Cyclosporine A, produces the active drugs belonging to distinct classes at some point in the metabolic process of the claimed compound. In many cases, cleavage of the first amide or ester bond will release one active, and cleavage of the second amide or ester bond will release the second active.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the present invention relates to a compound comprising a steroid and one molecule of Cyclosporine A, which are each separately connected via a covalent bond to a linker such that said compound degrades *in vivo* to yield the respective steroid independently and the respective Cyclosporine A drug, wherein each bond is an amide bond or an ester bond.

Applicants refer to the compounds of the invention as hybrid drugs, which have anti-inflammatory activity and are very useful compounds capable of producing the effect of an anti-inflammatory drug.

In another aspect, the present invention relates to a compound which is an active drug, which degrades *in vivo* into active anti-inflammatory drug(s).

The hybrid drugs of the invention provide a unique delivery of Cyclosporine A and a steroid for the treatment of ophthalmic inflammation. A single drug entity is advantageous to individual dosing of each drug because of the ability for simultaneous dosing and elimination of washout concerns when applying each drug separately.

The use of an anti-inflammatory hybrid drug is indicated where the risk of inflammation in the eye is high . The anti-inflammatory component of the composition is useful in treating inflammation associated with physical trauma to ophthalmic

tissues, inflammation associated with bacterial infections and inflammation resulting from surgical procedures. The anti-inflammatory component of the composition is also useful in post-operative inflammation where there is an increased chance of bacterial infection. Other examples of ophthalmic conditions which may be treated with the compositions of the present invention include infective conditions associated with inflammation and where the use of anti-inflammatory is acceptable. Such conditions may include, but are not limited to eye infections, endophthalmitis, conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum, corneal ulcers, anterior blepharitis, posterior blepharitis, meibomian gland dysfunction, dry eye disease, keratocojunctivitis sicca, ocular pain, ocular pain and inflammation post-ocular surgery ,bacterial conjunctivitis, anterior uveitis, post-surgical inflammation, inflammatory conditions of the palpebral, inflammatory conditions of the bulbar conjunctiva, inflammatory conditions of the cornea, inflammatory conditions of the anterior segment of the globe, allergic conjunctivitis, ocular rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, infective conjunctivitis, corneal injury from chemical radiation, , corneal injury from thermal burns, penetration of foreign bodies, allergy, and combinations thereof.

Further, the compounds disclosed herein comprise a steroidal drug selected from: Dexmethasone, Betamethasone, Triamcinolone acetonide, Prednisolone and Hydrocortisone.

Further, the compounds disclosed herein comprise a cyclosporine A.

The present invention relates to hybrid drugs comprising a cyclosporine A moiety and one steroid moiety, or a pharmaceutical salt thereof, which are separately connected via a covalent bond to a linker such that said covalent bonds degrade *in vivo* to yield the respective Cyclosporine A and steroid independently.

In another aspect, the present invention relates to hybrid drugs, which degrade *in vivo* into a cyclosporine A and a steroidal drug.

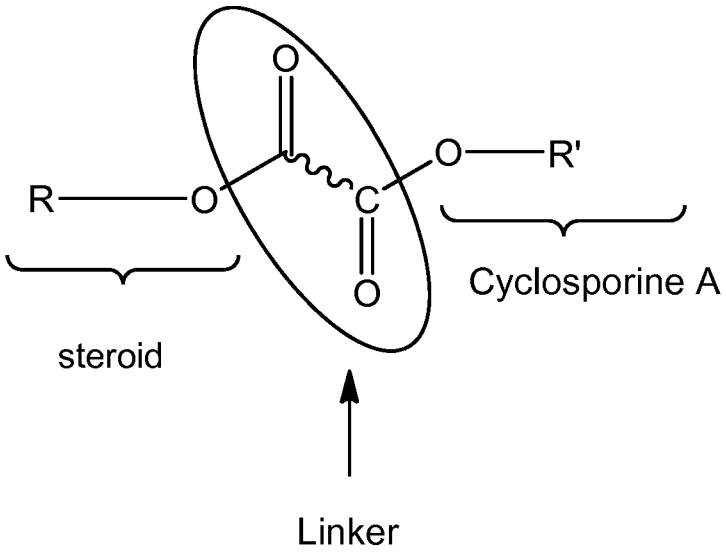
In another aspect, the present invention relates to hybrid drugs having two bonds, wherein said bonds are asymmetrically degraded *in vivo* to release the two independent drugs: a cyclosporine A and a steroidal drug.

In another aspect the invention provides a method comprising administrating to an eye of a mammal a pharmaceutical composition comprising a therapeutically active amount of a hybrid drug comprising a cyclosporine A moiety and one steroid moiety, which are connected via two separate covalent bonds to a linker such that said covalent bonds degrade *in vivo* to yield the cyclosporine A and the steroid, wherein each bond is an ester bond or an amide bond, wherein said method is effective in the treatment of a bacterial infection or an inflammation affecting said eye.

In another aspect the invention provides a pharmaceutical composition comprising a hybrid drug comprising a cyclosporine A moiety and a steroid, which are connected via two separate covalent bonds to a linker such that said covalent bonds degrade *in vivo* to yield the cyclosporine A moiety and the steroid moiety, and wherein each bond is an ester bond or an amide bond, and wherein said pharmaceutical composition is formulated for topical ophthalmic administration.

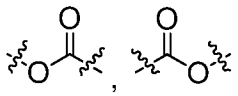
Depending of the bond formation site, the cyclosporine A moiety can be linked via an ester bond and the steroid moiety can be linked via an ester bond, as shown in the following scheme:

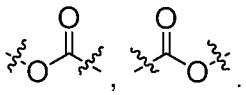
Scheme 1



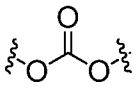
In another aspect the invention provides compounds which may comprise a linker moiety selected from, but not limited to, an ester, a carboxylate, a carbonyl, a carbonate, an amido, a carbamate, a ketone, an amino, an oxo, an ethylene glycol, a polyethylene glycol, an ethylene.

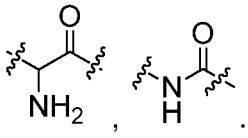
In another aspect, the invention provides compounds which may comprise a linker moiety comprising any combination of an ester, a carboxylate, a carbonyl, a carbonate, an amido, a carbamate, a ketone, an ethylene, an amino, an oxo, an ethylene glycol and/or a polyethylene glycol. Such linkers moieties and linker structures are exemplified in **Table 1**.

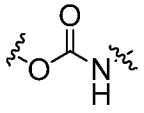
Examples of ester moieties comprised in the linkers are: .

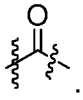
Examples of carboxylate moieties comprised in the linkers are: .

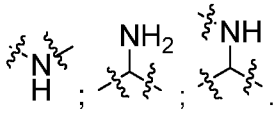
Example of a carbonyl moiety comprised in the linkers is .

Example of a carbonate moiety comprised in the linkers is: .

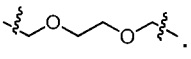
Examples of amido moieties comprised in the linkers are: .

Example of carbamate moiety comprised in the linkers is: .

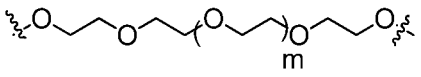
Example of a ketone moiety comprised in the linkers is: .

Examples of amino moieties comprised in the linkers are: .

Example of an oxo moiety comprised in the linker is: 

Example of ethylene glycol moieties comprised in the linkers are: .

Example of polyethylene glycol moiety comprised in the linkers is:

 wherein "m" is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

In another embodiment, the compounds disclosed herein comprise dexmethasone and cyclosporine A, such as:

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-4,21-dioxo-5,8,11,14,17,20-hexaoxatetracosane-1,24-dioate;

{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-butanedioate;

(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl 2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-2,2'-oxydiacetate;

1-{(2R,4E)-1-[(2S,5R,11S,14S,17R,20S,23R,26R,29S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl} 14-{2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-

3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} rel-3-methyl-4,7,11-trioxo-8,10-dioxa-3,6-diazatetradecane-1,14-dioate;

{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-4,15-dioxo-5,8,11,14-tetraoxaoctadecane-1,18-dioate.

In another embodiment, the compounds disclosed herein comprise betamethasone and cyclosporine A, such as:.

{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16S,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-4,15-dioxo-5,8,11,14-tetraoxaoctadecane-1,18-dioate;

rel-(2R)-4-({[({(2S,4E)-1-[(11R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methoxy)-2-[(4-{2-[(9S,10R,11R,13R,16R,17S)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy}-4-oxobutanoyl)amino]-4-oxobutanoic acid;

{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16S,17R)-9-

fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-butanedioate;

{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16S,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-4,18-dioxo-5,8,11,14,17-pentaoxahenicosane-1,21-dioate;

2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-(14R,16E)-13-[(2R,5R,11S,17R,29R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-14-methyl-4,7,11-trioxo-2-(propan-2-yl)-8,10,12-trioxa-3-azaoctadec-16-en-1-oate.

In another embodiment, the compounds disclosed herein comprise triamcinolone acetonide and cyclosporine A.

In another embodiment, the compounds disclosed herein comprise prednisolone and cyclosporine A, such as:

21-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} 1-({[({(2R,4E)-1-[(2S,11S,20S,26R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl) rel-(3R)-3-amino-4,18-dioxo-5,8,11,14,17-pentaoxahenicosane-1,21-dioate;

6-[(6-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy}-6-oxohexyl)oxy]-6-oxohexyl {[({(2R,4E)-1-[(11S,17R,32R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-

3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-butanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl (2E,5R)-6-[(11S,17R,26R,32R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-5-methyl-8,12,19-trioxo-7,9,11,18-tetraoxatetracos-2-en-24-yl rel-butanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl 6-({[({(2R,4E)-1-[(2S,11S,17R,23S,26R,32R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methoxy)-6-oxohexyl rel-butanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-(14R,16E)-13-[(2R,5R,11S,17R,29R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-14-methyl-4,7,11-trioxo-2-(propan-2-yl)-8,10,12-trioxa-3-azaoctadec-16-en-1-oate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-(10R,18R,20E)-10-amino-17-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-18-methyl-4,11,15-trioxo-12,14,16-trioxa-5-azadocos-20-en-1-oate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-benzene-1,4-dicarboxylate;

1-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} 4-({[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl) rel-(2R)-2-aminobutanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-(2E)-but-2-enedioate;

4-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} 1-({[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl) rel-(2S)-2-aminobutanedioate;

(2R)-2-amino-3-({[({(2R,4E)-1-[(5R,11S,26R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methoxy)-3-oxopropyl 2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-butanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl 1-{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}ethyl rel-4,15-dioxo-5,8,11,14-tetraoxaoctadecane-1,18-dioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-pentanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-butanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl (2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl rel-2,2'-oxydiacetate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-(12R,14E)-11-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-12-methyl-5,9-dioxo-3,6,8,10-tetraoxahexadec-14-en-1-oate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-4,15-dioxo-5,8,11,14-tetraoxaoctadecane-1,18-dioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-4,18-dioxo-5,8,11,14,17-pentaoxahenicosane-1,21-dioate;

14-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} 1-{(2R,4E)-1-[(11S,23S,26S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl} rel-3-methyl-4,7,11-trioxo-8,10-dioxa-3,6-diazatetradecane-1,14-dioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-4,21-dioxo-5,8,11,14,17,20-hexaoxatetracosane-1,24-dioate;

2-{2-[(4-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy}-4-oxobutanoyl)oxy]ethoxy}ethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-

3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-butanedioate;

8-[(4-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy}-4-oxobutanoyl)oxy]octyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-butanedioate;

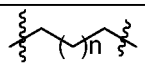
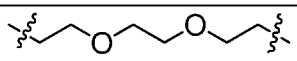
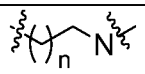
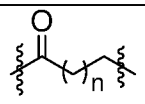
In another embodiment, the compounds disclosed herein comprise hydrocortisone and cyclosporine A.

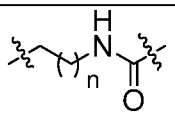
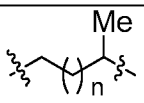
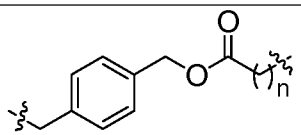
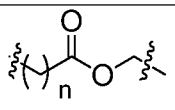
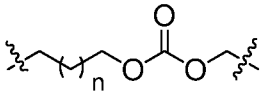
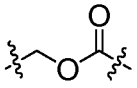
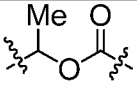
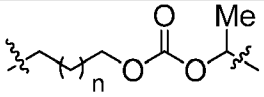
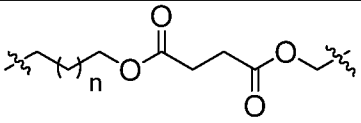
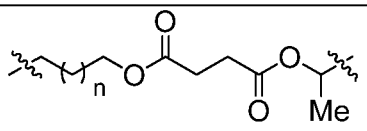
Further, the compounds disclosed herein may be pro-drugs, comprising a pro-drug group either at the steroid or at the cyclosporine site.

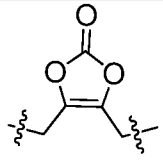
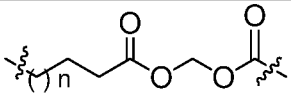
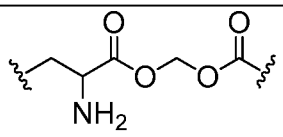
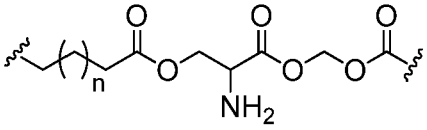
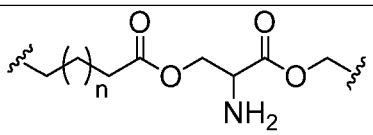
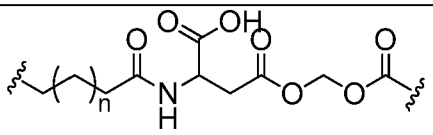
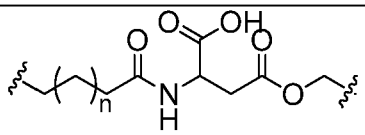
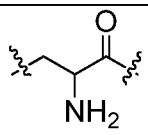
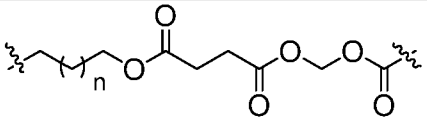
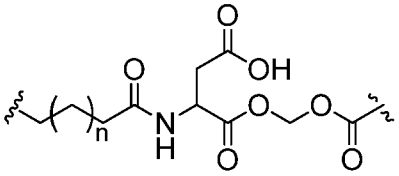
Further, the compounds disclosed herein comprise a steroidal drug and a cyclosporine A and a pro-drug moiety selected from, but not limited to, Table 2 in any possible combination.

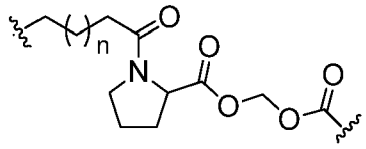
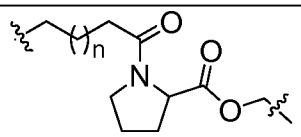
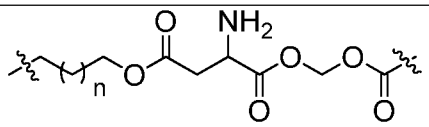
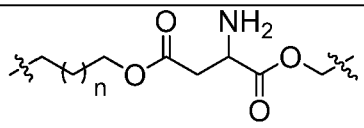
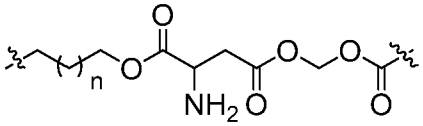
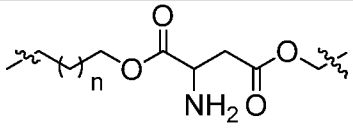
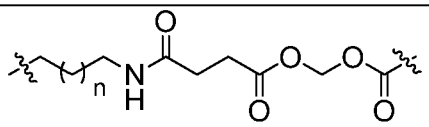
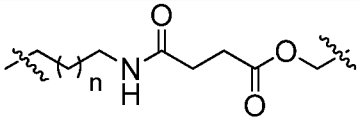
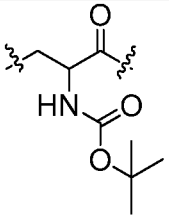
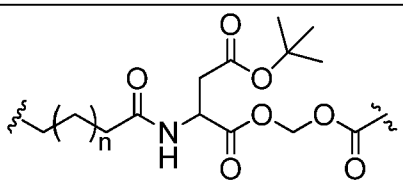
Further the compounds disclosed herein comprise a linker. Example of such linkers are shown in **Table 1**.

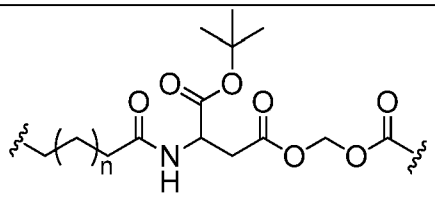
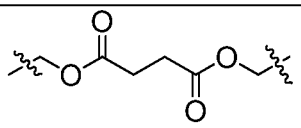
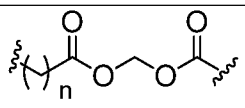
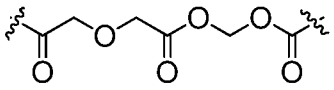
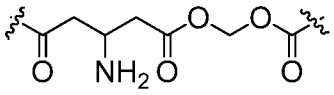
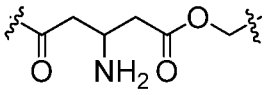
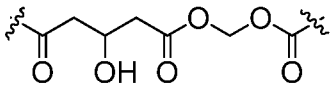
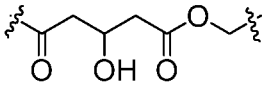
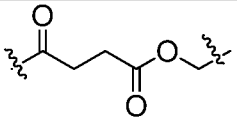
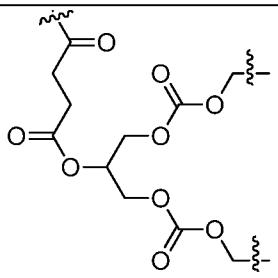
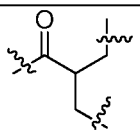
Table 1

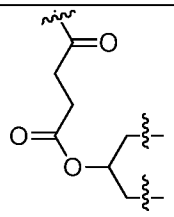
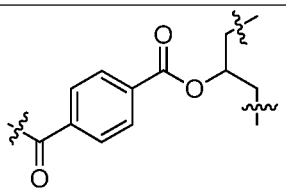
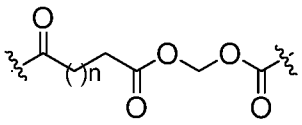
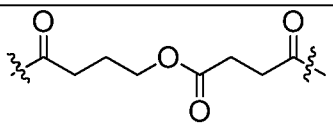
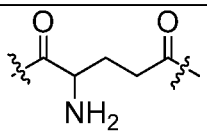
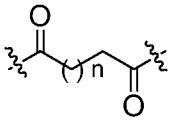
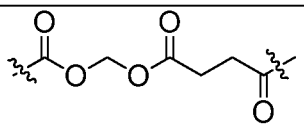
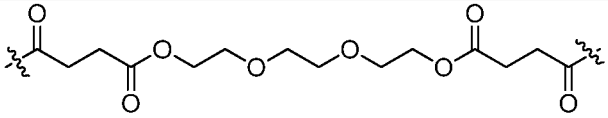
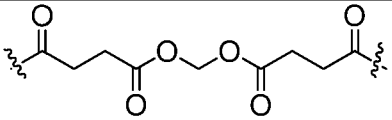
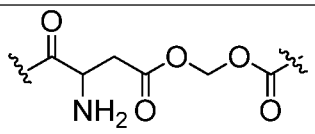
Linker Structure	Linker Number				
		n=0	n=1	n=2	n=3
		L2	L1		
	L3				
			L4		
		L35		L5	

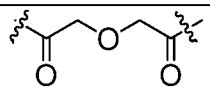
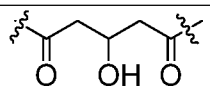
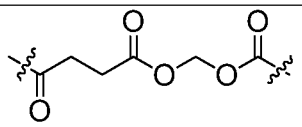
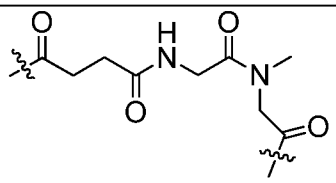
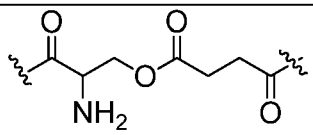
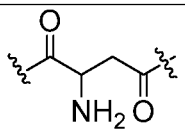
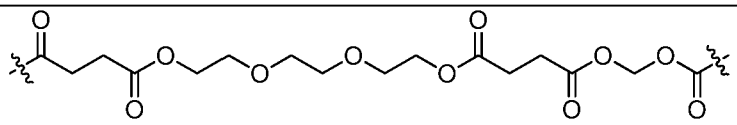
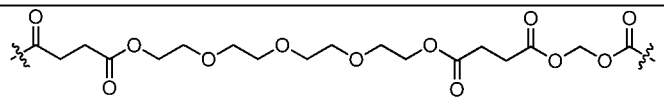
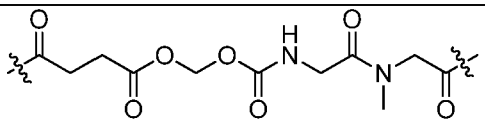
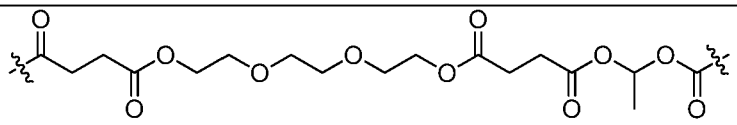
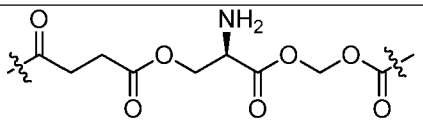
			L6		
	L7				
	L14				
			L15		
			L16		
		L46	L17		
			L8		
	L9				
	L10				
			L18		
			L11		
			L19		

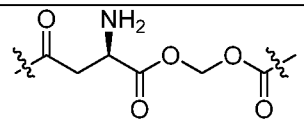
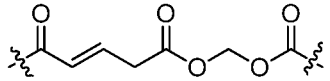
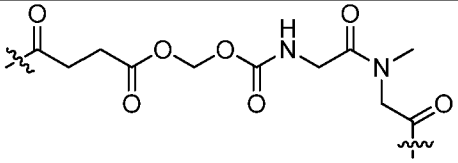
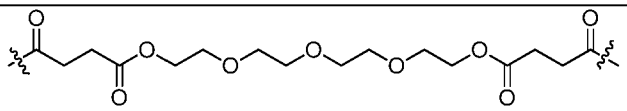
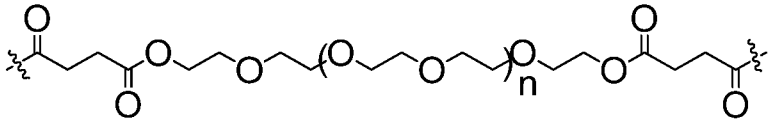
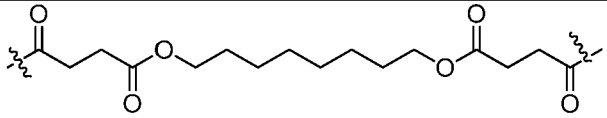
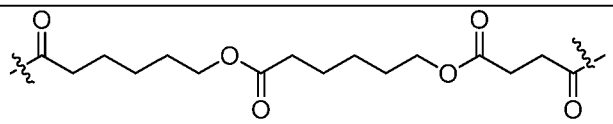
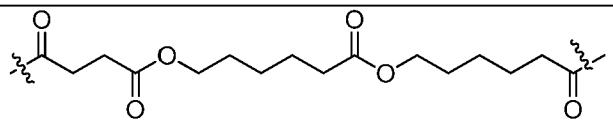
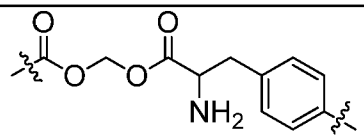
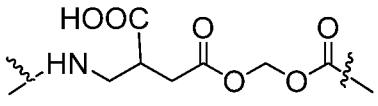
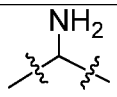
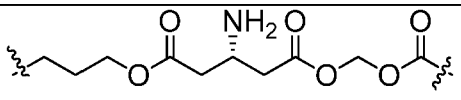
	L12				
			L13		
	L20				
			L21		
			L22		
			L23		
			L24		
	L25				
			L26		
			L27		

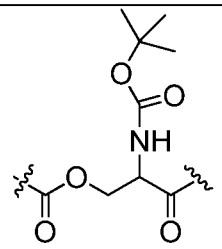
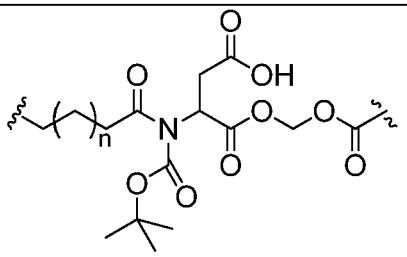
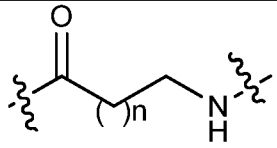
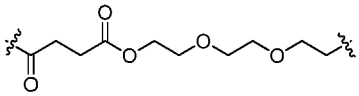
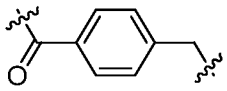
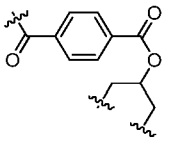
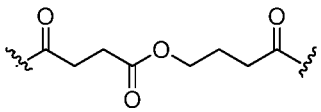
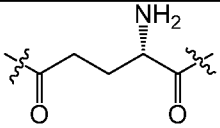
			L28		
			L29		
			L30		
			L31		
			L32		
			L33		
			L34		
			L35		
	L36				
			L37		

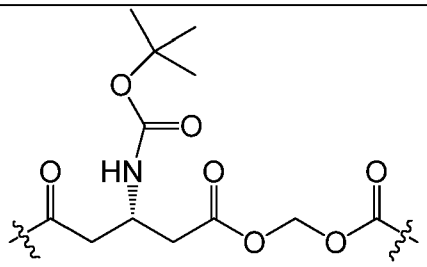
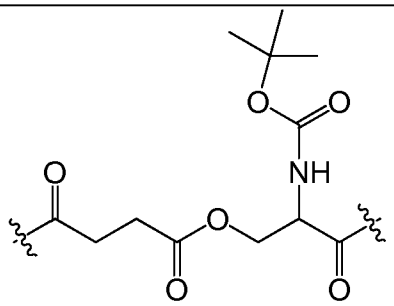
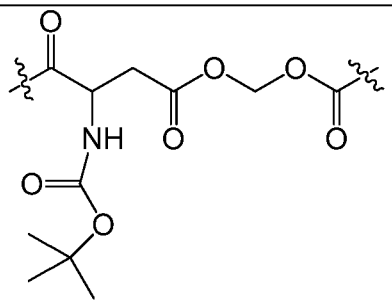
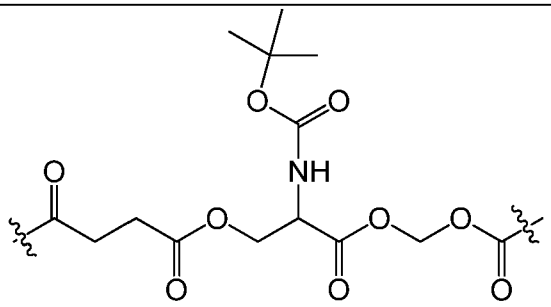
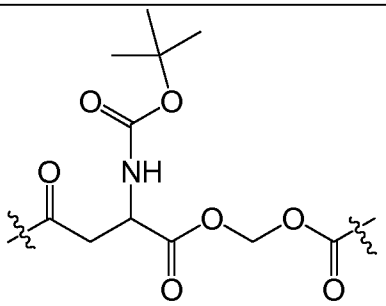
			L38		
	L39				
			L40		
	L41				
	L42				
	L43				
	L44				
	L45				
	L47				
	L48				
	L49				

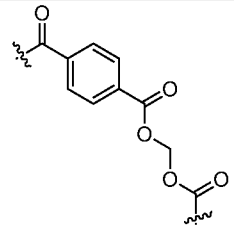
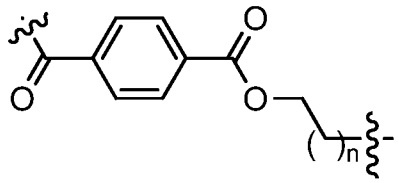
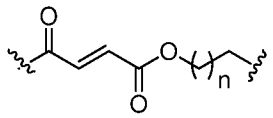
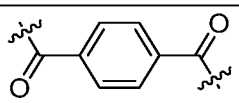
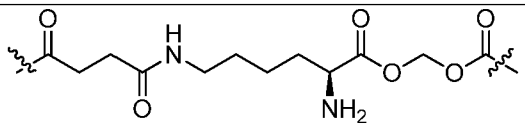
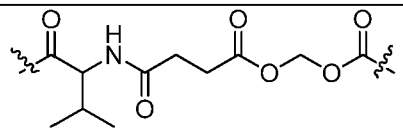
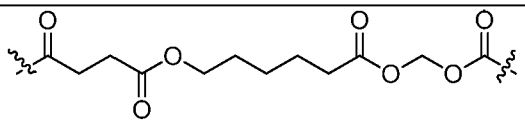
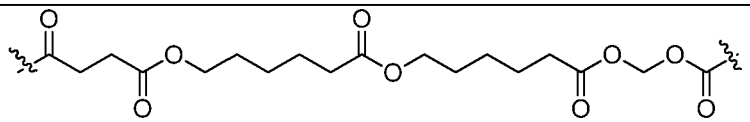
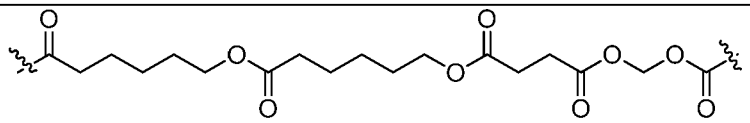
	L50				
	L51				
			L52	L67	
	L53				
	L54				
			L58		
	L56				
	L57				
	L59				
	L60				

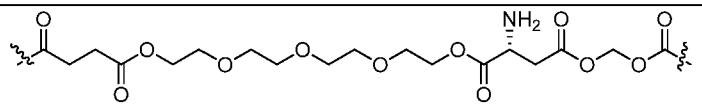
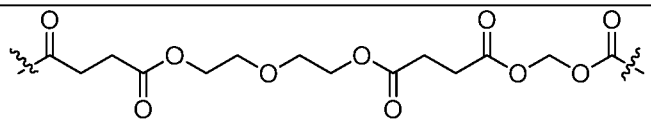
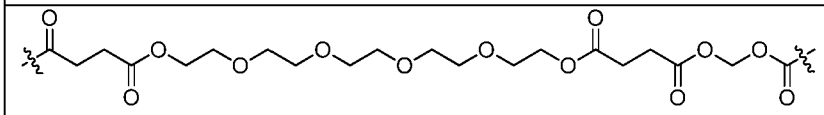
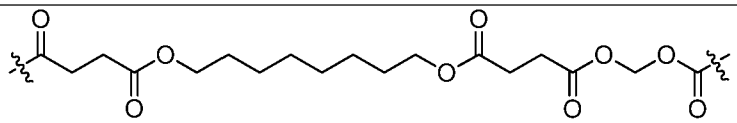
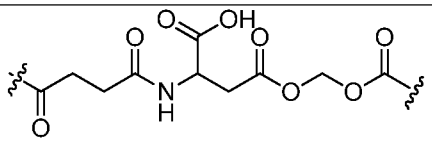
	L61				
	L62				
	L63				
	L64				
	L65				
	L66				
	L68				
	L69				
	L70				
	L71				
	L72				

	L73				
	L74				
	L75				
	L76				
			L77	L115	L116
	L78				
	L79				
	L80				
	L81				
	L82				
	L83				
	L84				

	L85				
			L86		
			L87	L88	
	L89				
	L90				
	L91				
	L92				
	L93				

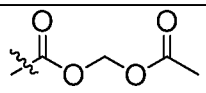
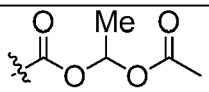
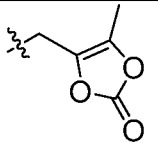
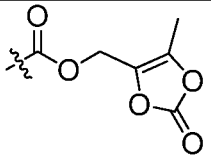
	L94				
	L95				
	L96				
	L97				
	L98				

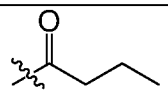
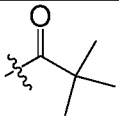
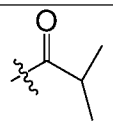
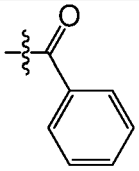
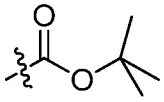
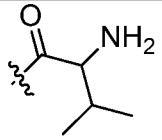
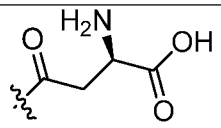
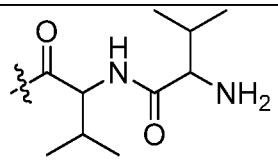
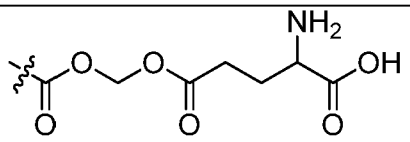
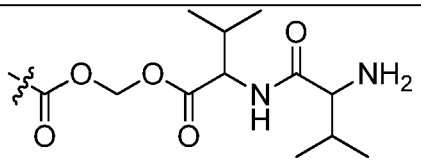
	L99				
		L100	L101	L102	
			L103		
	L104				
	L105				
	L106				
	L107				
	L108				
	L109				

	L110				
	L111				
	L112				
	L113				
	L114				

Further the compounds disclosed herein may comprise a pro-drug moiety selected from **Table 2**:

Table 2

Pro-drug Structure	Pro-drug Number
	P1
	P2
	P3
	P4

	P5
	P6
	P7
	P8
	P9
	P10
	P11
	P12
	P13
	P14
	P15

Compounds of the invention are shown in **Table 3**.

Table 3

Compound number	IUPAC Names
19	21-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} 1-({[({(2R,4E)-1-[(2S,11S,20S,26R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl) rel-(3R)-3-amino-4,18-dioxo-5,8,11,14,17-pentaoxahenicosane-1,21-dioate
18	6-[(6-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy}-6-oxohexyl)oxy]-6-oxohexyl {[({(2R,4E)-1-[(11S,17R,32R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-butanedioate
23	8-[(4-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy}-4-oxobutanoyl)oxy]octyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-butanedioate
17	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl (2E,5R)-6-[(11S,17R,26R,32R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-5-methyl-8,12,19-trioxo-7,9,11,18-tetraoxatetracos-2-en-24-yl rel-butanedioate
16	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-

	cyclopenta[a]phenanthren-17-yl]-2-oxoethyl 6-({[({(2R,4E)-1-[(2S,11S,17R,23S,26R,32R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methoxy)-6-oxohexyl rel-butanedioate
27	2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-(14R,16E)-13-[(2R,5R,11S,17R,29R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-14-methyl-4,7,11-trioxo-2-(propan-2-yl)-8,10,12-trioxa-3-azaoctadec-16-en-1-oate
15	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-(14R,16E)-13-[(2R,5R,11S,17R,29R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-14-methyl-4,7,11-trioxo-2-(propan-2-yl)-8,10,12-trioxa-3-azaoctadec-16-en-1-oate
22	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-4,21-dioxo-5,8,11,14,17,20-hexaoxatetracosane-1,24-dioate
21	2-{2-[(4-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy}-4-oxobutanoyl)oxy]ethoxy}ethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-butanedioate
28	{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-

	1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16S,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-4,15-dioxo-5,8,11,14-tetraoxaoctadecane-1,18-dioate
26	rel-(2R)-4-({[({(2S,4E)-1-[(11R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methoxy)-2-[(4-{2-[(9S,10R,11R,13R,16R,17S)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy}-4-oxobutanoyl)amino]-4-oxobutanoic acid
14	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-(10R,18R,20E)-10-amino-17-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-18-methyl-4,11,15-trioxo-12,14,16-trioxa-5-azadocos-20-en-1-oate
13	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-benzene-1,4-dicarboxylate
12	1-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} 4-({[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl) rel-(2R)-2-aminobutanedioate
11	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-

	tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-(2E)-but-2-enedioate
25	{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16S,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-4,18-dioxo-5,8,11,14,17-pentaoxahenicosane-1,21-dioate
20	{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-4,18-dioxo-5,8,11,14,17-pentaoxahenicosane-1,21-dioate
32	{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-4,15-dioxo-5,8,11,14-tetraoxaoctadecane-1,18-dioate
10	4-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} 1-({[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl) rel-(2S)-2-aminobutanedioate
9	(2R)-2-amino-3-({[({(2R,4E)-1-[(5R,11S,26R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methoxy)-3-oxopropyl 2-

	[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-butanedioate
8	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl 1-{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}ethyl rel-4,15-dioxo-5,8,11,14-tetraoxaoctadecane-1,18-dioate
31	1-{(2R,4E)-1-[(2S,5R,11S,14S,17R,20S,23R,26R,29S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl} 14-{2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} rel-3-methyl-4,7,11-trioxo-8,10-dioxa-3,6-diazatetradecane-1,14-dioate
7	14-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} 1-{(2R,4E)-1-[(11S,23S,26S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl} rel-3-methyl-4,7,11-trioxo-8,10-dioxa-3,6-diazatetradecane-1,14-dioate
6	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-4,18-dioxo-5,8,11,14,17-pentaoxahenicosane-1,21-dioate
5	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-

	yl}oxy)carbonyl]oxy}methyl rel-4,15-dioxo-5,8,11,14-tetraoxaoctadecane-1,18-dioate
30	(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl 2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-2,2'-oxydiacetate
4	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-(12R,14E)-11-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-12-methyl-5,9-dioxo-3,6,8,10-tetraoxahexadec-14-en-1-oate
29	{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-butanedioate
24	{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16S,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-butanedioate
3	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-pentanedioate
2	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-

	5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-butanedioate
1	2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl (2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl rel-2,2'-oxydiacetate

Some compounds of the invention have at least one stereogenic center in their structure. This stereogenic center may be present in an R or S configuration, said R and S notation is used in correspondence with the rules described in Pure Appli. Chem. (1976), 45, 11-13.

The term “pharmaceutically acceptable salts” refers to salts or complexes that retain the desired biological activity of the above identified compounds and exhibit minimal or no undesired toxicological effects. The “pharmaceutically acceptable salts” according to the invention include therapeutically active, non-toxic base or acid salt forms, which the compounds of the invention are able to form.

The acid addition salt form of a compound of the invention that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; or an organic acid such as for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, fumaric acid, maleic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, citric, methylsulfonic, ethanesulfonic, benzenesulfonic, formic acid and the like (Handbook of Pharmaceutical Salts, P. Heinrich Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta- Zürich, 2002, 329-345).

The base addition salt form of a compound of the invention that occurs in its acid form can be obtained by treating the acid with an appropriate base such as an inorganic base, for example, sodium hydroxide, magnesium hydroxide, potassium hydroxide, calcium hydroxide, ammonia and the like; or an organic base such as for example, L-Arginine, ethanolamine, betaine, benzathine, morpholine and the like. (Handbook of Pharmaceutical Salts, P. Heinrich Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta- Zürich, 2002, 329-345).

Compounds of the invention and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

In still another embodiment of the invention, there are provided methods for treating or preventing eye conditions such as: conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum, corneal ulcers, anterior blepharitis, posterior blepharitis, meibomian gland dysfunction, dry eye disease (keratocojunctivitis sicca) ocular pain, ocular pain and inflammation post-ocular surgery ,bacterial conjunctivitis, anterior uveitis, in a patient suffering thereof. Such methods can be performed, for example, by administering to a subject in need thereof a therapeutically effective amount of at least one compound of the invention, or any combination thereof, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms thereof.

The present invention concerns the use of a compound of the invention or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum, corneal ulcers, anterior blepharitis, posterior blepharitis, meibomian gland dysfunction, dry eye disease (keratocojunctivitis sicca) ocular pain, ocular pain and inflammation post-ocular surgery ,bacterial conjunctivitis, anterior uveitis.

The actual amount of the compound to be administered in any given case will be determined by a physician taking into account the relevant circumstances, such as the severity of the condition, the age and weight of the patient, the patient's general physical condition, the cause of the condition, and the route of administration.

The patient will be administered the compound orally in any acceptable form, such as a tablet, liquid, capsule, powder and the like, or other routes may be desirable or necessary, particularly if the patient suffers from nausea. Such other routes may include, without exception, transdermal, parenteral, subcutaneous, intranasal, via an implant stent, intrathecal, intravitreal, topical to the eye, back to the eye, intramuscular, intravenous, and intrarectal modes of delivery. Additionally, the formulations may be designed to delay release of the active compound over a given period of time, or to carefully control the amount of drug released at a given time during the course of therapy.

In another embodiment of the invention, there are provided pharmaceutical compositions including at least one compound of the invention in a pharmaceutically acceptable carrier thereof. The phrase "pharmaceutically acceptable" means the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an emulsion, a dispersion, a patch, a micelle, a liposome, and the like, wherein the resulting composition contains one or more compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for enteral or parenteral applications. Invention compounds may be combined, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. Invention compounds are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

Pharmaceutical compositions containing invention compounds may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or

syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets containing invention compounds in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the invention compounds are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the invention compounds are mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

The compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the invention compounds with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

The compounds of the invention may also be administered as pharmaceutical compositions in a form suitable for topical use, for example, as oily suspensions, as solutions or suspensions in aqueous liquids or nonaqueous liquids, or as oil-in-water or water-in-oil liquid emulsions.

Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable salt thereof, as an active ingredient with conventional ophthalmically acceptable pharmaceutical excipients and by preparation of unit dosage suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.001 and about 5% (w/v), preferably about 0.001 to about 2.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 4.5 and 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. The formulations may also contain conventional pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate.

A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose cyclodextrin and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar manner an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place of or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	0-10
buffer	0.01-10
pH adjustor	q .s. pH 4.5-7.8
antioxidant	as needed
surfactant	as needed
purified water	to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a

dropper, to facilitate application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution. One package may contain one or more unit doses. Especially preservative-free solutions are often formulated in non-resealable containers containing up to about ten, preferably up to about five units doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop usually is about 20-35 µl.

Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner.

The compounds and pharmaceutical compositions described herein are useful as medicaments in mammals, including humans, for treatment of diseases and/or alleviations of conditions such as conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum, corneal ulcers, anterior blepharitis, posterior blepharitis, meibomian gland dysfunction, dry eye disease (keratocojunctivitis sicca) ocular pain, ocular pain and inflammation post-ocular surgery ,bacterial conjunctivitis, anterior uveitis, post-surgical inflammation, inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, such as allergic conjunctivitis, ocular rosacea, dry eye, blepharitis, meibomian gland dysfunction, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis, corneal injury from chemical radiation, or thermal burns, penetration of foreign bodies, allergy, and combinations thereof.

Thus, in further embodiments of the invention, there are provided methods for treating conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum, corneal ulcers, anterior blepharitis, posterior blepharitis, meibomian gland dysfunction, dry eye disease (keratocojunctivitis sicca) ocular pain, ocular pain and inflammation post-ocular surgery ,bacterial conjunctivitis, anterior uveitis, post-surgical inflammation, inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, such as allergic conjunctivitis, ocular rosacea, dry eye, blepharitis, meibomian gland dysfunction, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis, corneal injury from chemical

radiation, or thermal burns, penetration of foreign bodies, allergy, and combinations thereof.

Such methods can be performed, for example, by administering to a subject in need thereof a pharmaceutical composition containing a therapeutically effective amount of at least one invention compound. As used herein, the term "therapeutically effective amount" means the amount of the pharmaceutical composition that will elicit the biological or medical response of a subject in need thereof that is being sought by the researcher, veterinarian, medical doctor or other clinician. In some embodiments, the subject in need thereof is a mammal. In some embodiments, the mammal is human.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention claimed. As used herein, the use of the singular includes the plural unless specifically stated otherwise.

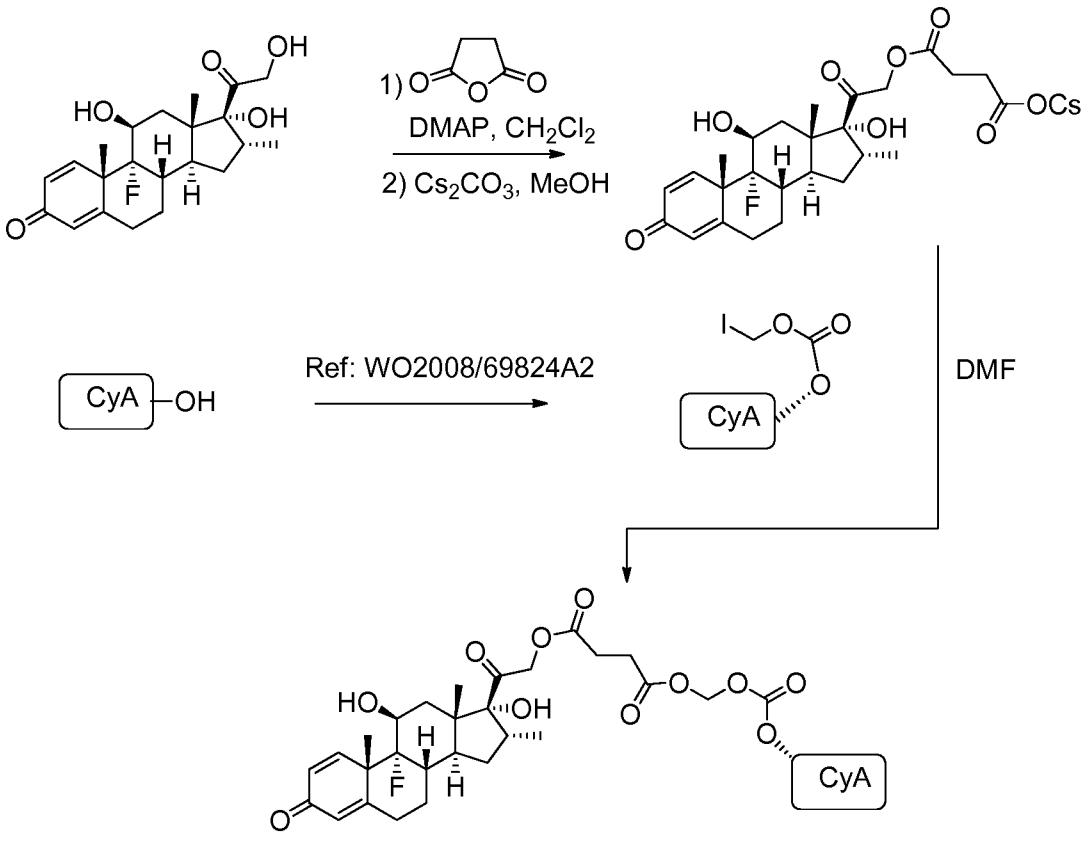
The following abbreviations are used in the general schemes and in the examples:

Boc	tert-Butyloxycarbonyl
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Boc_2O	di-tert-butyl dicarbonate
THF	tetrahydrofuran
NaOH	sodium hydroxide
DMAP	4-dimethylaminopyridine
CH_2Cl_2	dichloromethane
HCl	hydrochloric acid
M	molar
$NaHCO_3$	sodium bicarbonate
CHCl3	chloroform
EtOH	ethanol
DMF	*N*,*N*-dimethylformamide
MeOH	methanol
NaOAc	sodium acetate
FA	fumaric acid
PG	protecting group

General Synthesis

In **Scheme 1A** the synthesis of hybrid analogs were started with the steroid. EDCI coupling with a linker gave a steroid linker ester, which was converted to the cesium salt with cesium carbonate. This salt reacted with iodo CyA prepared according to WO2008/069824 A2 and yielded the desired hybrid compound. It should be noted that the brief description on each of the arrows for each conversion has been added for illustration purpose sonly and should not be regarded as limiting with respect to the sequence of each individual step.

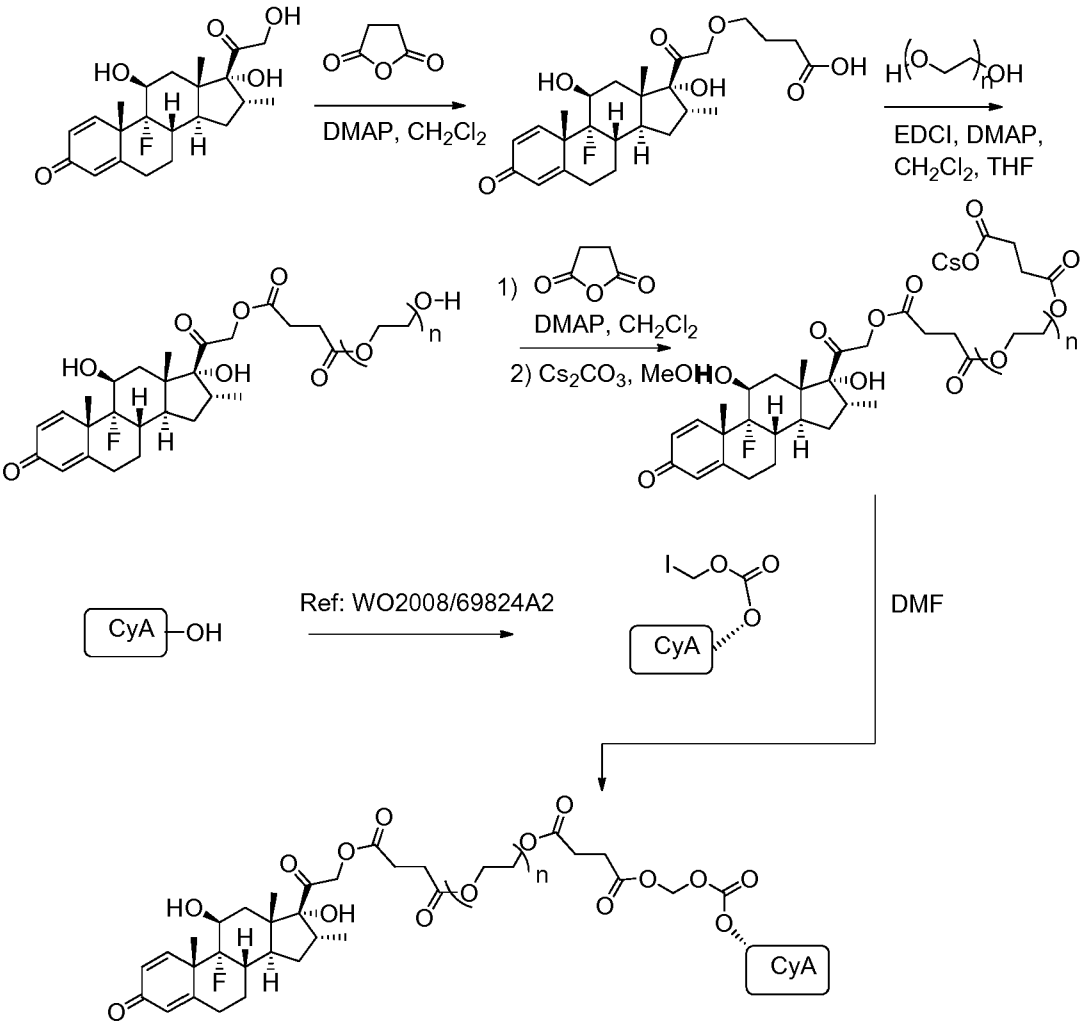
Scheme 1A



CYCLOSPORINE A is CyA—OH

In general **Scheme 1B** another hybrid compound according to the invention was prepared. This hybrid compound has a polyethylene /keto type of linker.

Scheme 1B



It will be readily apparent to those skilled in the art that some of the compounds of the invention may contain one or more asymmetric centers, such that the compounds may exist in enantiomeric as well as in diastereomeric forms. Unless it is specifically noted otherwise, the scope of the present invention includes all enantiomers, diastereomers and racemic mixtures. Some of the compounds of the invention may form salts with pharmaceutically acceptable acids or bases, and such pharmaceutically acceptable salts of the compounds described herein are also within the scope of the invention.

The present invention includes all pharmaceutically acceptable isotopically enriched compounds. Any compound of the invention may contain one or more isotopic atoms enriched or different than the natural ratio such as deuterium ^{2}H (or D) in place of hydrogen ^{1}H (or H) or use of ^{13}C enriched material in place of ^{12}C and the like. Similar substitutions can be employed for N, O and S. The use of isotopes may assist in analytical as well as therapeutic aspects of the invention. For example, use of deuterium may increase the in vivo half-life by altering the metabolism (rate) of the compounds of the invention. These compounds can be prepared in accord with the preparations described by use of isotopically enriched reagents.

The following examples are for illustrative purposes only and are not intended, nor should they be construed as limiting the invention in any manner. Those skilled in the art will appreciate that variations and modifications of the following examples can be made without exceeding the spirit or scope of the invention.

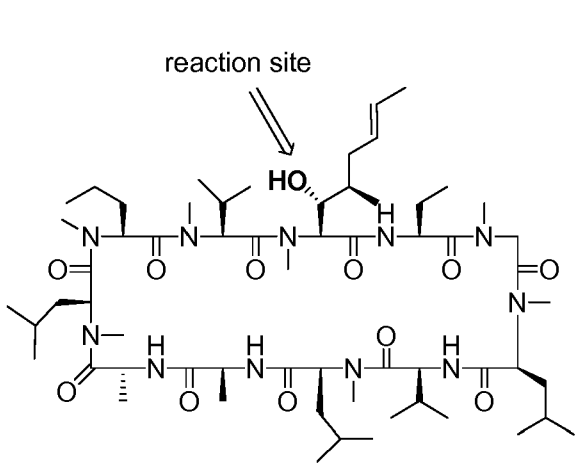
As will be evident to those skilled in the art, individual isomeric forms can be obtained by separation of mixtures thereof in conventional manner. For example, in the case of diasteroisomeric isomers, chromatographic separation may be employed.

Compound names were generated with ACDLabs version 12.5 or ChemBioDraw Ultra version 12.0.2.

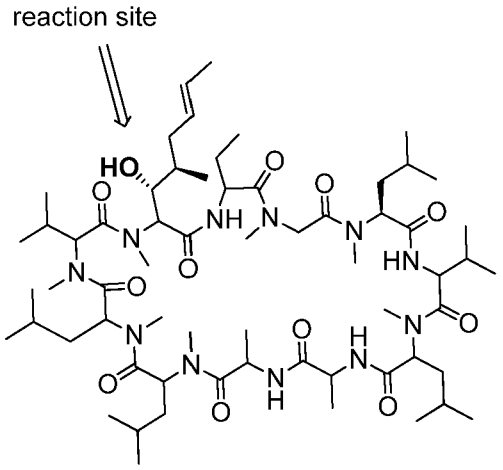
In general, characterization of the compounds is performed according to the following methods. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian 300 or 600 MHz spectrometer in deuterated solvent. Chemical shifts were reported as δ (delta) values in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard (0.00 ppm) and multiplicities were reported as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Data were reported in the following format: chemical shift (multiplicity, coupling constant(s) *J* in hertz (Hz), integrated

intensity). The mass spectrometry data were determined on a Shimadzu LCMS-IT-TOF instrument.

The Cyclosporine A molecule can be also represented by either structures:



Cyclosporine A



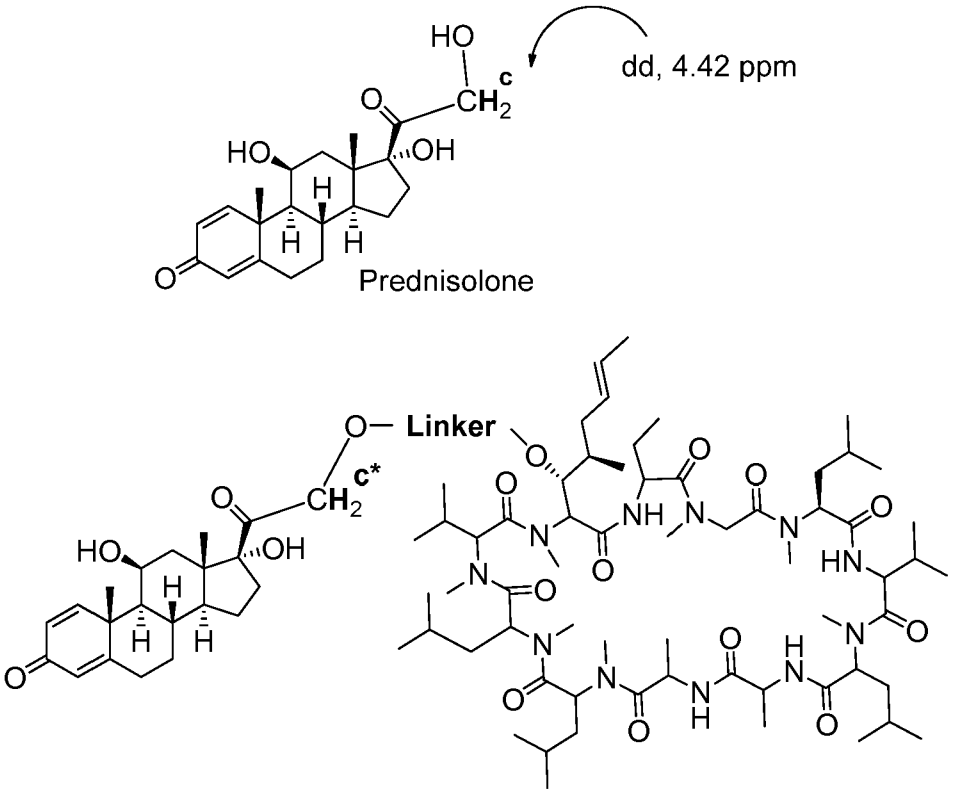
Cyclosporine A

The formation of the hybrid compounds was checked by ^{1}H-NMR, comparing the chemical shifts of the protons from the CH_2 group identified in the schemes shown below, and identified as "**H**^{a}", "**H**^{b}" , "**CH**$_2^{c}$" for the starting material and as as "**H**^{a*}", "**H**^{b*} "**CH**$_2^{c*}$" or "**c***" for of the corresponding protons on the newly formed hybrid molecule wherein "*" indicates the hybrid compound. Applicants have indicated with arrows the location of these protons and the reaction site of the pro-drug moiety, where available. Each scheme shows the formation of the new hybrid drug. Each table describes the results for the new hybrid drug and the linker number and the pro-drug number, where existing. The linker and pro-drug moiety numbers are as described in Table 1 and 2 respectively.

Examples of compounds of the invention

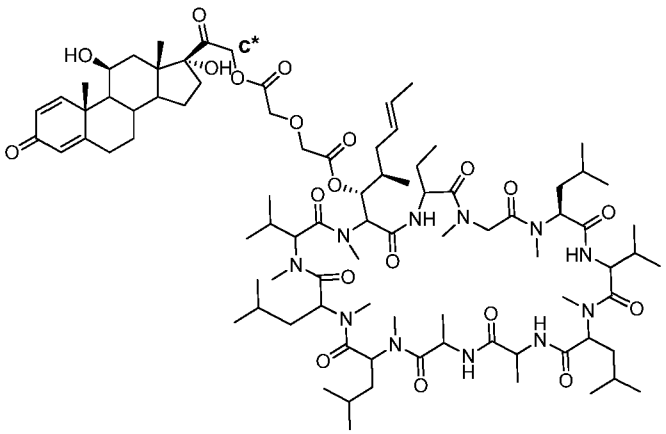
Prednisolone reacted with one molecule of **Cyclosporine A** to form the following hybrid compounds as shown in **Scheme 2** with the results described in **Table 4.**

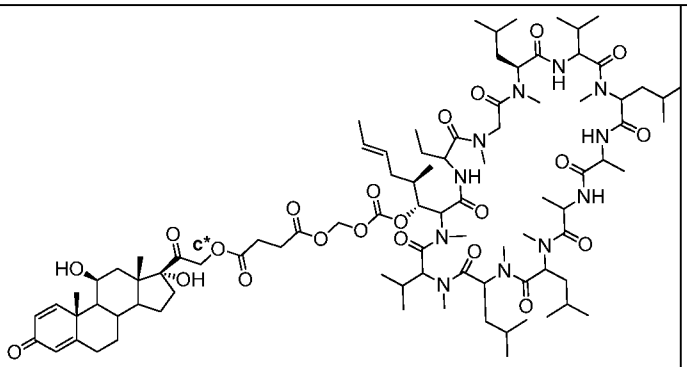
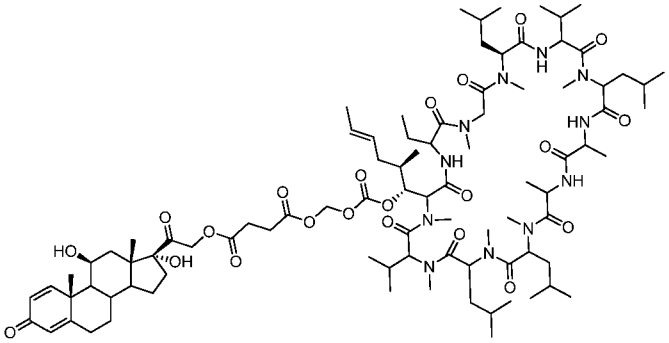
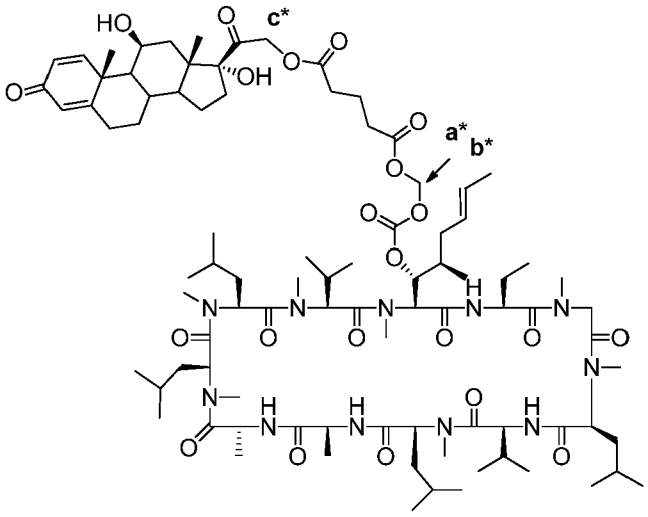
Scheme 2

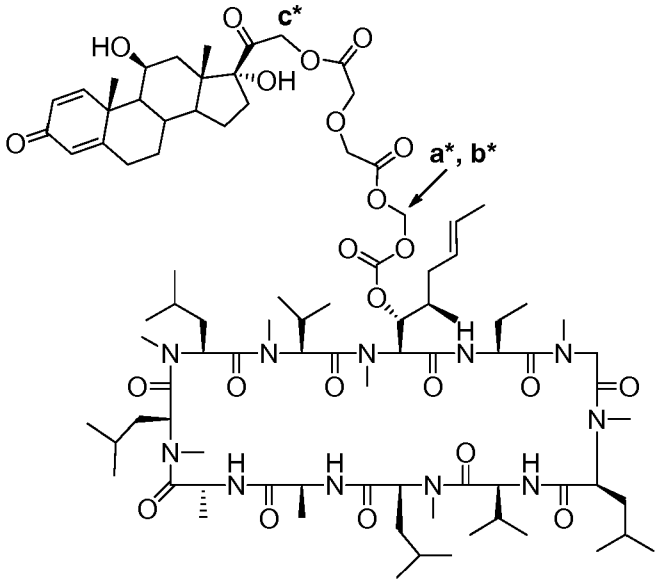
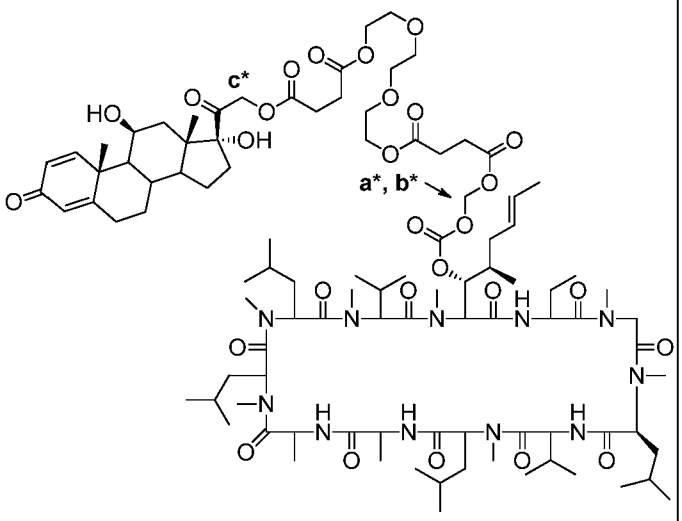


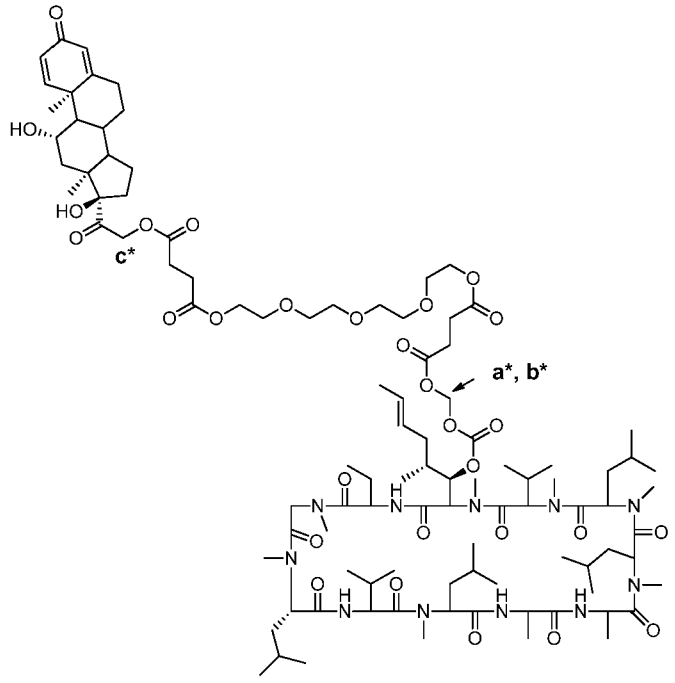
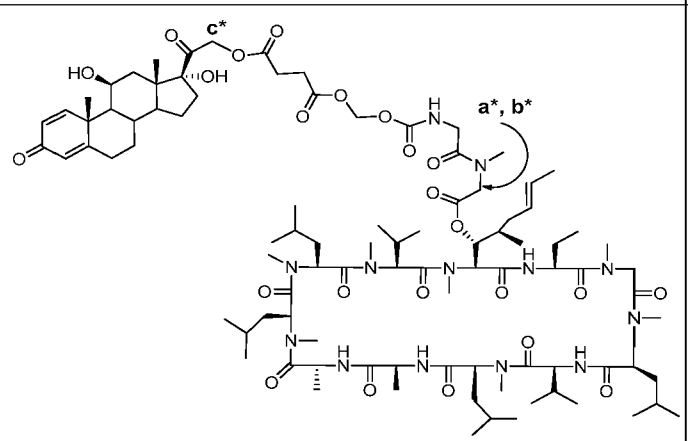
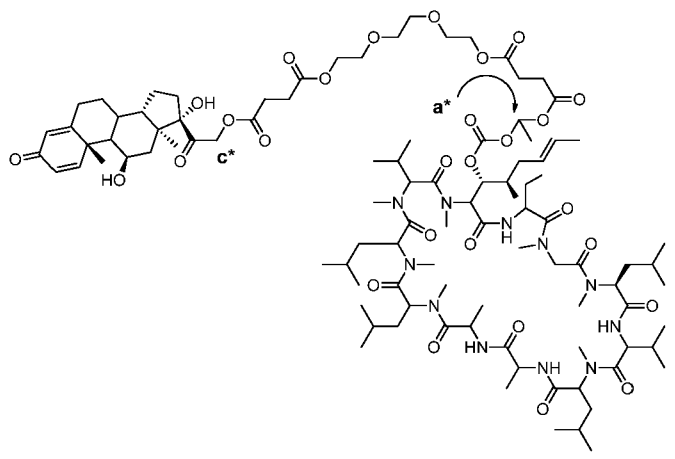
5

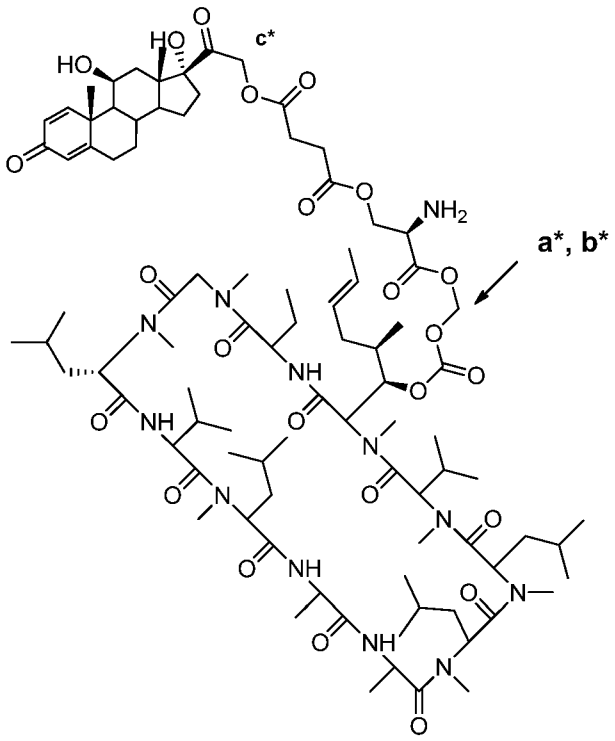
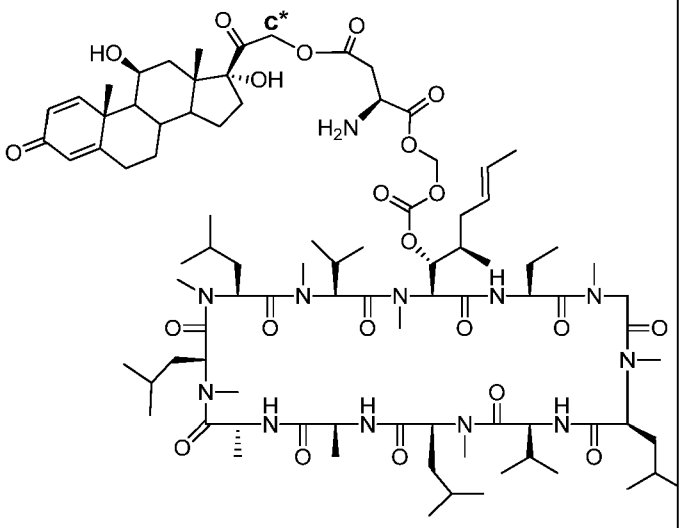
Table 4

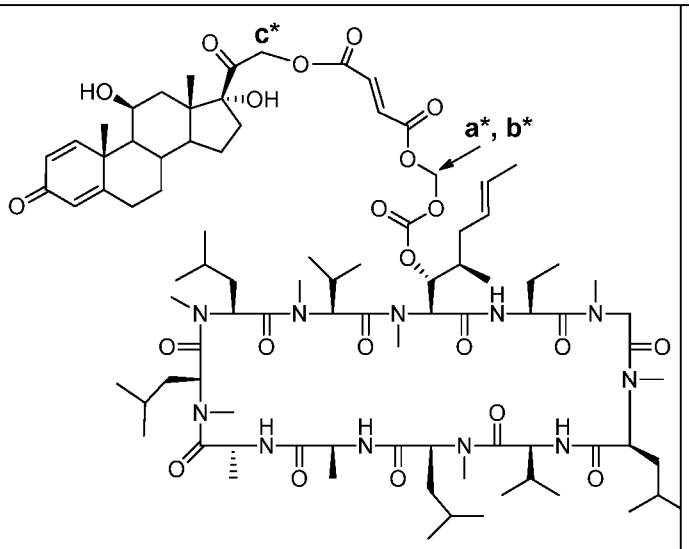
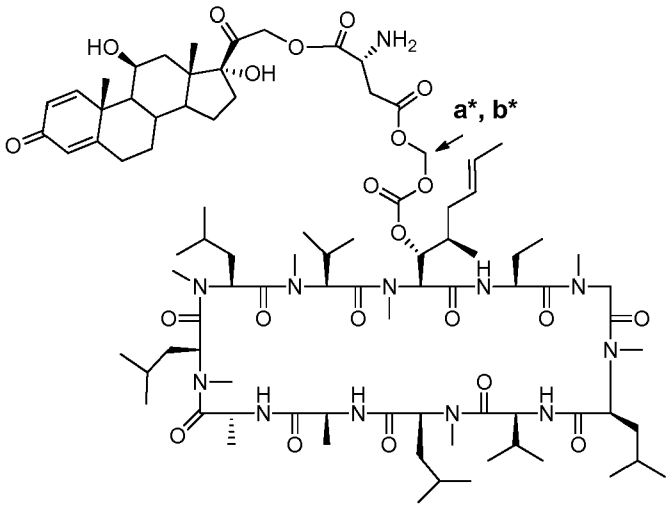
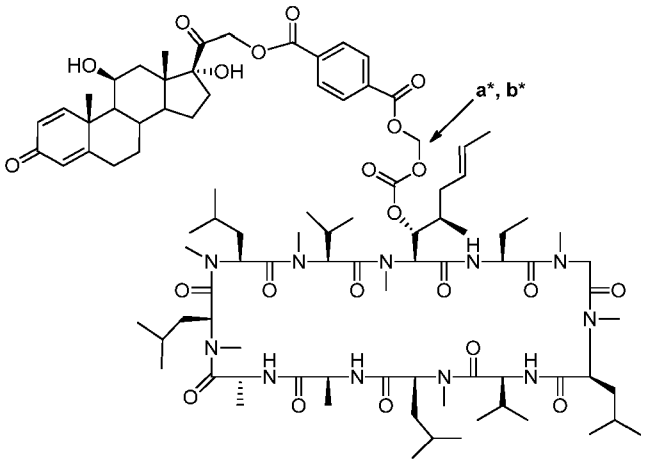
* Comp. Linker	Structure	CH_2^{c*} δ(ppm)	Mass
1 L61		4.99 (dd)	1683 MNa^+

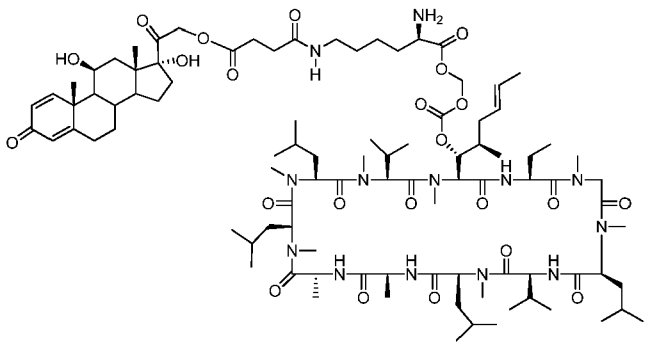
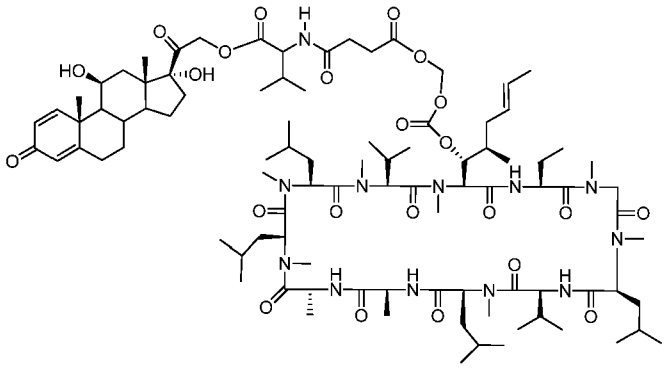
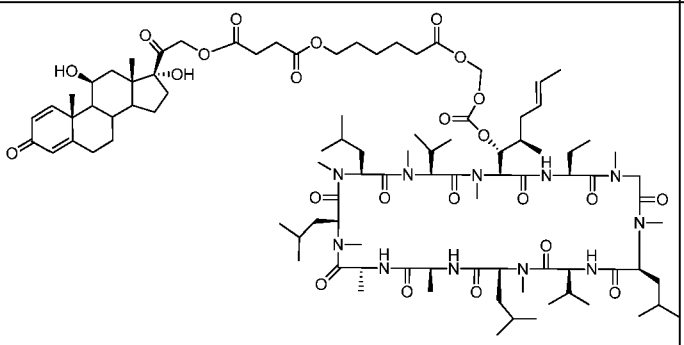
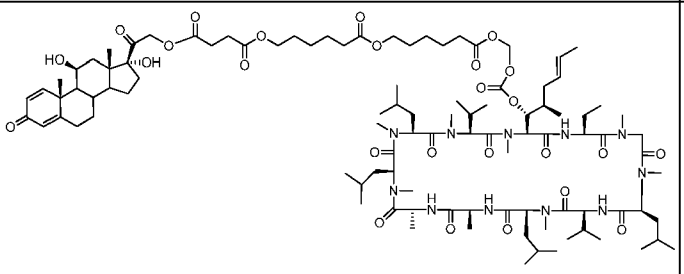
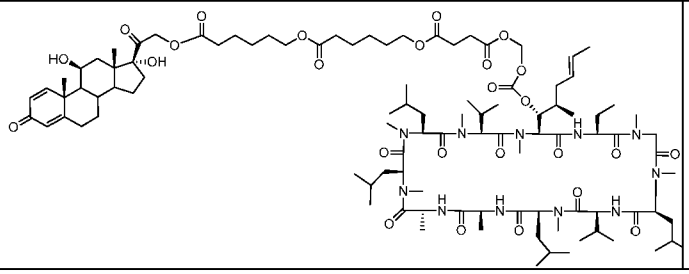
2 L63		4.97 (dd)		1742 MNa^+
* Comp. Linker	Structure	Ha*	Hb*	Mass
2 L63		5.84	5.70	1742 MNa^+
L67 3		5.79	5.70	1756 MNa+

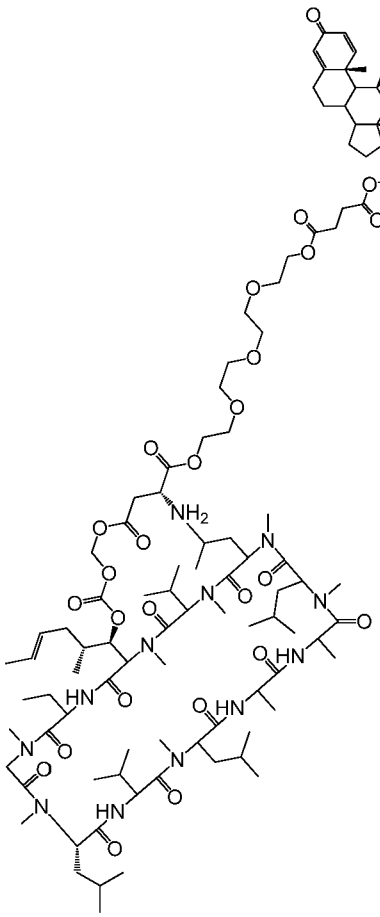
L414		5.85	5.79	1759 MNa+
L685		5.87	5.70	1974 MNa+

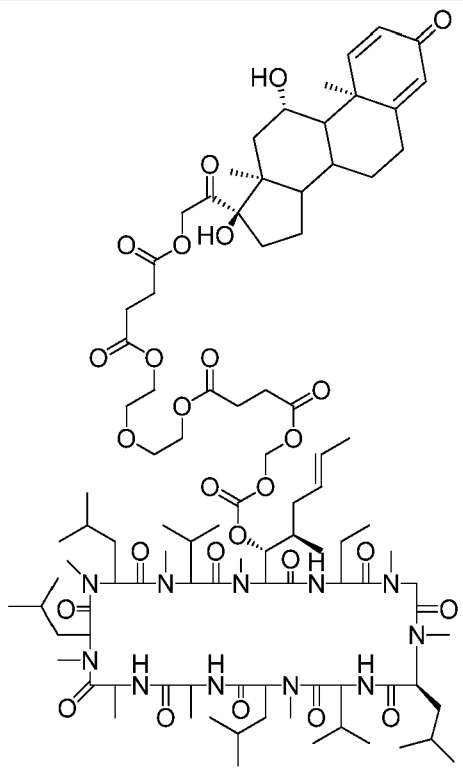
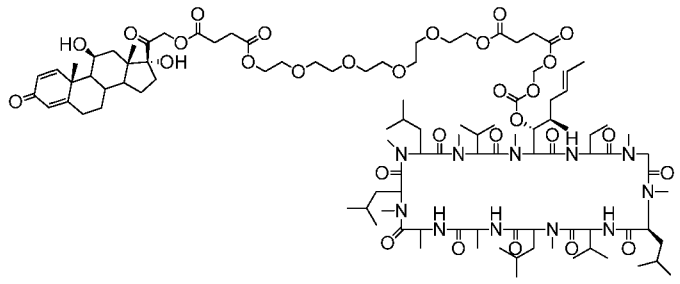
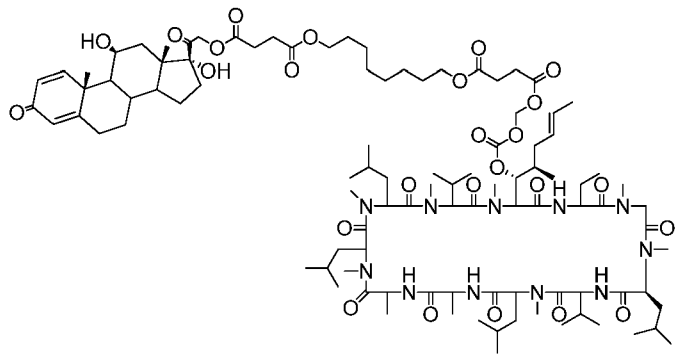
L69 6		5.82	5.89	2018 MNa+
L70 7		5.73	5.73	1069 MNa+
L71 8		5.68		1987 MNa+

L72 **9**		**5.67**	**1806** **MNa+**
L73 **10**		**5.65**	

L74 11		5.94	5.80	1739 MNa+
12 L60		5.94	5.80	1739 MNa+
13 L99		6.03	5.98	1789 MNa+

14 L105		5.83		1870 MNa+
15 L106		5.77	5.72	1840 MNa+
16 L107		5.80	5.66	1855 MNa+
17 L108		5.81	5.66	1969 MNa+
18 L109		5.81	5.68	1969 MNa+

19 **L110**		**5.85**	**5.67**	**2031** **MNa+**

21 **L111**		**5.81**	**5.69**	**1929** **MNa+**
22 **L112**		**5.82**	**5.69**	**2061** **MNa+**
23 **L113**		**5.82**	**5.69**	**1970** **MNa+**

Betamethasone reacted with one molecule of **Cyclosporine A** to form the following hybrid compounds as shown in **Scheme 3** with the results described in **Table 5.**

Scheme 3

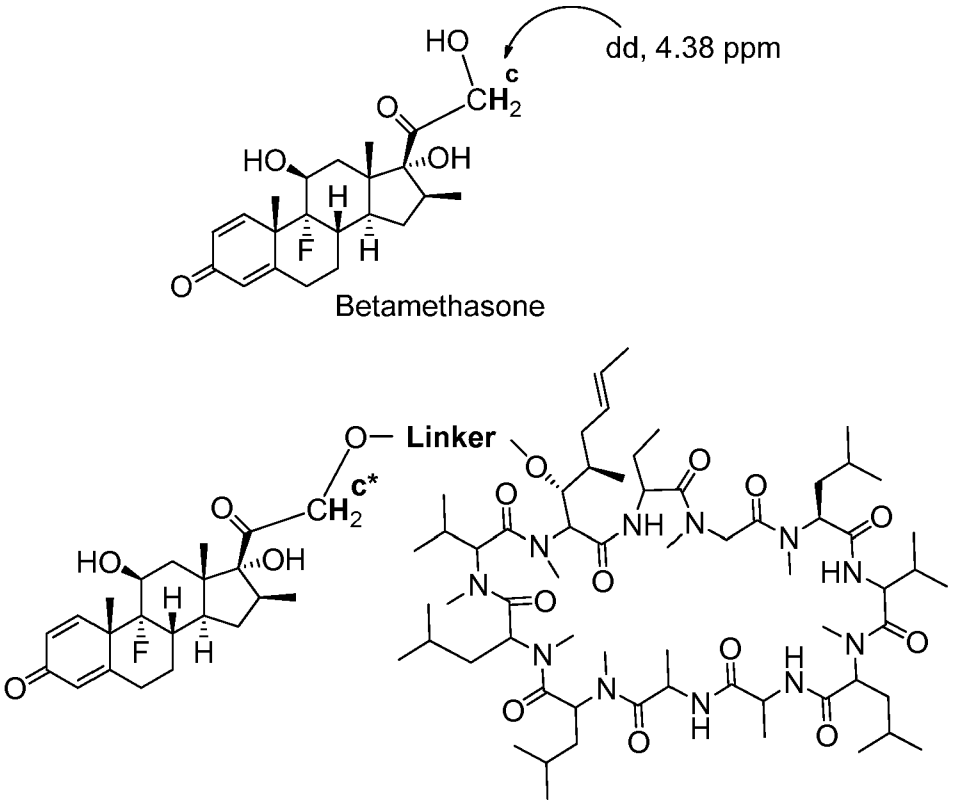
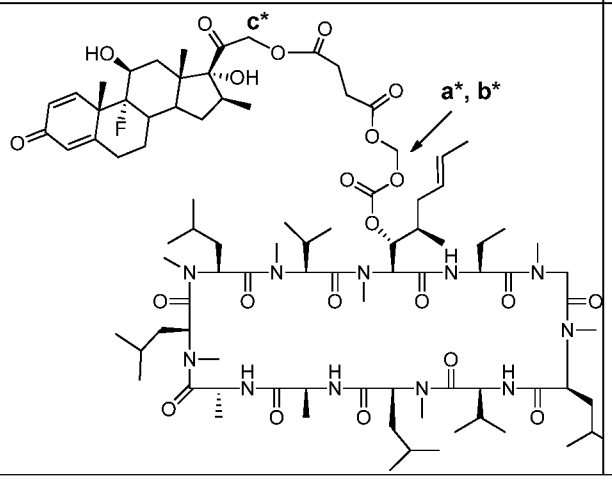
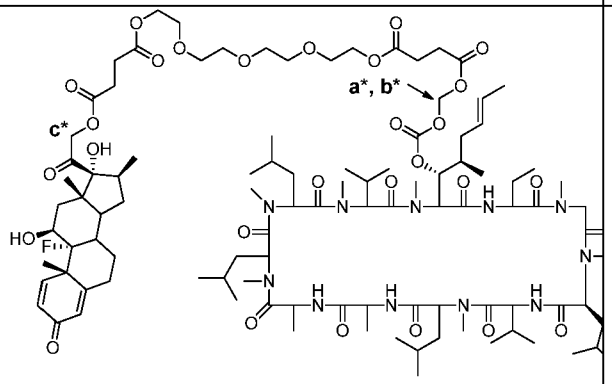
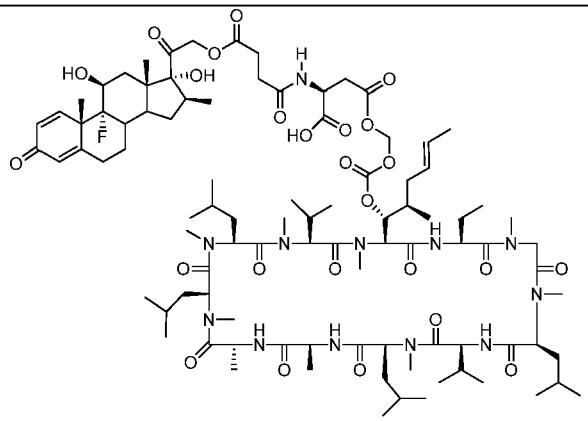
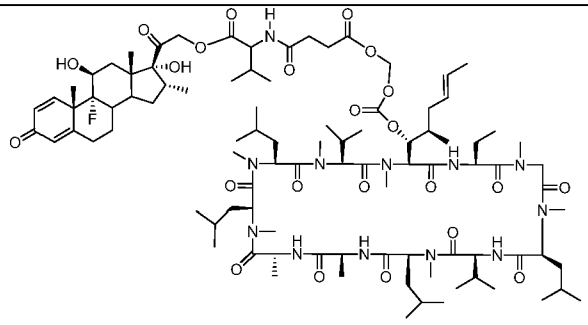
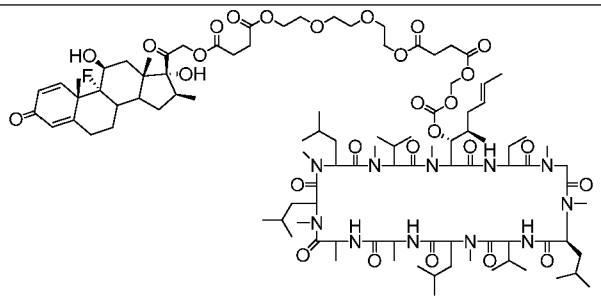


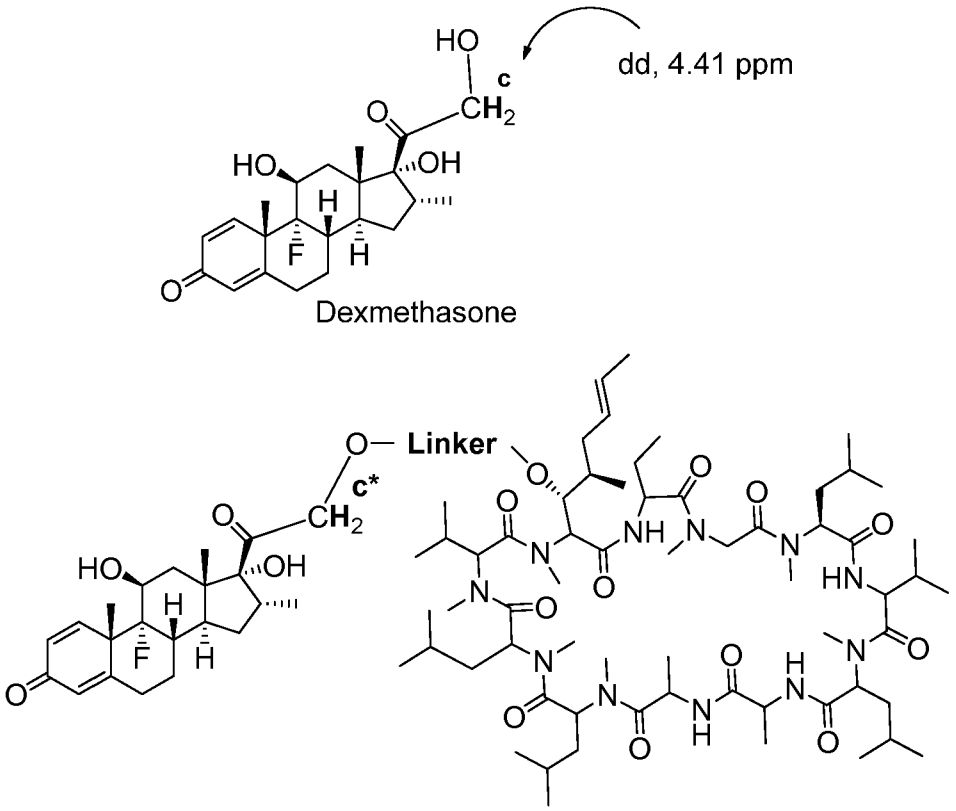
Table 5

* Comp. Linker	Structure	Ha* δ(ppm)	Hb* δ(ppm)	Mass
24 **L63**		**5.93**	**5.61**	**1773** **MNa+**

25 L69		5.81	5.69	2050 MNa+
26 L114		5.62	5.50	1889 MNa+
27 L106		5.79	5.72	1872 MNa+
28 L68		5.81	5.69	2006 MNa+

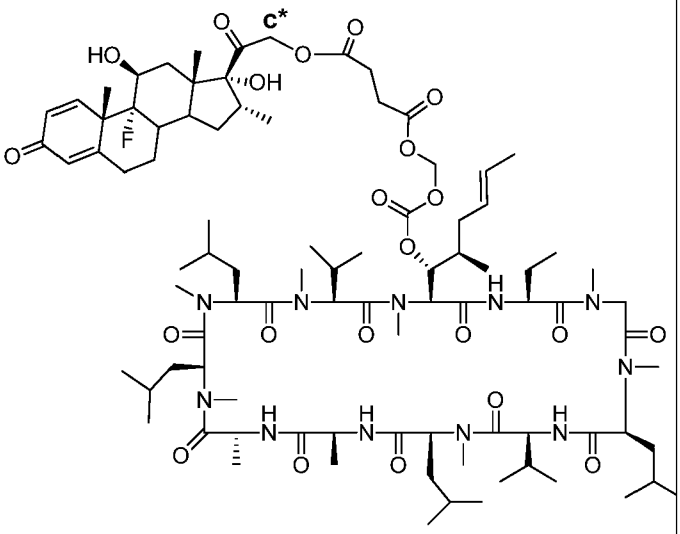
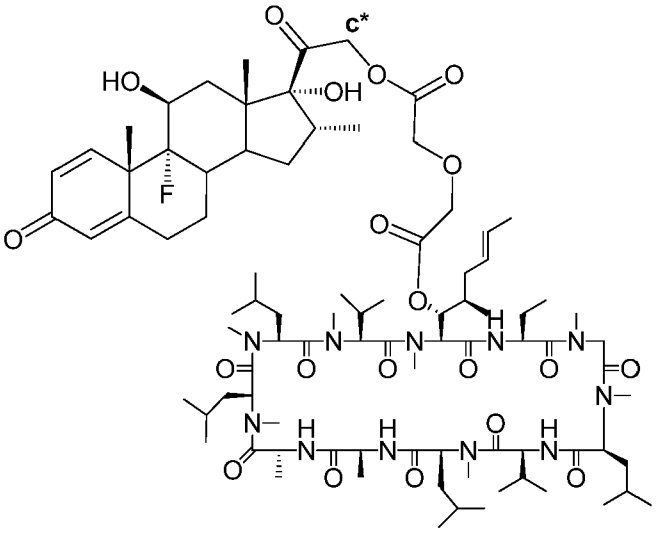
Dexmethasone reacted with one molecule of **Cyclosporine A** to form the following hybrid compounds as shown in **Scheme 4** with the results described in **Table 6.**

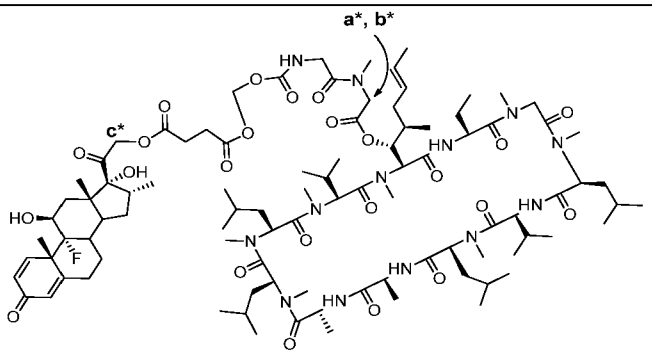
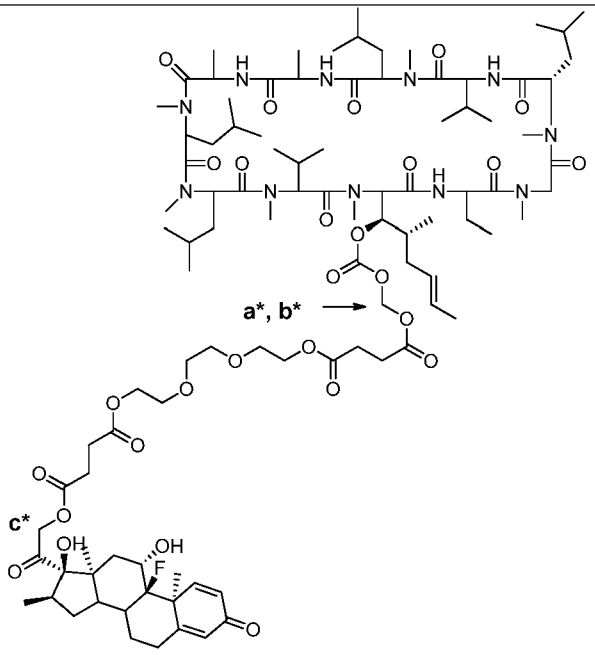
Scheme 4

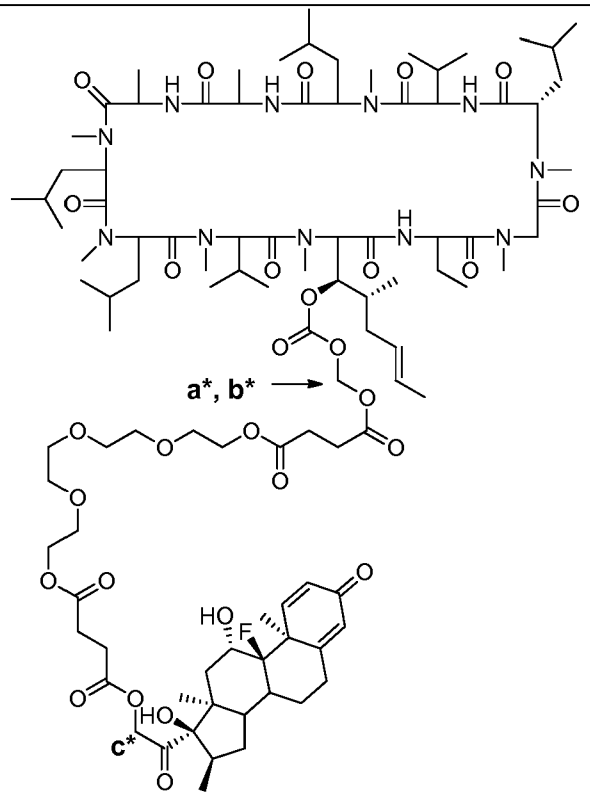


5

Table 6

* Comp. Linker	Structure	Ha* δ(ppm)	Hb* δ(ppm)	Mass
29 L63		5.94	5.58	1773 MNa+
30 L61				

31 L75		5.73		1901 MNa+
32 L68		5.82	5.69	2005 MNa+

20 L69		5.82	5.69	2050 MNa+

***In vitro* Metabolic Stability in Human Recombinant Carboxylesterases**

Human recombinant carboxylesterases were purchased from a commercial vendor (BD Gentest™, Bedford, Massachusettes). All metabolic stability experiments were performed in triplicate in 96-well plate format. The final incubation mixture contained 1 μM test compound and 0.1 mg/mL human recombinant carboxylesterase mixture in a final volume of 0.5 mL 0.1M potassium phosphate buffer (pH=6.0). The final percentage of solvent in the incubation was less than 1.0% to prevent inhibition of enzymatic activity. Following a pre-incubation at 37°C, test article was added to initiate the reaction. At designated time points (typically 120 minutes to capture the linear range of metabolite formation), 0.05 mL aliquots were removed from the incubation mixtures using a clean pipet tip and immediately placed in organic solvent to stop any esterase activity. The hydrolysis to the metabolites was confirmed to be due to esterase activity and not chemical lability.

The samples were analyzed by liquid chromatography with mass spectrometry (LC-MS/MS) detection to determine the metabolite concentrations resulting from the metabolism of the hybrid compounds. Internal standards were

used to compensate for variability from sample processing, chromatographic elution, mass spectrometer response and ion suppression by matrix components.

Results

Table 7 Lists the rate of metabolite formation in human recombinant carboxylesterases.

Table 7

Comp. No.	Rate of formation Metabolite 1 (nM/min/mg)	Rate of formation Metabolite 2 (nM/min/mg)
5	84.4 ± 7.52 Prednisolone	35.6 ± 0.63 Cyclosporine A
6	30.4 ± 1.06 Prednisolone	34.4 ± 3.85 Cyclosporine A
7	4.26 ± 1.31 Prednisolone	1.31 ± 0.18 Cyclosporine A
32	20.4 ± 3.18 Dexamethasone	13.4 ± 1.31 Cyclosporine A
20	12.0 ± 0.88 Dexamethasone	13.9 ± 1.11 Cyclosporine A
21	20.0 ± 1.32 Prednisolone	21.6 ± 0.03 Cyclosporine A

22	38.4 ± 3.32 Prednisolone	46.5 ± 3.16 Cyclosporine A

The data demonstrate that linkage of cyclosporine A and a steroid (e.g. dexamethasone and prednisolone) as a single hybrid compound was hydrolyzed enzymatically in human recombinant carboxylesterases to their respective individual cyclosporine A and steroid drugs.

What is claimed is:

1. A hybrid drug comprising at one Cyclosporine A moiety and one steroid moiety, or a pharmaceutical salt thereof, which are connected via two separate covalent bonds to a linker such that said covalent bonds degrade *in vivo* to yield the Cyclosporine A and the steroid independently.
2. The hybrid drug according to claim 1 wherein the steroid moiety is selected from: dexmethasone, betamethasone, triamcinolone acetonide, prednisolone and hydrocortisone.
3. The hybrid compound according to claim 1, wherein said linker comprises an ester, a carboxylate, a carbonyl, a carbonate, an amido, a carbamate, a ketone, an amino, an oxo, an ethylene glycol, a polyethylene glycol or an alkylene moiety.
4. The hybrid compound according to claim 1, comprising a linker having two bonds, wherein said bonds are asymmetrically degraded *in vivo* to release independently the Cyclosporine A moiety and the steroid moiety.
5. The hybrid compound according to claim 1, comprising a hydrocortisone moiety and a cyclosporine A moiety.
6. The hybrid compound according to claim 1, comprising a prednisolone moiety and a cyclosporine A moiety.
7. The hybrid compound according to claim 1, comprising a betamethasone moiety and a cyclosporine A moiety.
8. The hybrid compound according to claim 1, comprising a dexmethasone moiety and a cyclosporine A moiety.
9. The hybrid compound according to claim 1, further comprising a pro-drug moiety, either at the steroid or at the cyclosporine site.
10. The compound according to claim 1, selected from:
    21-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} 1-({[({(2R,4E)-1-[(2S,11S,20S,26R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-

3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl) rel-(3R)-3-amino-4,18-dioxo-5,8,11,14,17-pentaoxahenicosane-1,21-dioate;

6-[(6-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy}-6-oxohexyl)oxy]-6-oxohexyl {[({(2R,4E)-1-[(11S,17R,32R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-butanedioate;

8-[(4-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy}-4-oxobutanoyl)oxy]octyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-butanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl (2E,5R)-6-[(11S,17R,26R,32R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-5-methyl-8,12,19-trioxo-7,9,11,18-tetraoxatetracos-2-en-24-yl rel-butanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl 6-({[({(2R,4E)-1-[(2S,11S,17R,23S,26R,32R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methoxy)-6-oxohexyl rel-butanedioate;

2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-(14R,16E)-13-[(2R,5R,11S,17R,29R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-14-methyl-4,7,11-trioxo-2-(propan-2-yl)-8,10,12-trioxa-3-azaoctadec-16-en-1-oate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-(14R,16E)-13-[(2R,5R,11S,17R,29R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-14-methyl-4,7,11-trioxo-2-(propan-2-yl)-8,10,12-trioxa-3-azaoctadec-16-en-1-oate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-4,21-dioxo-5,8,11,14,17,20-hexaoxatetracosane-1,24-dioate;

2-{2-[(4-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy}-4-oxobutanoyl)oxy]ethoxy}ethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-butanedioate;

{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16S,17R)-9-

fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-4,15-dioxo-5,8,11,14-tetraoxaoctadecane-1,18-dioate;

rel-(2R)-4-({[({(2S,4E)-1-[(11R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methoxy)-2-[(4-{2-[(9S,10R,11R,13R,16R,17S)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy}-4-oxobutanoyl)amino]-4-oxobutanoic acid;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-(10R,18R,20E)-10-amino-17-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-18-methyl-4,11,15-trioxo-12,14,16-trioxa-5-azadocos-20-en-1-oate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-benzene-1,4-dicarboxylate;

1-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} 4-({[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl) rel-(2R)-2-aminobutanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-(2E)-but-2-enedioate;

{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16S,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-4,18-dioxo-5,8,11,14,17-pentaoxahenicosane-1,21-dioate;

{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-4,18-dioxo-5,8,11,14,17-pentaoxahenicosane-1,21-dioate;

{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-4,15-dioxo-5,8,11,14-tetraoxaoctadecane-1,18-dioate;

4-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} 1-({[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-

undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl) rel-(2S)-2-aminobutanedioate;

(2R)-2-amino-3-({[({(2R,4E)-1-[(5R,11S,26R)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methoxy)-3-oxopropyl 2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-butanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl 1-{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}ethyl rel-4,15-dioxo-5,8,11,14-tetraoxaoctadecane-1,18-dioate;

1-{(2R,4E)-1-[(2S,5R,11S,14S,17R,20S,23R,26R,29S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl} 14-{2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} rel-3-methyl-4,7,11-trioxo-8,10-dioxa-3,6-diazatetradecane-1,14-dioate;

14-{2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl} 1-{(2R,4E)-1-[(11S,23S,26S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl} rel-3-methyl-4,7,11-trioxo-8,10-dioxa-3,6-diazatetradecane-1,14-dioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-4,18-dioxo-5,8,11,14,17-pentaoxahenicosane-1,21-dioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-4,15-dioxo-5,8,11,14-tetraoxaoctadecane-1,18-dioate;

(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl 2-[(9R,10S,11S,13S,16R,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-2,2'-oxydiacetate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-(12R,14E)-11-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-12-methyl-5,9-dioxo-3,6,8,10-tetraoxahexadec-14-en-1-oate;

{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16R,17R)-9-

fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-butanedioate;

{[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl 2-[(9R,10S,11S,13S,16S,17R)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl rel-butanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-pentanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl {[({(2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl}oxy)carbonyl]oxy}methyl rel-butanedioate;

2-[(10R,11S,13S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl (2R,4E)-1-[(11S)-5-ethyl-1,7,10,16,20,23,25,28,31-nonamethyl-11,17,26,29-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-14,32-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl]-2-methylhex-4-en-1-yl rel-2,2'-oxydiacetate.

11. A pharmaceutical composition comprising a hybrid drug comprising a Cyclosporine A moiety and a steroid moiety, which are connected via two separate covalent bonds to a linker, wherein said covalent bonds degrade *in vivo* to yield the Cyclosporine A moiety and the steroid moiety, and wherein each bond is an ester bond or an amide bond, and wherein said

pharmaceutical composition is formulated for topical ophthalmic administration.

12. A method comprising administrating to an eye of a mammal a pharmaceutical composition comprising a therapeutically active amount of a hybrid drug comprising a Cyclosporine A moiety and a steroid moiety, which are connected via two separate covalent bonds to a linker such that said covalent bonds degrade *in vivo* to yield the Cyclosporine A and the steroid, wherein each bond is an ester bond or an amide bond, wherein said method is effective in the treatment of a bacterial infection or an inflammation affecting said eye.

13. The method according to claim 12, wherein the bacterial infection is selected from: conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum, corneal ulcers, anterior blepharitis, posterior blepharitis, endophthalmitis, meibomian gland dysfunction, dry eye disease (keratocojunctivitis sicca) ocular pain, ocular pain and inflammation post-ocular surgery ,bacterial conjunctivitis, anterior uveitis, post-surgical inflammation, inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, such as allergic conjunctivitis, ocular rosacea, blepharitis, meibomian gland dysfunction, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis, corneal injury from chemical radiation, or thermal burns, penetration of foreign bodies and allergy.

14. The method according to claim 12, wherein the mammal is a human.