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(54) Benævnelse: **SUBSTITUEREDE TETRACYKLINFORBINDELSER TIL BEHANDLING AF INFLAMMATORISKE HUDLIDELSER**

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DESCRIPTION

Background of the Invention

[0001] Acne is a disorder resulting from the actions of hormones on the sebaceous glands, which leads to plugged pores and outbreaks of lesions, commonly called pimples. Nearly 17 million people in the United States have acne, making it the most common skin disease. Severe acne can lead to disfiguring, permanent scarring.

[0002] Acne is described as a disorder of the pilosebaceous units (PSUs). Found over most of the body, PSUs consist of a sebaceous gland connected to a canal, called a follicle that contains a fine hair. These units are most numerous on the face, upper back and chest. The sebaceous glands make an oily substance called sebum that normally empties onto the skin surface through the opening of the follicle, also called a pore. Cells called keratinocytes line the follicle.

[0003] The hair, sebum and keratinocytes that fill the narrow follicle may produce a plug, which is an early sign of acne. The plug prevents sebum from reaching the surface of the skin through a pore. The mixure of oil and cells allows bacteria *Propionibacterium acnes* (*P. acnes*) that normally live on the skin to grow in the plugged follicles. The bacteria produce chemicals and enzymes and attract white blood cells that cause inflammation. Then the wall of the plugged follicle breaks down, the sebum, shed skin cells and bacteria disseminate into the nearby tissues, leading to lesions or pimples.

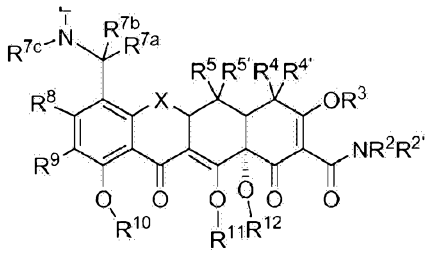
[0004] For patients with moderate to severe acne, the doctor often prescribes oral antibiotics. Oral antibiotics are thought to help control acne by curbing the growth of bacteria and reducing inflammation. Tetracyclines have been used because of their anti-bacterial and anti-inflammatory properties.

Summary of the Invention

[0005] The present invention pertains, at least in part, to a compound for use in treating an inflammatory skin disorder in a subject by administering an effective amount of a substituted tetracycline compound to the subject. Advantageously, the substituted tetracycline compounds used in the invention have one or more of the following characteristics: 1) narrow spectrum anti-bacterial activity against gram-positive bacteria; 2) anti-inflammatory activity; 3) less phototoxicity than doxycycline; and 4) oxidatively more stability than minocycline.

[0006] In a first aspect, the present invention pertains to a compound for use in treating an inflammatory skin disorder in a subject by administering an effective amount of a substituted tetracycline compound of formula I:

F



(I)

wherein

X is CHC(R^{13}Y'Y), C$R^{6'}R^{6}$, C=C$R^{6'}R^{6}$, S, NR^{6}, or O;

E is N$R^{7d}R^{7e}$ or OR^{7f};

W is O, S, NR^{7h}, or C$R^{7i}R^{7j}$;

W' is O, S, or NR^{7k};

R^{2}, $R^{2'}$, $R^{4'}$, R^{4a} and R^{4b} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, or heteroaromatic;

R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen

R^{4} is N$R^{4a}R^{4b}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R^{5} and $R^{5'}$ are each independently hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are each independently hydrogen, methylene, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, and R^{7f}, are each independently hydrogen, allyl, alkyl, alkenyl, alkynyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, alkylamino, aminoalkyl, acyl, aryl, arylalkyl, alkylcarbonyloxy, or arylcarbonyloxy, or R^{7c} and R^{7d} or R^{7c} and R^{7f} are linked to form a ring;

R^{8} is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{9} is hydrogen, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, aminoalkyl, amido, arylalkenyl, arylalkynyl, thionitroso, or $-(CH_2)_{0-3}(NR^{9c})_{0-1}C(=Z')ZR^{9a}$;

Z is C$R^{9d}R^{9e}$, S, NR^{9b} or O;

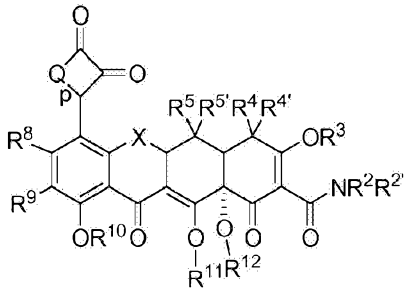
Z' is O, S, or NR^{9f};

R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e} and R^{9f} are each independently hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, or heteroaromatic;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, amido, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl, and pharmaceutically acceptable salts thereof.

[0007] In a second aspect, the present invention pertainsto a compound for use in treating an inflammatory skin disorder in a subject by administering an effective amount of a substituted tetracycline compound of formula VI:



(VI)

wherein

X is $CHC(R^{13}Y'Y)$, $CR^{6'}R^{6}$, $C{=}CR^{6'}R^{6}$, S, NR^{6}, or O;

p is a single bond or a double bond;

Q is CR^{7s} when p is a double bond or Q is $CR^{7s'}R^{7s''}$ when p is a single bond;

R^{2}, $R^{2'}$, $R^{4'}$. R^{4a} and R^{4b} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, or heteroaromatic;

R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen

R^{4} is $NR^{4a}R^{4b}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R^{5} and $R^{5'}$ are each independently hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are each independently hydrogen, methylene, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{7s}, $R^{7s'}$ and $R^{7s''}$ are each hydrogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxy, alkylthio,

alkylsulfinyl, alkylsulfonyl, amino, aminoalkyl, alkylamino, aryl, acyl, arylalkyl, alkyl carbonyloxy, or arylcarbonyloxy;

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is hydrogen, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, aminoalkyl, amido, arylalkenyl, arylalkynyl, thionitroso or $-(CH_2)_{0-3}(NR^{9c})_{0-1}C(=Z')ZR^{9a}$;

Z is $CR^{9d}R^{9e}$, S, NR^{9b} or O;

Z' is O, S, or NR^{9f};

R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e} and R^{9f} are each independently hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, or heteroaromatic;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, amido, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl, and pharmaceutically acceptable salts thereof.

[0008] Also described is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a substituted tetracycline compound for the treatment of an inflammatory skin disorder, wherein said compound is of formula I or VI.

Brief Description of the Drawings

[0009] Figure 1 is a graphical comparison of the modulation of carregeenan induced inflammation in the rat paw edema model between minocycline and compound P.

Detailed Description of the Invention

[0010] In accordance with the first and second aspects, the present invention is directed to a compound for use in treating an inflammatory skin disorder in a subject by administering an effective amount of a substituted tetracycline compound to the subject. Advantageously, the tetracycline compound used in the invention has one or more of the following characteristics:

1) narrow spectrum anti-bacterial activity against gram-positive bacteria; 2) anti-inflammatory activity; 3) a phototoxicity less than or equal to doxycycline; and 4) an oxidative potential less than or equal to minocycline.

[0011] The term "inflammatory skin disorder" includes, for example, eczema, dermatitis, psoriasis, pyoderma gangrenosum, acne and rosacea.

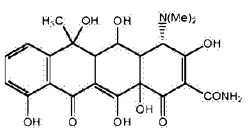
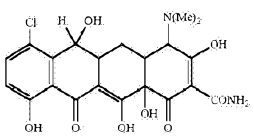
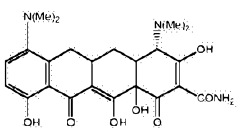
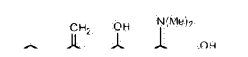
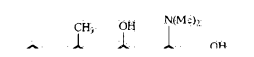
[0012] The term "subject" includes animals (*e.g.,* mammals, *e.g.,* cats, dogs, horses, pigs, cows, sheep, rodents, rabbits, squirrels, bears, primates (*e.g.*, chimpanzees, gorillas, and humans)) which are capable of (or currently) suffering from an inflammatory skin disorder. It also includes transgenic animal models.

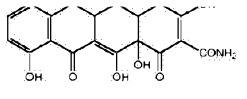
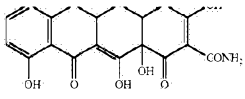
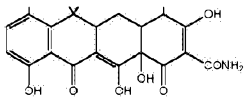
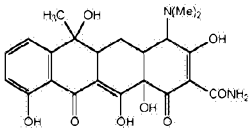
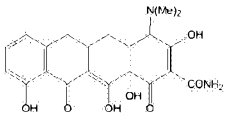
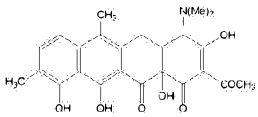
[0013] The term "treated," "treating" or "treatment" includes therapeutic and/or prophylactic treatment of inflammatory skin disorders. The treatment includes the diminishment or alleviation of at least one symptom associated with an inflammatory skin disorder. For example, treatment can be diminishment of one or several symptoms of the inflammatory skin disorder or complete eradication of the inflammatory skin disorder.

[0014] The language "effective amount" of the tetracycline compound is that amount necessary or sufficient to treat or prevent the inflammatory skin disorder in a subject, e.g. prevent the various symptoms of the inflammatory skin disorder. The effective amount can vary depending on such factors as the size and weight of the subject, the type of inflammatory skin disorder, or the particular tetracycline compound. For example, the choice of the tetracycline compound can affect what constitutes an "effective amount." One of ordinary skill in the art would be able to study the aforementioned factors and make the determination regarding the effective amount of the tetracycline compound without undue experimentation.

[0015] The term "tetracycline compound" includes substituted tetracycline compounds or compounds with a similar ring structure to tetracycline. Examples of tetracycline compounds include: chlortetracycline, oxytetracycline, demeclocycline, methacycline, sancycline, chelocardin, rolitetracycline, lymecycline, apicycline; clomocycline, guamecycline, meglucycline, mepylcycline, penimepicycline, pipacycline, etamocycline, penimocycline, etc. Other derivatives and analogues comprising a similar four ring structure are also included (See Rogalski, "Chemical Modifications of Tetracyclines," the entire contents of which are hereby incorporated herein by reference). Table 1 depicts tetracycline and several known other tetracycline derivatives.

Table 1

		
Oxytetracycline	Demeclocycline	Minocycline
		

		
Methacycline	Doxycycline	Chlortetracycline
		
Tetracycline	Sancycline	Chelocardin

[0016] Other tetracycline compounds which may be modified include, but are not limited to, 6-demethyl-6-deoxy-4-dedimethylaminotetracycline; tetracyclino-pyrazole; 7-chloro-4-dedimethylaminotetracycline; 4-hydroxy-4-dedimethylaminotetracycline; 12α-deoxy-4-dedimethylaminotetracycline; 5-hydroxy-6α-deoxy-4-dedimethylaminotetracycline; 4-dedimethylamino-12α-deoxyanhydrotetracycline; 7-dimethylamino-6-demethyl-6-deoxy-4-dedimethylaminotetracycline; tetracyclinonitrile; 4-oxo-4-dedimethylaminotetracycline 4,6-hemiketal; 4-oxo-11a Cl-4-dedimethylaminotetracycline-4,6-hemiketal; 5a,6-anhydro-4-hydrazon-4-dedimethylamino tetracycline; 4-hydroxyimino-4-dedimethylamino tetracyclines; 4-hydroxyimino-4-dedimethylamino 5a,6-anhydrotetracyclines; 4-amino-4-dedimethylamino-5a,6 anhydrotetracycline; 4-methylamino-4-dedimethylamino tetracycline; 4-hydrazono-11a-chloro-6-deoxy-6-demethyl-6-methylene-4-dedimethylamino tetracycline; tetracycline quaternary ammonium compounds; anhydrotetracycline betaines; 4-hydroxy-6-methyl pretetramides; 4-keto tetracyclines; 5-keto tetracyclines; 5a, 11a dehydro tetracyclines; 11a Cl-6, 12 hemiketal tetracyclines; 11a Cl-6-methylene tetracyclines; 6, 13 diol tetracyclines; 6-benzylthiomethylene tetracyclines; 7, 11a -dichloro-6-fluoro-methyl-6-deoxy tetracyclines; 6-fluoro (α)-6-demethyl-6-deoxy tetracyclines; 6-fluoro (β)-6-demethyl-6-deoxy tetracyclines;6-α acetoxy-6-demethyl tetracyclines; 6-β acetoxy-6-demethyl tetracyclines; 7, 13-epithiotetracyclines; oxytetracyclines; pyrazolotetracyclines; 11a halogens of tetracyclines; 12a formyl and other esters of tetracyclines; 5, 12a esters of tetracyclines; 10, 12a- diesters of tetracyclines; isotetracycline; 12-a-deoxyanhydro tetracyclines; 6-demethyl-12a-deoxy-7-chloroanhydrotetracyclines; B-nortetracyclines; 7-methoxy-6-demethyl-6-deoxytetracyclines; 6-demethyl-6-deoxy-5a-epitetracyclines; 8-hydroxy-6-demethyl-6-deoxy tetracyclines; monardene; chromocycline; 5a methyl-6-demethyl-6-deoxy tetracyclines; 6-oxa tetracyclines, and 6 thia tetracyclines.

[0017] The term "substituted tetracycline compound" includes tetracycline compounds with one or more additional substituents, e.g., at the 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 11a, 12, 12a or 13 position or at any other position which allows the substituted tetracycline compound to perform its intended function, *e.g.,* treat a skin disorder. The substituted tetracycline compounds for use in the invention are compounds of formual I or VI. It does not include unsubstituted minocycline, unsubstituted doxycycline or sancycline.

[0018] In one embodiment, the substituted tetracycline compound has an MIC (*e.g.,* as measured in Example 2) of between about 0.001 to 64 μg/mL, preferably between about 0.001

and 16 µg/mL and more preferably between about 0.001 and 4 µg/mL.

[0019] The substituted tetracycline compound may exhibit antibacterial activity. In another embodiment, the substituted tetracycline compound exhibits anti-inflammatory activity. The substituted tetracycline compound may exhibit both antibacterial and anti-inflammatory activities. The term "anti-inflammatory activity" includes activity that prevents, reduces or ameliorates the symptoms of acute or chronic inflammation. The substituted tetracycline compounds for use in the invention may treat, prevent, reduce or ameliorate the symptoms of inflammation (*e.g.*, redness, swelling, heat, pain, loss of function, tissue destruction, etc.) and/or may effect the biochemical pathways that cause inflammation in the body to treat, prevent, reduce or ameliorate inflammation.

[0020] The substituted tetracycline compounds for use in the invention may have one or more; two or more; three or more; or all of the following characteristics: 1) narrow spectrum anti-bacterial activity; 2) anti-inflammatory activity; 3) a phototoxicity less than or equal to doxycycline and 4) an oxidative potential less than or equal to minocycline.

[0021] The substituted tetracycline compound may have narrow spectrum antibiotic activity. The term "narrow spectrum" includes activity against specific types of bacteria. The substituted tetracycline compounds may exhibit greater antibacterial activity against gram positive bacteria than against gram negative bacteria. Examples of gram positive bacteria include, for example, *S. aureus, S. pneumoniae, P. granulosum* and *P. acnes.*

[0022] In one embodiment, the substituted tetracycline compound used in the invention has an MIC of less than 64 µg/mL, less than 32 µg/mL, less than 16 µg/mL, less than 8 µg/mL, less than 4 µg/mL or less than 1 µg/mL against gram positive bacteria, *e.g., P. acnes,* and/or *P. granulosum.*

[0023] In one embodiment, the substituted tetracycline compound used in the methods of the invention has a minimum inhibitory concentration (MIC) less than that of doxycycline or minocycline for *S. aureus, P. granulosum, S. pneumoniae,* or *P. acnes.*

[0024] The tetracycline compounds for use in the invention have narrow spectrum antibacterial activity. The term "narrow spectrum" includes tetracycline compounds which do have substantial antibacterial activity against gram positive bacteria, *e.g.,* tetracycline compounds with an MIC of less than about 64 µg/mL, less than about 32 µg/mL, less than about 16 µg/mL, less than about 8 µg/mL, less than about 4 µg/mL or less than about 1 µg/mL against *S. aureus, P. granulosum, P. acnes* or *S. pneumoniae* (*e.g.,* as tested in the assay described in Example 2).

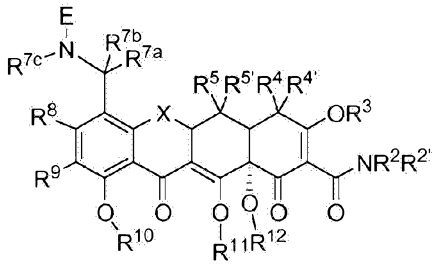
[0025] The term "narrow spectrum" includes tetracycline compounds which do not have substantial antibacterial activity against gram negative bacteria, *e.g.,* tetracycline compounds with an MIC of greater than about 1 µg/mL, greater than about 4 µg/mL, greater than about 8 µg/mL, greater than about 16 µg/mL, greater than about 32 µg/mL, or greater than about 64

µg/mL against gram negative bacteria such as *E. coli* or *B. thetaiotaomicron* (*e.g.,* as tested in the assay described in Example 2).

[0026] In another embodiment, the substituted tetracycline compounds used in the invention has anti-inflamatory activity, *e.g.,* as determined in the rat-paw edema model described in Example 7.

[0027] The substituted tetracycline compounds used in the invention may have a phototoxicity equal to or less than that of doxycycline (*e.g.*, such as measured in the assay described in Example 4). The substituted tetracycline compounds used in the invention may have an oxidative potential less than or equal to the oxidative potential of minocycline (*e.g.*, such as measured in the assay described in Example 5).

[0028] In accordance with the first aspect, the substituted tetracycline compound of the invention is of the formula I:



(I)

wherein

X is $CHC(R^{13}Y'Y)$, $CR^{6'}R^{6}$, $C{=}CR^{6'}R^{6}$, S, NR^{6}, or O;

E is $NR^{7d}R^{7e}$ or OR^{7f};

R^{2}, $R^{2'}$, $R^{4'}$, R^{4a} and R^{4b} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, or heteroaromatic;

R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen

R^{4} is $NR^{4a}R^{4b}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R^{5} and $R^{5'}$ are each independently hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are each independently hydrogen, methylene, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, and R^{7f} are each independently hydrogen, allyl, alkyl, alkenyl, alkynyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, alkylamino, aminoalkyl, acyl, aryl, arylalkyl, alkylcarbonyloxy, or arylcarbonyloxy, or R^{7c} and R^{7d} or R^{7c} and R^{7f} are linked to form a ring;

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is hydrogen, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, aminoalkyl, amido, arylalkenyl, arylalkynyl, thionitroso, or $-(CH_2)_{0-3}(NR^{9c})_{0-1}C(=Z')ZR^{9a}$;

Z is $CR^{9d}R^{9e}$, S, NR^{9b} or O;

Z' is O, S, or NR^{9f};

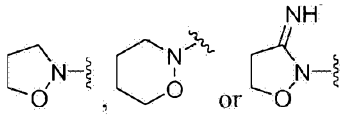
R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e} and R^{9f} are each independently hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, or heteroaromatic;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, amido, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl, and pharmaceutically acceptable salts thereof.

[0029] In one embodiment, X is $CR^{6'}R^6$, R^4 is $NR^{4a}R^{4b}$, R^{4a} and R^{4b} are each alkyl *(e.g.,* methyl); R^2, $R^{2'}$, R^3, $R^{4'}$ R^5, $R^{5'}$ R^6, $R^{6'}$, R^{7a}, R^{7b}, R^{7c}, R^8, R^9, R^{10}, R^{11} and R^{12} are each hydrogen; E is OR^{7f}; R^{7f} is allyl (*e.g.,* CH_2=$CHCH_2$-) or alkyl (*e.g.,* ethyl; isopropyl; t-butyl; alkoxy substituted alkyl (*e.g.,* methoxyethyl); halogen substituted alkyl *(e.g.,* alkyl substituted with fluorine, for example, FCH_2CH_2-; F_2CHCH_2-; CF_3CH_2- or CF_2H-); alkylcarbonylalkyl (*e.g.*, $CH_3CO(CH_2)_n$-, in which n is an integer from 0-6, for example 1); alkoxycarbonylalkyl (*e.g.*, $CH_3OCO(CH_2)_m$-, in which m is an integer from 0-6, for example 1) or carboxylatealkyl ($HOOC(CH_2)_q$-, in which q is an integer from 0-6, for example 1).

[0030] In one embodiment, X is $CR^{6'}R^6$, R^4 is $NR^{4a}R^{4b}$, R^{4a} and R^{4b} are each alkyl (*e.g.,* methyl); R^2, $R^{2'}$, R^3, $R^{4'}$ R^5, $R^{5'}$ R^6, $R^{6'}$, R^{7a}, R^{7b}, R^8, R^9, R^{10}, R^{11} and R^{12} are each hydrogen; E is OR^{7f} and R^{7c} and R^{7f} are linked to join a ring, for example, a 5- or 6-membered ring (*e.g.,*



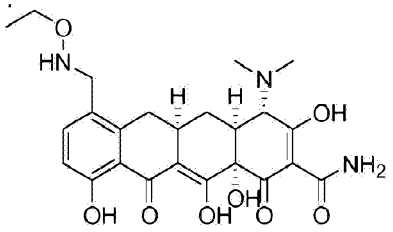
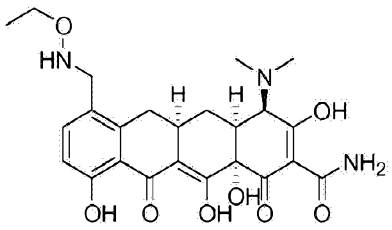
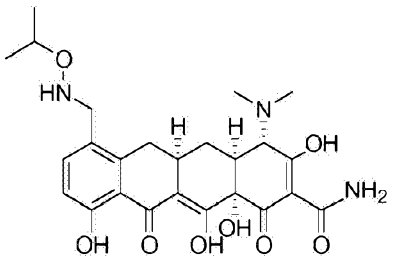
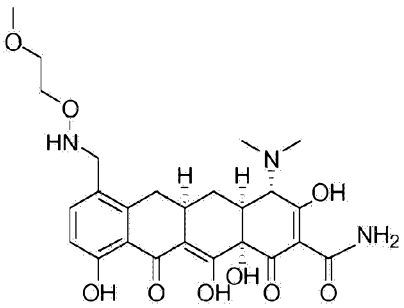
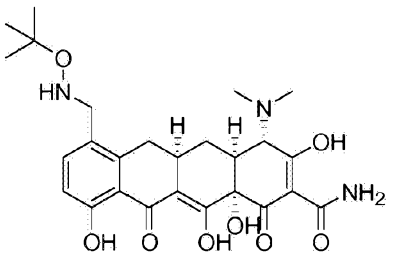
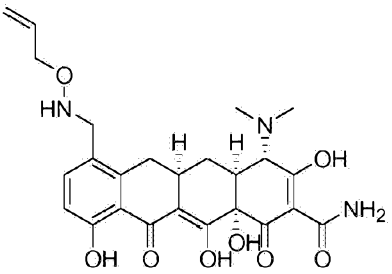
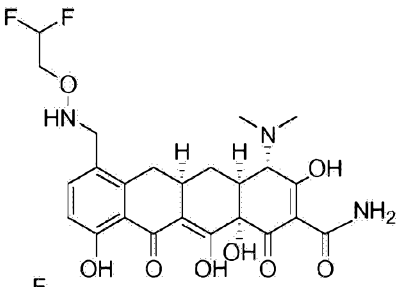
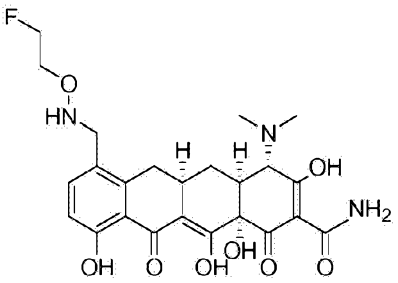
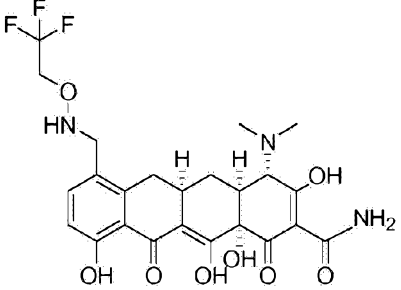
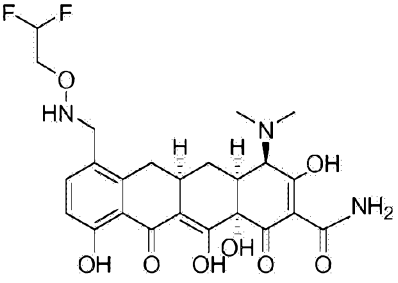
).

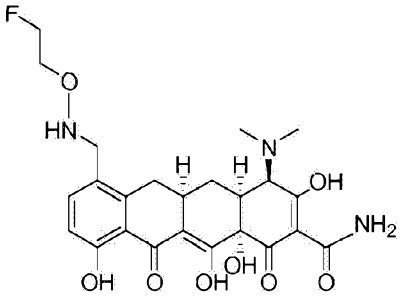
[0031] In another embodiment, X is $CR^{6'}R^6$, R^4 is $NR^{4a}R^{4b}$, R^{4a} and R^{4b} are each alkyl *(e.g.,*

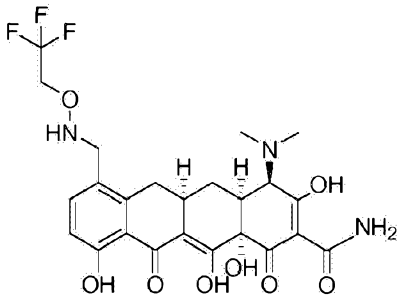
methyl); R^2, $R^{2'}$, R^3, $R^{4'}$ R^5, $R^{5'}$ R^6, $R^{6'}$, R^{7a}, $R^{7b}R^8$, R^9, R^{10}, R^{11} and R^{12} are each hydrogen; E is OR^{7f}; R^{7c} and R^{7f} may be each independently alkyl *(e.g.,* methyl or ethyl).

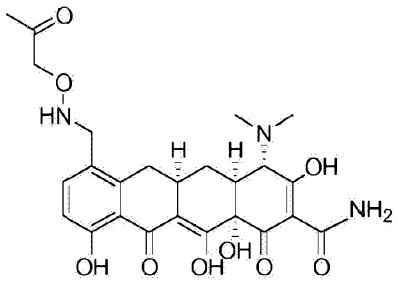
[0032] In yet another embodiment, X is $CR^{6'}R^6$, R^4 is $NR^{4a}R^{4b}$, R^{4a} and R^{4b} are each alkyl (*e.g.,* methyl); R^2, $R^{2'}$, R^3, $R^{4'}$ R^5, $R^{5'}$ R^6, $R^{6'}$, R^{7a}, R^{7b}, R^{7c}, R^8, R^9, R^{10}, R^{11} and R^{12} are each hydrogen; E is $NR^{7d}R^{7e}$; R^{7c} is alkyl (*e.g.,* ethyl); R^{7d} is hydrogen and R^{7e} is alkyl (*e.g.,* ethyl).

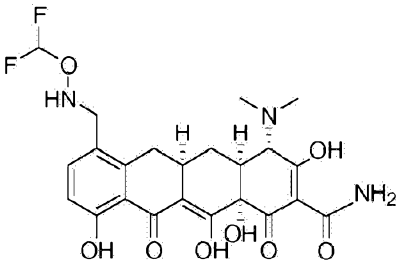
[0033] Examples of substituted tetracycline compounds of formula I include, for example:

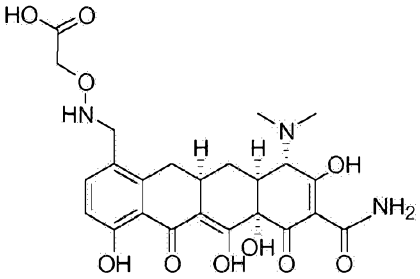











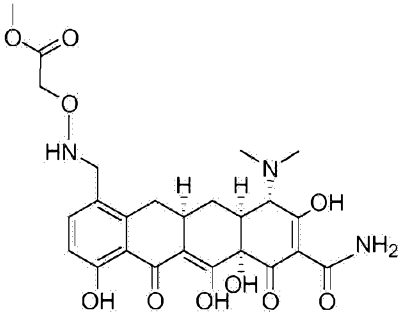


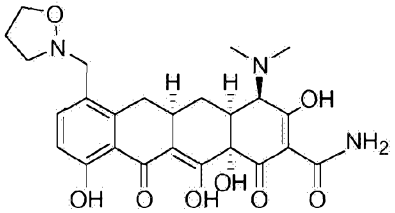


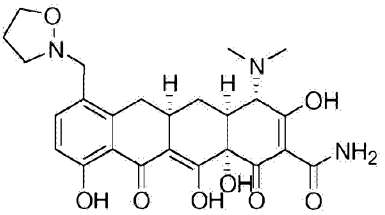


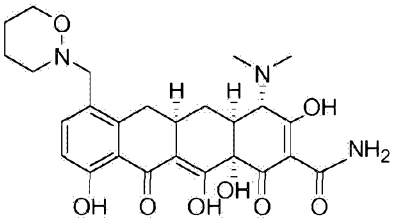


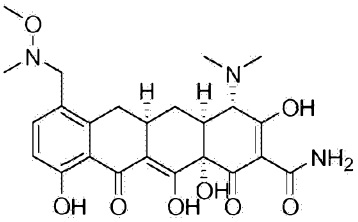


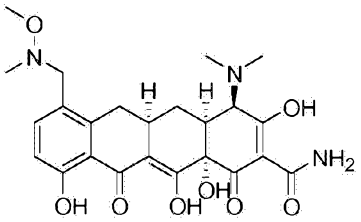


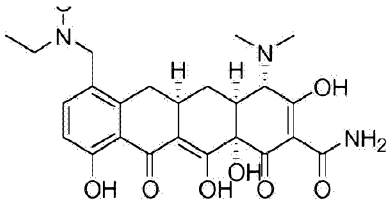


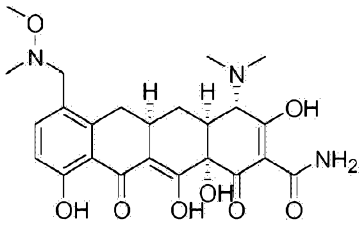


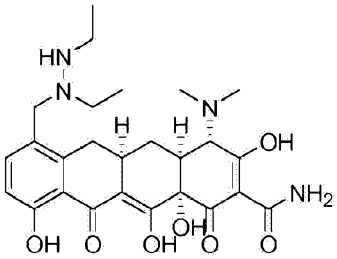






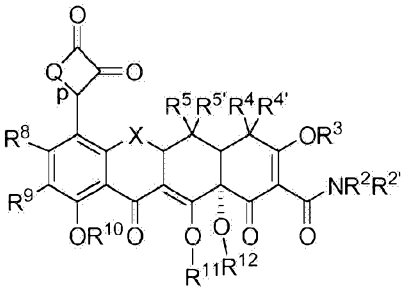






and pharmaceutically acceptable salts thereof.

[0034] In accordance with the second aspect, the substituted tetracycline compound for use in the invention is a compound of formula VI:



(VI)

wherein

X is $CHC(R^{13}Y'Y)$, $CR^{6'}R^{6}$, $C{=}CR^{6'}R^{6}$, S, NR^{6}, or O;

p is a single bond or a double bond;

Q is CR^{7s} when p is a double bond or Q is $CR^{7s'}R^{7s''}$ when p is a single bond;

R^{2}, $R^{2'}$, $R^{4'}$, R^{4a} and R^{4b} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, orheteroaromatic;

R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen

R^{4} is $NR^{4a}R^{4b}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;

R^{5} and $R^{5'}$ are each independently hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are each independently hydrogen, methylene, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{7s}, $R^{7s'}$ and $R^{7s''}$ are each hydrogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, aminoalkyl, alkylamino, aryl, acyl, arylalkyl, alkyl carbonyloxy, or arylcarbonyloxy;

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is hydrogen, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, aminoalkyl, amido, arylalkenyl, arylalkynyl, thionitroso or $-(CH_2)_{0-3}(NR^{9c})_{0-1}C(=Z')ZR^{9a}$;

Z is $CR^{9d}R^{9e}$, S, NR^{9b} or O;

Z' is O, S, or NR^{9f};

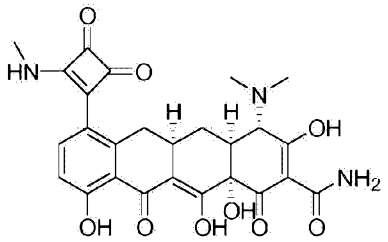
R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e} and R^{9f} are each independently hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, or heteroaromatic;

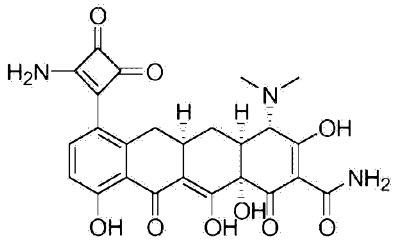
R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, amido, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl, and pharmaceutically acceptable salts thereof.

[0035] In one embodiment, X is $CR^{6'}R^6$, R^4 is $NR^{4a}R^{4b}$, R^{4a} and R^{4b} are each alkyl *(e.g.,* methyl) and R^2, $R^{2'}$, R^3, $R^{4'}$, R^5, $R^{5'}$, R^6, $R^{6'}$, R^8, R^9, R^{10}, R^{11} and R^{12} are each hydrogen. In another embodiment, p is a double bond and Q is CR^{7s}. In a further embodiment, R^{7s} is amino, alkylamino *(e.g.,* methylamino) or dialkylamino *(e.g.,* dimethylamino).

[0036] Examples of substituted tetracycline compounds of formula VI include, for example:



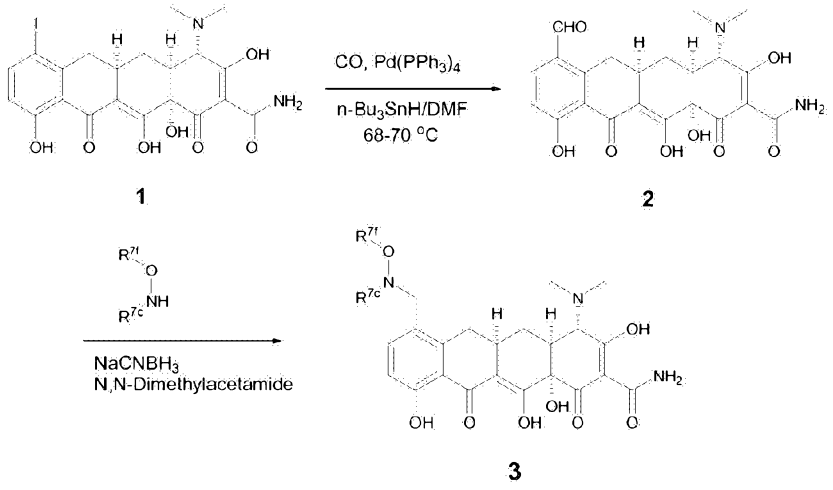


and pharmaceutically acceptable salts thereof.

[0037] The tetracycline compounds for use in this invention can be synthesized using the methods described in the Schemes and/or by other techniques known to those of ordinary skill

in the art. The substituted tetracycline compounds for use in the invention can be synthesized using the methods described in the following schemes and by using art recognized techniques.

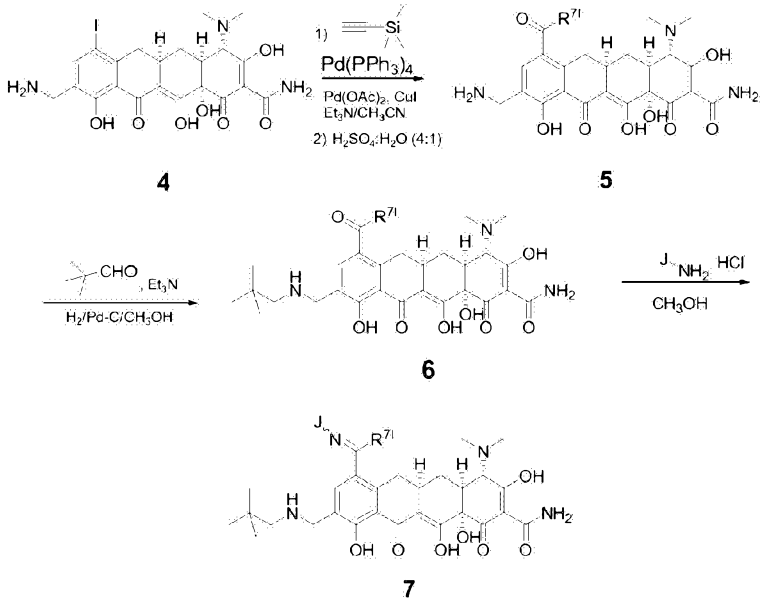
[0038] In Scheme 1, a general synthetic scheme for synthesizing 7-substituted tetracyclines is shown. A palladium catalyzed coupling of an iodosancycline (**1**) is performed to form a 7-substituted aldehyde intermediate (**2**). The aldehyde intermediate is reduced in the presence of a hydroxylamine to give the desired product (**3**).



1 2 3

Scheme 1

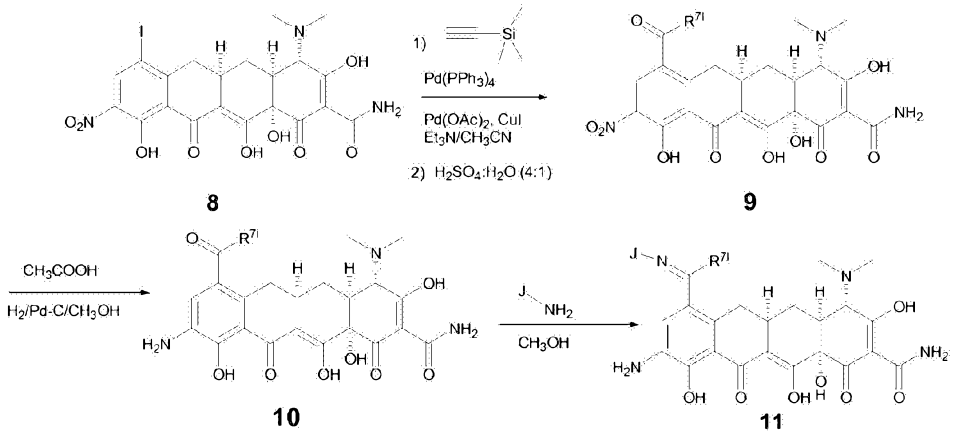
[0039] 7- and 9-substituted tetracycline compounds may be synthesized by reacting the 7-iodo-9-aminoalkyl sancycline derivative (**4**) with trimethylsilylethyne in the presence of a palladium catalyst to yield a 7-substituted alkynyl intermediate. Subsequent acid hydrolysis yields the 7-acyl intermediate (**5**). Further derivitization of the 9-position may be accomplished by reductive alkylation of the amino group with t-butyl aldehyde, hydrogen and palladium on carbon to form compound **6,** which can then be reacted with a primary hydroxylamine to form the oxime **7.**



4 5 6 7

Scheme 2

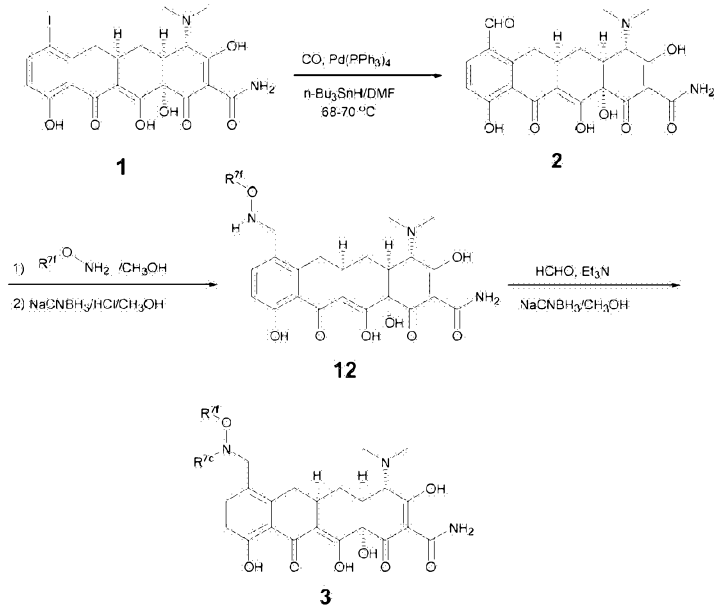
[0040] 7- and 9-substituted tetracycline compounds may also be prepared as shown in Scheme 3. Beginning with a 7-iodo-9-nitro substituted sancycline derivative (**8**), a Hiyama coupling followed by acid hydrolysis yields a 7-acyl-9-nitro intermediate (**9**). The nitro moiety may then be reduced to the amino group by hydrogen gas in the presence of a palladium catalyst (**10**). Reaction of the acyl group with a primary hydroxylamine provides the product **11.**



8 **9** **10** **11**

Scheme 3

[0041] Scheme 4 also provides a method for synthesizing 7-substituted tetracyclines. As described above, a palladium catalyzed carbonylation of an iodosancycline (**1**) is performed to form a 7-substituted aldehyde intermediate (**2**). The aldehyde intermediate is reduced in the presence of a hydroxylamine to give compound **12,** which may then be reacted with formaldehyde and triethylamine, followed by reduction to give the desired product (**3**).



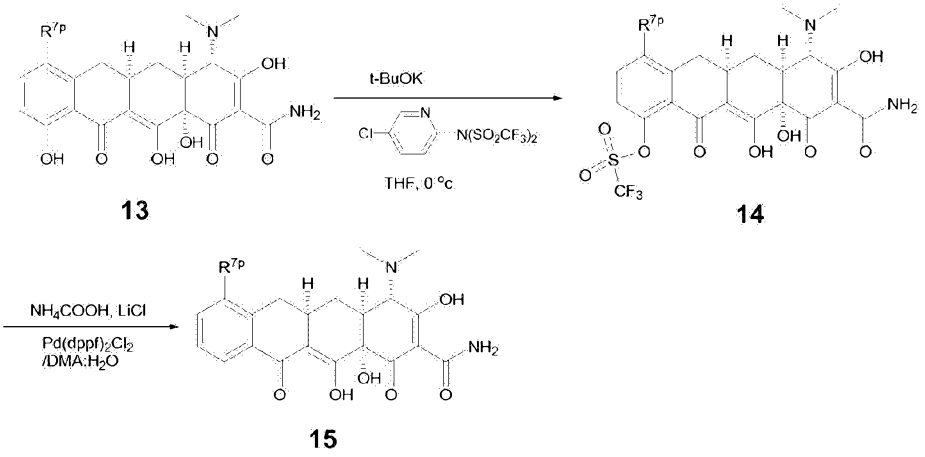
1 **2** **12**

3

Scheme 4

[0042] Scheme 5 details the synthesis of substituted tetracyclines with hydroxy in the 10-position. A 7-substituted tetracycline compound may be reacted with N-(5-chloro-2-

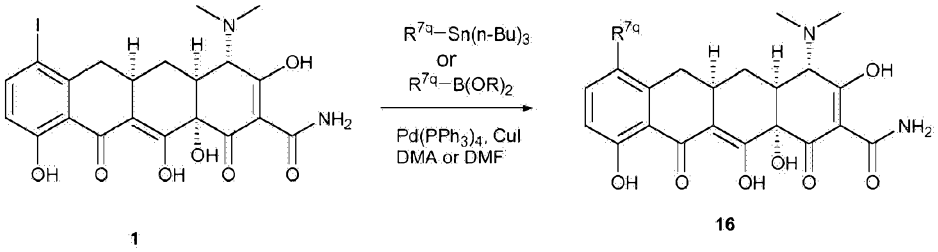
pyridyl)bis(trifluoromethanesulfonimide) to form a trifluoromethane substituted intermediate (**14**), which can then be reacted with ammonium formate in the presence of a palladium catalyst to form the desired product (**15**).



13 14 15

Scheme 5

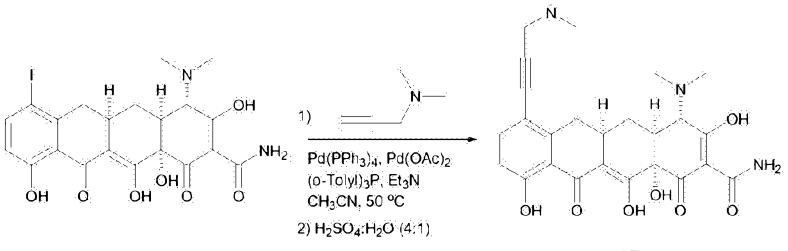
[0043] Scheme 6 outlines the general synthesis of 7-substituted tetracyclines. A 7-iodo sancycline derivative (**1**) may undergo a Stille coupling or a Suzuki coupling by reacting with an alkyl tin derivative or a boronic acid derivative in the presence of a palladium catalyst to form the desired product (**16**).



1 16

Scheme 6

[0044] The 7-substituted oxime derivatives may also be prepared as shown in Scheme 7. An 7-iodo sancycline derivative (**1**) can be reacted with a substituted alkyne in the presence of palladium to synthesize the alkynyl derivative **17.** Compound **17** may be converted to the acyl substituted compound **18** by any technique known in the art. The desired oxime product **19** can be obtained by reacting the acyl moiety with a primary hydroxylamine.



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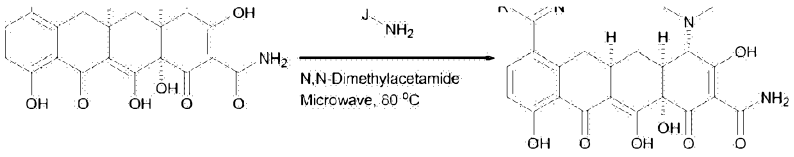
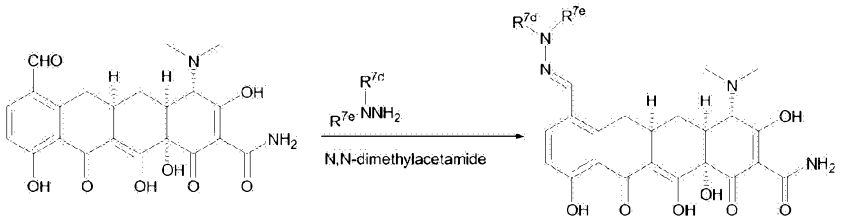


18 19

Scheme 7

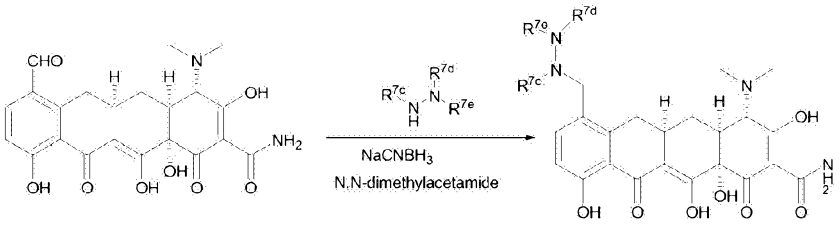
[0045] Scheme 8 is a general synthetic scheme showing the synthesis of 7-substitued hydrazone compounds. A 7-substituted aldehyde tetracycline derivative, prepared as described above in Scheme 4, is combined with a primary hydrazone to form the desired product **20.**



2 20

Scheme 8

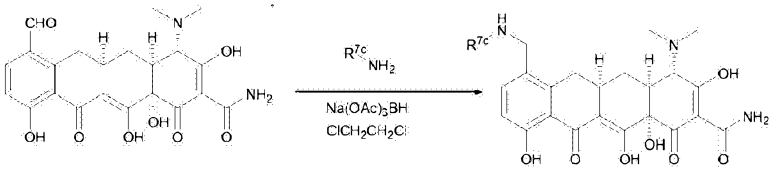
[0046] 7-substituted hydrazines may also be synthesized as shown in Scheme 9. Starting with compound **2,** synthesized as described in Scheme 4 above, may be reacted with a secondary hydrazine in the presence of a reducing agent to form compound **21.**



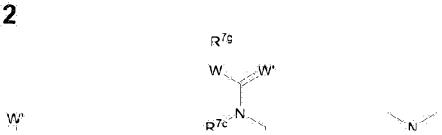
2 21

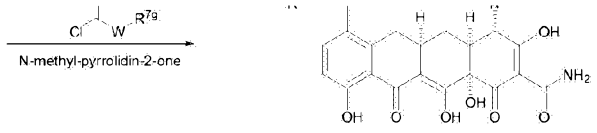
Scheme 9

[0047] Scheme 10 further depicts a method of synthesizing a 7-substituted aminoalkyl tetracycline compound. Compound **2** is reacted with a primary amine in the presence of a reducing agent to form the secondary amine intermediate (**22**), which is then mixed with an acid chloride to form compound **23.**



2 22

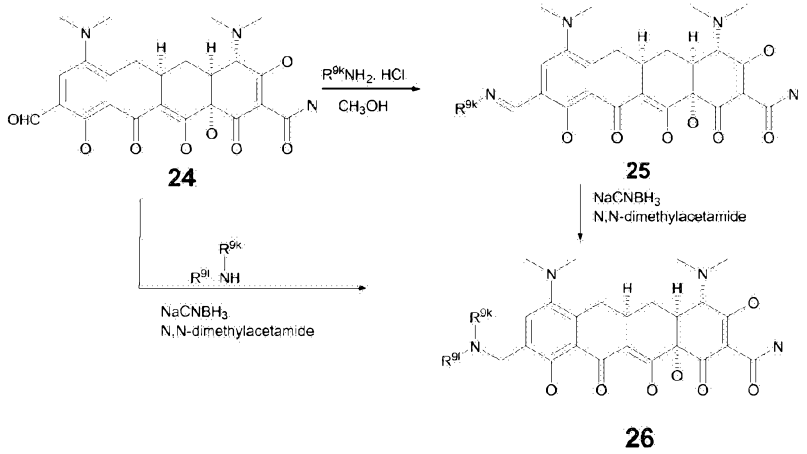




23

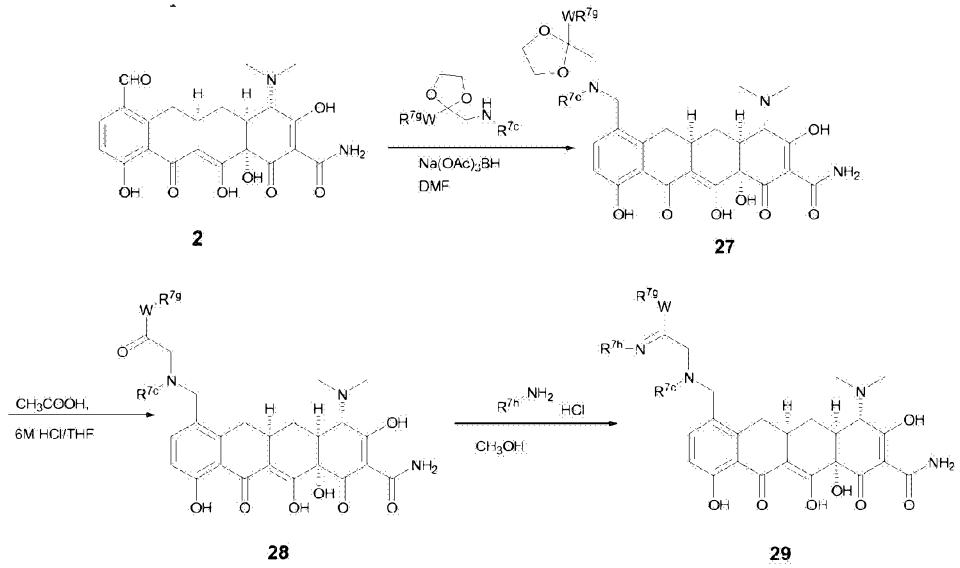
Scheme 10

[0048] Scheme 11 describes a general method for preparing 9-substituted aminoalkyl substituted tetracycline compounds. Compound **24** may be reacted directly with a secondary amine to form compounds similar to **26.** Alternatively, compound **24** may be mixed with a primary amine to yield the substituted imine **25,** which may be further reduced to produce the aminoalkyl compound **26.**



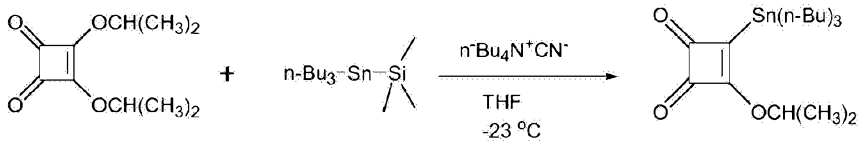
Scheme 11

[0049] 7-substituted tetracycline may also be prepared as shown in Scheme 12. Starting again with compound **2,** reductive alkylation with a dioxalanyl secondary amine yields the intermediate **27.** Subsequently exposing **27** to acidic conditions removes the protecting group to form intermediate **28,** which may then be reacted with a primary amine to form product **29.**



Scheme 12

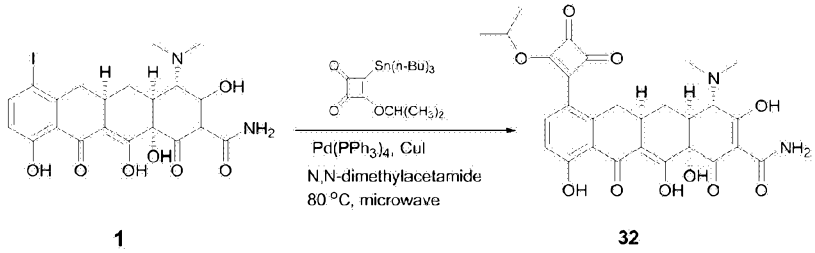
[0050] Schemes 13 and 14 illustrate the general synthesis of cyclobutene 7-substituted tetracycline compounds. Beginning with **30,** tin regeant **31** is synthesized by reacting **30** with a trimethylsilyl substituted alkyltin derivative.



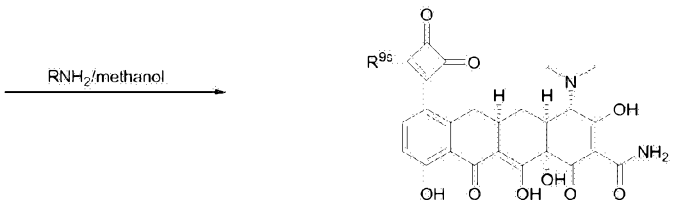
30 31

Scheme 13

[0051] Scheme 14 continues to show the synthesis of cyclobutenedione 7-substituted tetracycline compounds, by reacting building block **31** with 7-iodo substituted sancycline (**1**) in a Stille coupling reaction to form **32.** The amino substitution of product **33** is accomplished by reacting **32** with a primary amine in methanol.



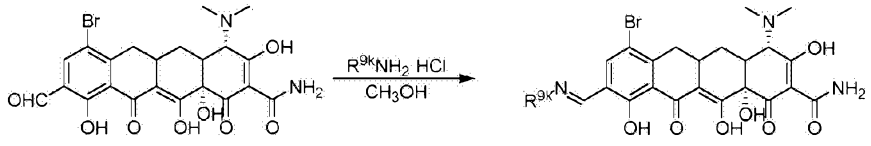
1 32



33

Scheme 14

[0052] Scheme 15 illustrates the general synthesis of 9-substituted aminoalkyl substituted tetracycline compounds. A 7-bromo-9-formyl substituted tetracycline **34** may be reacted with a primary amine to yield the 9-substituted imino derivative **35.** This intermediate may be exposed to a reducing agent (*e.g.*, sodium cyanoborohydride) to yield the 7-bromo-9-aminoalkyl substituted compound **36.** Alternatively, compound **36** may be prepared by reacting the starting material **34** with a reducing agent (*e.g.,* sodium cyanoborohydride) in the presence of a secondary amine. The 7-position may be dehalogenated in the presence of ammonium formate, indium trichloride and a palladium catalyst to give the desired product **37.**



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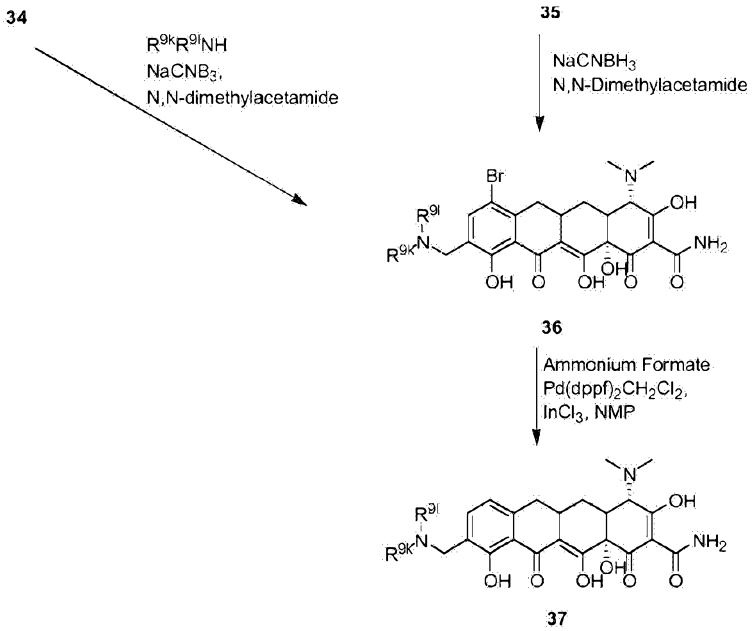


Scheme 15

[0053] The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, etc.), cycloalkyl (alicyclic) groups (cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has 6 or fewer carbon atoms in its backbone (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and more preferably 4 or fewer. Likewise, preferred cycloalkyls have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_1-C_6 includes alkyl groups containing 1 to 6 carbon atoms.

[0054] Moreover, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, e.g., with the substituents described above. An "alkylaryl" or an "arylalkyl" moiety is an alkyl substituted with an aryl (*e.g.*, phenylmethyl (benzyl)). The term "alkyl" also includes the side chains of natural and unnatural amino acids.

[0055] The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, phenyl, pyrrole, furan, thiophene, thiazole, isothiaozole, imidazole, triazole, tetrazole, pyrazole, oxazole, isooxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, *e.g.,* tricyclic, bicyclic, *e.g.,* naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, napthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles," "heterocycles," "heteroaryls" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (*e.g.,* tetralin).

[0056] The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond.

[0057] For example, the term "alkenyl" includes straight-chain alkenyl groups (*e.g.*, ethylenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_2-C_6 includes alkenyl groups containing 2 to 6 carbon atoms.

[0058] Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls," the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido,

nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0059] The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond.

[0060] For example, the term "alkynyl" includes straight-chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term C_2-C_6 includes alkynyl groups containing 2 to 6 carbon atoms.

[0061] Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls," the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0062] Unless the number of carbons is otherwise specified, "lower alkyl" includes an alkyl group, as defined above, but having from one to five carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, 2-5 carbon atoms.

[0063] The term "acyl" includes compounds and moieties which contain the acyl radical (CH_3CO-) or a carbonyl group. It includes substituted acyl moieties. The term "substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, amino carbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0064] The term "acylamino" includes moieties wherein an acyl moiety is bonded to an amino

group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

[0065] The term "aroyl" includes compounds and moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc.

[0066] The terms "alkoxyalkyl," "alkylaminoalkyl" and "thioalkoxyalkyl" include alkyl groups, as described above, which further include oxygen, nitrogen or sulfur atoms replacing one or more carbons of the hydrocarbon backbone, e.g., oxygen, nitrogen or sulfur atoms.

[0067] The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, amino carbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, etc.

[0068] The term "amine" or "amino" includes compounds where a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term includes "alkyl amino" which comprises groups and compounds wherein the nitrogen is bound to at least one additional alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. The term "alkylarylamino," "alkylaminoaryl" or "arylaminoalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term "alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group.

[0069] The term "amide," "amido" or "aminocarbonyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarbonyl" or "alkylaminocarbonyl" groups which include alkyl, alkenyl, aryl or alkynyl groups bound to an amino group bound to a carbonyl group. It includes arylaminocarbonyl and arylcarbonylamino groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarbonyl," "alkenylaminocarbonyl," "alkynylaminocarbonyl,"

"arylaminocarbonyl," "alkylcarbonylamino," "alkenylcarbonylamino," "alkynylcarbonylamino," and "arylcarbonylamino" are included in term "amide." Amides also include urea groups (aminocarbonylamino) and carbamates (oxycarbonylamino).

[0070] The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. The carbonyl can be further substituted with any moiety which allows the compounds of the invention to perform its intended function. For example, carbonyl moieties may be substituted with alkyls, alkenyls, alkynyls, aryls, alkoxy, aminos, etc. Examples of moieties which contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

[0071] The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom.

[0072] The term "ether" includes compounds or moieties which contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to another alkyl group.

[0073] The term "ester" includes compounds and moieties which contain a carbon or a heteroatom bound to an oxygen atom which is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxycarboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, etc. The alkyl, alkenyl, or alkynyl groups are as defined above.

[0074] The term "thioether" includes compounds and moieties which contain a sulfur atom bonded to two different carbon or hetero atoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include compounds with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom which is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" and alkthioalkynyls" refer to compounds or moieties wherein an alkyl, alkenyl, or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

[0075] The term "hydroxy" or "hydroxyl" includes groups with an -OH or $-O^-$.

[0076] The term "halogen" includes fluorine, bromine, chlorine, iodine, etc. The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

[0077] The terms "polycyclyl" or "polycyclic radical" refer to two or more cyclic rings (*e.g.*, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, *e.g.,* the rings are "fused rings." Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example,

halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, alkylaminoacarbonyl, arylalkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkyl carbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amido, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0078] The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

[0079] It will be noted that the structure of some of the tetracycline compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (*e.g.*, all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof.

[0080] In another further embodiment, the substituted tetracycline compound is administered in combination with a second agent.

[0081] The language "in combination with" a second agent includes co-administration of the tetracycline compound with the second agent, administration of the tetracycline compound first, followed by the second agent and administration of the second agent, followed by the tetracycline compound. The second agent may be any agent which is known in the art to treat, prevent, or reduce the symptoms of a skin disorder. Furthermore, the second agent may be any agent of benefit to the subject when administered in combination with the administration of an tetracycline compound.

[0082] In another embodiment, the compound for use is formulated as a medicament comprising an effective amount of the substituted tetracycline compound for the treatment of an inflammatory skin disorder and a pharmaceutically acceptable carrier.

[0083] The language "pharmaceutically acceptable carrier" includes substances capable of being coadministered with the tetracycline compound(s), and which allow both to perform their intended function, *e.g.,* treat or prevent an inflammatory skin disorder. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, *e.g.,* lubricants,

preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously react with the active compounds of the invention.

[0084] The tetracycline compounds for use in the invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of the tetracycline compounds for use in the invention that are basic in nature are those that form non-toxic acid addition salts, *i.e.,* salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and palmoate [*i.e.,* 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. Although such salts must be pharmaceutically acceptable for administration to a subject, *e.g.,* a mammal, it is often desirable in practice to initially isolate a tetracycline compound of the invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds for use this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The preparation of other tetracycline compounds for use in the invention not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

[0085] The tetracycline compounds for use in the invention that are acidic in nature are capable of forming a wide variety of base salts. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those tetracycline compounds of the invention that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmaceutically acceptable cations such as alkali metal cations (*e.g.,* potassium and sodium) and alkaline earth metal cations (*e.g.,* calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines. The pharmaceutically acceptable base addition salts of tetracycline compounds for use in the invention that are acidic in nature may be formed with pharmaceutically acceptable cations by conventional methods. Thus, these salts may be readily prepared by treating the tetracycline compound of the invention with an aqueous solution of the desired pharmaceutically acceptable cation and evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, a lower alkyl alcohol solution of the tetracycline compound for use in the invention may be mixed with an alkoxide of the desired metal and the solution

subsequently evaporated to dryness.

[0086] The tetracycline compounds for use in the invention and pharmaceutically acceptable salts thereof can be administered via either the oral, parenteral or topical routes. In general, these compounds are most desirably administered in effective dosages, depending upon the weight and condition of the subject being treated and the particular route of administration chosen. Variations may occur depending upon the species of the subject being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out.

[0087] The tetracycline compounds for use in the invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the routes previously mentioned, and the administration may be carried out in single or multiple doses. For example, the novel therapeutic agents can be administered advantageously in a wide variety of different dosage forms, *i.e.,* they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays (e.g., aerosols, etc.), creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds for use in this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

[0088] For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. The compositions of the invention may be formulated such that the tetracycline compositions are released over a period of time after administration.

[0089] For parenteral administration (including intraperitoneal, subcutaneous, intravenous, intradermal or intramuscular injection), solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous

injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. For parenteral application, examples of suitable preparations include solutions, preferably oily or aqueous solutions as well as suspensions, emulsions, or implants, including suppositories. Therapeutic compounds may be formulated in sterile form in multiple or single dose formats such as being dispersed in a fluid carrier such as sterile physiological saline or 5% saline dextrose solutions commonly used with injectables.

[0090] Additionally, tetracycline compounds for use in the present invention may be administered topically when treating inflammatory conditions of the skin. Examples of methods of topical administration include transdermal, buccal or sublingual application. For topical applications, therapeutic compounds can be suitably admixed in a pharmacologically inert topical carrier such as a gel, an ointment, a lotion or a cream. Such topical carriers include water, glycerol, alcohol, propylene glycol, fatty alcohols, triglycerides, fatty acid esters, or mineral oils. Other possible topical carriers are liquid petrolatum, isopropylpalmitate, polyethylene glycol, ethanol 95%, polyoxyethylene monolauriate 5% in water, sodium lauryl sulfate 5% in water, and the like. In addition, materials such as anti-oxidants, humectants, viscosity stabilizers and the like also may be added if desired.

[0091] In addition to treatment of human subjects, the compounds for use in the therapeutic methods of the invention also will have significant veterinary applications, *e.g.* for treatment of livestock such as cattle, sheep, goats, cows, swine and the like; poultry such as chickens, ducks, geese, turkeys and the like; horses; and pets such as dogs and cats.

[0092] It will be appreciated that the actual preferred amounts of active compounds used in a given therapy will vary according to the specific compound being used, the particular compositions formulated, the mode of application, the particular site of administration, etc. Optimal administration rates for a given protocol of administration can be readily ascertained by those skilled in the art using conventional dosage determination tests conducted with regard to the foregoing guidelines.

[0093] In general, compounds for use in the invention for treatment can be administered to a subject in dosages used in prior tetracycline therapies. See, for example, the *Physicians' Desk Reference*. For example, a suitable effective dose of one or more compounds for use in the invention will be in the range of from 0.01 to 100 milligrams per kilogram of body weight of recipient per day, preferably in the range of from 0.1 to 50 milligrams per kilogram body weight of recipient per day, more preferably in the range of 1 to 20 milligrams per kilogram body weight of recipient per day. The desired dose is suitably administered once daily, or several sub-doses, e.g., 2 to 5 sub-doses, are administered at appropriate intervals through the day, or other appropriate schedule.

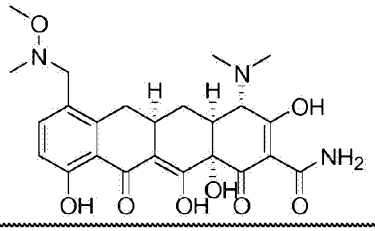
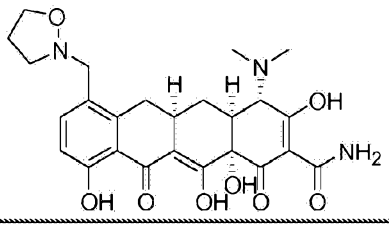
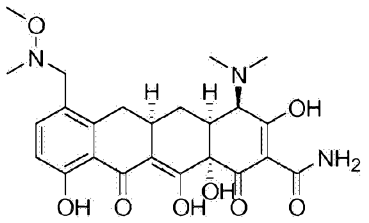
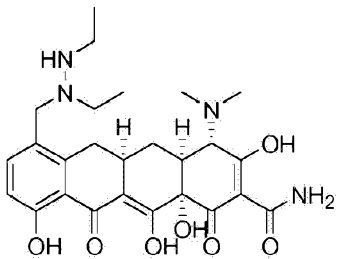
[0094] It will also be understood that normal, conventionally known precautions will be taken regarding the administration of tetracyclines generally to ensure their efficacy under normal

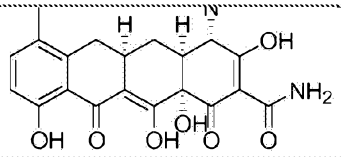
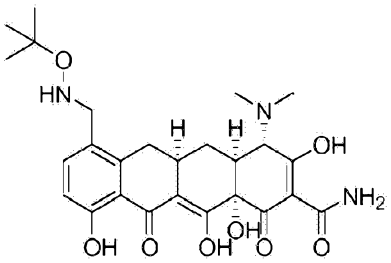
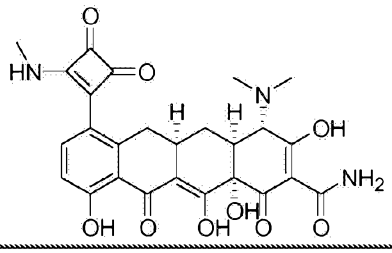
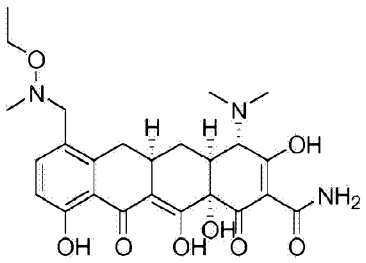
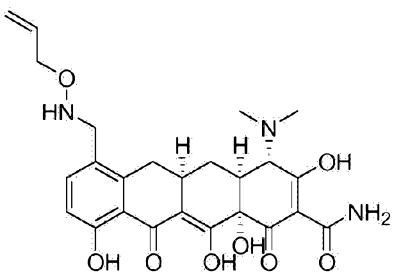
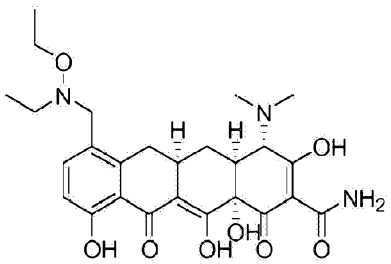
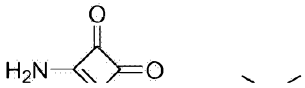
use circumstances. Especially when employed for therapeutic treatment of humans and animals *in vivo,* the practitioner should take all sensible precautions to avoid conventionally known contradictions and toxic effects. Thus, the conventionally recognized adverse reactions of gastrointestinal distress and inflammations, the renal toxicity, hypersensitivity reactions, changes in blood, and impairment of absorption through aluminum, calcium, and magnesium ions should be duly considered in the conventional manner.

[0095] Furthermore, as described herein, the invention also pertains to the use of a substituted tetracycline of the invention, for the preparation of a medicament. The medicament may include a pharmaceutically acceptable carrier and the tetracycline compound is an effective amount, *e.g.,* an effective amount to treat an inflammatory skin disorder.

[0096] In one embodiment, the compounds of the invention are compounds of Table 2.

Table 2

Compound Code	Compound
P	
U	
Y	
Z	
	

Compound Code	Compound
AA	
AB	
AD	
AE	
AF	
AG	
	

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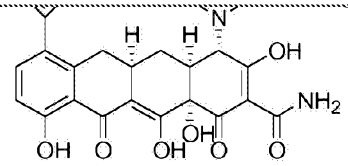
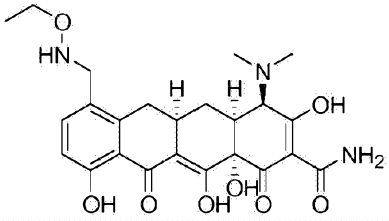
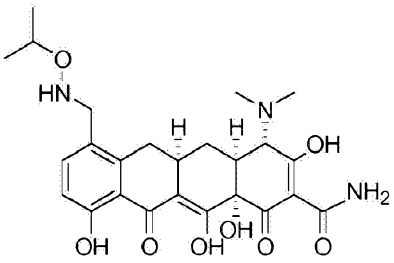
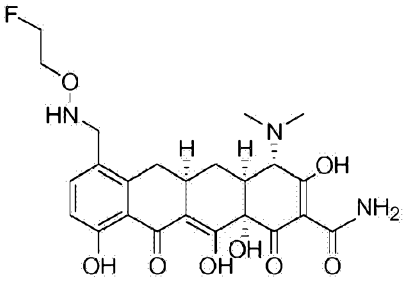
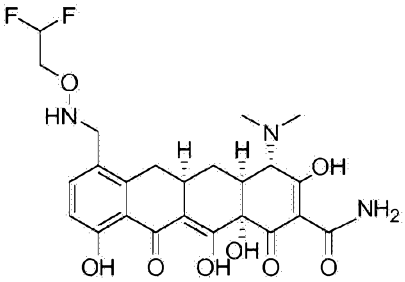
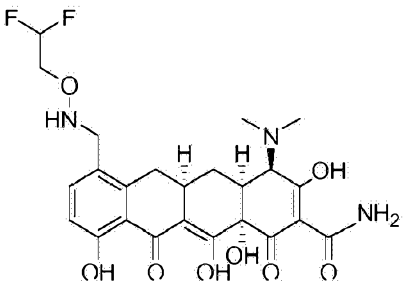
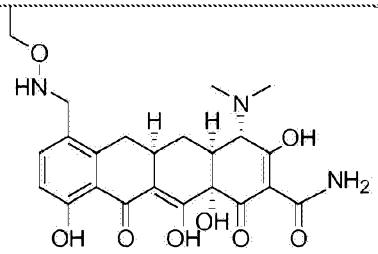
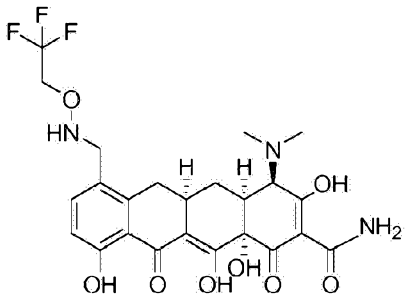
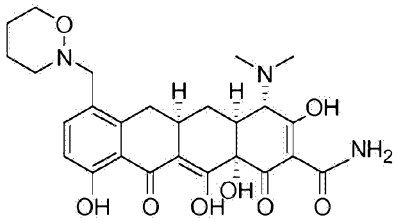
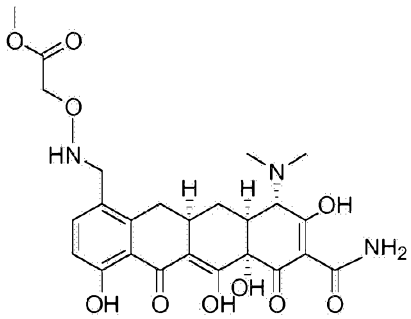
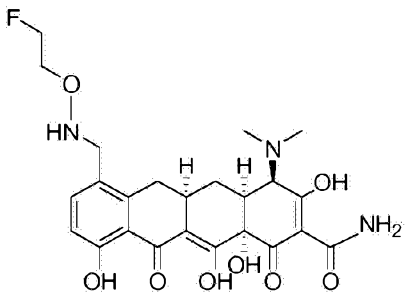
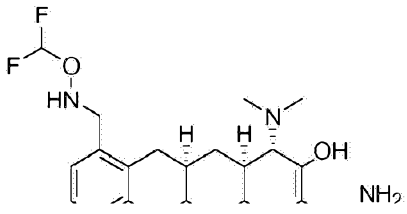
AI	
AM	
AN	
AO	
AR	
AS	
	

Compound Code	Compound
AT	
AU	
AV	
AX	
AY	
BA	

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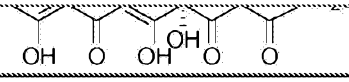
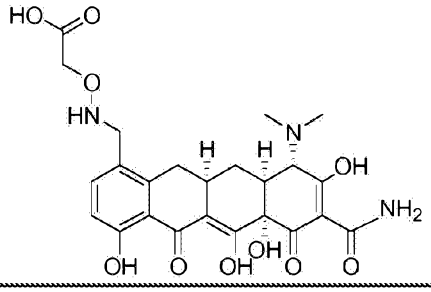
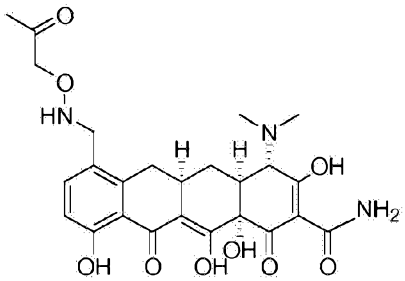
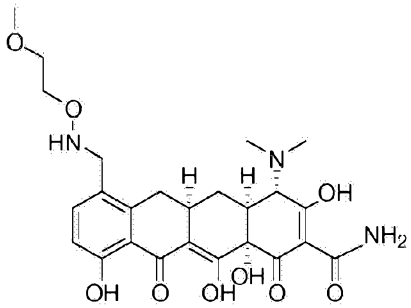
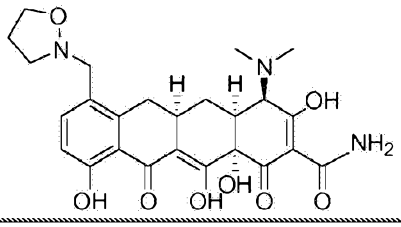
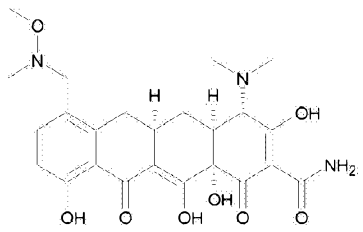
	
BB	
BC	
BD	
BF	

Exemplification of the Invention:

Example 1. Synthesis of Selected Compounds of the Invention

(4S,4aS,5aR,12aS)-4-Dimethylamino-3,10,12,12a-tetrahydroxy-7-[(methoxy-methyl-amino)-methyl]-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydro-naphthacene-2-carboxylic acid amide (Compound P)

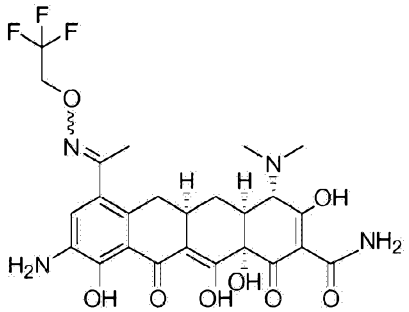
[0097]



[0098] A solution of 7-formylsancycline TFA salt (2.23 g) and N,O-dimethylhydroxylamine hydrochloride (780 mg) in N,N-dimethylacetamide (15 mL) was stirred for 10 minutes at room temperature under argon atmosphere. To this solution was added sodium cyanoborohydride (302 mg). The solution was stirred for 5 minutes and monitored by LC-MS. The reaction mixture was poured into diethyl ether, and the resulting precipitates were collected by filtration under vacuum. The crude product was purified by prep-HPLC using a C18 column (linear gradient 10-40% acetonitrile in 20 mM aqueous triethanolamine, pH 7.4). The prep-HPLC fractions were collected, and the organic solvent (acetonitrile) was evaporated in vacuo. The resulting aqueous solution was loaded onto a clean PDVB SPE column, washed with distilled water, then with a 0.1 M sodium acetate solution followed by distilled water. The product was eluted with 0.1% TFA in acetonitrile. After concentrating under vacuum, 565 mg was obtained as a TFA salt. The TFA salt was converted to the hydrochloride salt by adding methanolic HCl followed by in vacuo evaporation. This process was repeated twice to give a yellow solid: MS (Mz+1 = 488). ^{1}H NMR (300 MHz, CD_3OD) δ 7.46 (d, 1H, J = 8.6 Hz), 6.81 (d, 1H, J = 8.6 Hz), 4.09 (d, 1H, J = 1.0 Hz), 3.79 (d, 1H, J = 13.1 Hz), 3.73 (d, 1H, J = 13.1 Hz), 3.36 (m, 1H), 3.27 (s, 3H), 3.08-2.95 (8H), 2.61 (s, 3H), 2.38 (t, 1H, J = 14.8), 2.22 (m, 1H), 1.64 (m, 1H). Compounds Y, U and AV were also prepared in a similar manner and compound BF may also be prepared in a similar manner.

(4S,4aS,5aR,12aS)-9-Amino-4-dimethylamino-3,10,12,12a-tetrahydroxy-1,1,1-dioxo-7-[1-(2,2,2-trifluoro-ethoxyimino)-ethyl]-1,4,4a,5,5a,6,11,12a-octahydro-naphthacene-2-carboxylic acid amide (Compound A W)

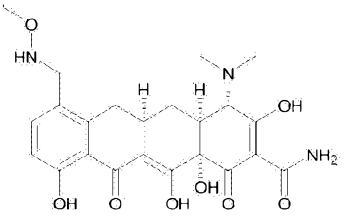
[0099]



[0100] A solution of 7-acetyl-9-amino-sancycline (1.5 mmol) and 2,2,2-trifluoroethylhydroxylamine hydrochloride (3 mmol) in methanol (20mL) was stirred overnight. The methanol was evaporated and the crude product was purified by prep-HPLC using C18 column (linear gradient 10-35% acetonitrile in water with 0.1% TFA) to give a yellow solid: MS (Mz+1 = 569); ^{1}H NMR (300 MHz, CD_3OD) δ 7.48 (s, 1H), 4.63 (d, 1H, J = 8.9 Hz), 4.57 (d, 1H, J = 8.9 Hz), 4.12 (d, 1H, J = 0.9 Hz), 3.10-2.96 (9H), 2.50 (m, 1H), 2.22 (s, 3H), 2.18 (m, 1H), 1.62 (m, 1H). Compounds M and R were also prepared in a similar manner and compound BE may alsobe prepared in a similar manner.

(4S,4aS,5aR,12aS)-4-Dimethylamino-7-(ethoxyamino-methyl)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydro-naphthacene-2-carboxylic acid amide (Compound AA)

[0101]



[0102] An amount of 7-formyl-sancycline (1.5 g, 3.39 mmol) was combined with methanol (30 mL) and O-(ethoxy)methylamine (1.5 g, 15.5 mmol) and was stirred at room temperature under a blanket of argon. The reaction was monitored by HPLC and LC/MS, which indicated that the reaction was complete in about 3 hours. The solvent was evaporated *in vacuo* and the resulting yellow solid was dried. A yellow solid (2.3 g) was isolated as an oxime. LC/MS: (m/z + 1) 485.

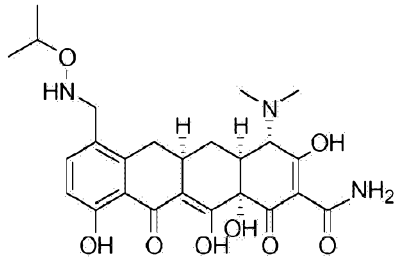
[0103] The oxime (2.3 g, 4.72 mmol) was suspended in methanol saturated with HCl (45mL) and cooled in an ice bath. An amount of $NaCNBH_3$ (585 mg, 9.44 mmol) was added in small batches followed by a few drops of methanol saturated with HCl via syringe. The reducing agent was added over the course of about two hours. The reaction was monitored by HPLC and LC/MS and was complete within 2 hours. The solvent was evaporated *in vacuo* and was purified in 5 batches on preparatory HPLC using C18 column (linear gradient 10-45% acetonitrile in 20mM aqueous triethanolamine, pH 7.4).

[0104] The purified compound was dried *in vacuo* and redissolved in methanol (20mL) saturated with HCl to exchange the salt. The compound was dried overnight over P_2O_5 to yield the product (0.21mg, 13%) as a yellow powder. ESI-MS: (MH+) = 488. ^{1}H NMR (300 MHz, CD_3OD) δ 7.63 (1H, d, J = 9Hz), 6.93 (1H, d, J = 9Hz), 4.53 (s, 1H), 4.17 (m, 3H), 3.25 (m,

1H), 3.07 (m, 8H), 2.44 (m, 1H), 2.31 (m, 1H), 1.62 (m, 1H), 1.29 (3H, t, J = 7 Hz). Compounds AM, AB, AE, AR, AS, AT, AU, AY, AF and AX were also prepared in a similar manner and compounds AG, BA, BB, BC and BD may be prepared in a similar manner.

(4S,4aS,5aR,12aS)-4-Dimethylamino-3,10,12,12a-tetrahydroxy-7-(isopropoxyamino-methyl)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydro-naphthacene-2-carboxylic acid amide (Compound AN)

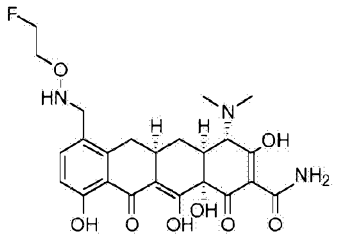
[0105]



[0106] A solution of 7-formylsancycline (1.8 mmol) and O-isopropylhydroxylamine hydrochloride (9 mmol) in methanol (25 mL) was stirred overnight. The solvent was reduced and the crude product was used for the next reaction without further purification. A solution of 7-(isopropoxyimino-methyl)-sancycline (2 mmol) in methanol saturated with HCl was cooled in an ice-bath and $NaCNBH_3$ was added portion-wise while stirring at the same temperature. The solvent was reduced and the crude product was purified by prep-HPLC using C18 column (linear gradient 15-30% acetonitrile in 20 mM aqueous triethanolamine, pH 7.4) to give a yellow solid: MS (Mz+1 = 502); ^1H NMR (300 MHz, CD_3OD) δ 7.63 (d, 1H, J = 8.7 Hz), 6.92 (d, 1H, J = 8.7 Hz), 4.44 (m,1H), 4.14 (d, 1H, J = 1.2 Hz), 3.27-2.97 (9H), 2.43 (t, 1H, J = 14.4), 2.27 (m, 1H), 1.29 (m, 6H). Compounds AM, AB, AE, AR, AS, AT, AU, AY, AF and AX were prepared in a similar manner and compounds AG, BA, BB, BC and BD may be prepared in a similar manner.

(4S,4aS,5aR,12aS)-4-Dimethylamino-7-[(2-fluoro-ethoxyamino)-methyl]-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydro-naphthacene-2-carboxylic acid amide (Compound AO)

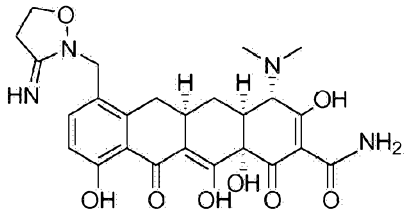
[0107]



[0108] A solution of 7-formylsancyline (4 mmol) and 2-fluoroethylhydroxylamine hydrochloride (10 mmol) in methanol (50 mL) was stirred overnight, after which LC-MS showed completion of the reaction. The methanol was reduced and the crude product was used for the next reaction without further purification. To a cooled solution of 7-(2'-fluoro-ethoxyimino-methyl)-sancycline (2 mmol) in methanol saturated with HCl was added portion-wise $NaCNBH_3$ (8 mmol) over 8 hours while stirring at the same temperature. The solvent was reduced and the crude product was purified by prep-HPLC using C18 column (linear gradient 10-40% acetonitrile in 20 mM aqueous triethanolamine, pH 7.4) to give a yellow solid: MS (Mz +1 = 506); ^1H NMR (300 MHz, CD_3OD) δ 7.65 (d, 1H, J = 8.8 Hz), 6.93 (d, 1H, J = 8.8 Hz), 4.75 (m,1H), 4.61-4.55 (3H), 4.46 (m, 1H), 4.36 (m, 1H), 4.16 (d, 1H, J = 1.2 Hz), 3.26-2.97 (9H), 2.45 (t, 1H, J = 14.4), 2.31 (m, 1H), 1.63 (m, 1H). Compounds AM, AB, AE, AR, AS, AT, AU, AY, AF and AX were prepared in a similar manner and compounds AG, BA, BB, BC and BD may be prepared in a similar manner.

***4S,4aS,5aR,12aS)-4-Dimethylamino-3,10,12,12a-tetrahydroxy-7-(3-imino-isoxazolidin-2-ylmethyl)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydro-naphthacene-2-carboxylic acid amide* (Reference Compound)**

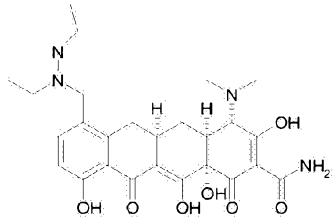
[0109]



[0110] A solution of 7-formylsancycline (2 mmol) and 3-aminooxy-propiononitrile (4 mmol) in methanol (30 mL) was stirred overnight. The solvent was reduced and the crude product was used for the next reaction without further purification. A solution of 7-(2'-cyanoethoxyimmuno-methyl)-sancycline in methanol with HCl was cooled with an ice-bath. An amount of $NaCNBH_3$ was added portion-wise and stirred for 1.5 hours. The solvent was evaporated and purified by prep-HPLC using C-18 column (linear gradient 10-40% acetonitrile in 20 mM aqueous triethanolamine, pH 7.4) to give a yellow solid: MS (Mz+1 = 513); ^1H NMR (300 MHz, CD_3OD) δ 7.47 (d, 1H, J = 8.8 Hz), 6.86 (d, 1H, J = 8.8 Hz), 5.11 (d, 1H, J = 15.9 Hz), 4.96 (d, 1H, J = 15.9 Hz), 4.41 (m,2H), 4.11 (s, 1H), 3.50 (t, 2H, J = 8.4 Hz), 3.20-2.94 (9H), 2.38 (t, 1H, J = 15.3 Hz), 2.28 (m, 1H), 1.60 (m, 1H). Compounds AM, AB, AE, AR, AS, AT, AU, AY, AF and AX were prepared in a similar manner and compounds AG, BA, BB, BC and BD may be prepared in a similar manner.

(4S,4aS,5aR,12aS)-7-(N,N"-Diethyl-hydrazinomethyl)-4-dimethylamino-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydro-naphthacene-2-carboxylic acid amide (Compound Z)

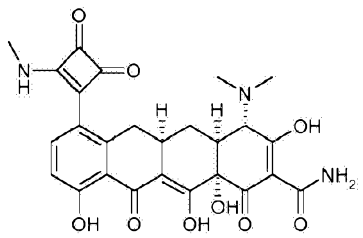
[0111]



[0112] An amount of 7-formyl sancycline (0.5 g, 1.13 mmol) was combined with 1,2-diethylhydrazine (0.546 g, 3.39 mmol), triethylamine (0.472 g, 3.39 mmol), and DMA (10mL) in a glass vial. The resulting heterogeneous mixture was stirred at room temperature under a blanket of argon for 45 minutes. An amount of $NaCNBH_3$ (0.084 g, 1.36 mmol) was added to the reaction mixture and stirred overnight at room temperature. The reaction mixture was poured into water (0.1% TFA), loaded onto a prepared 5 g DVB cartridge, and eluted with CH_3CN (0.1% TFA). After evaporating volatiles, the crude product was purified on a prep-HPLC using C18 column (linear gradient 5-60% acetonitrile in 20mM aqueous triethanolamine, pH 7.4). The purified compound was dried *in vacuo* and redissolved in methanol (20 mL) saturated with HCl to exchange the salt. The compound was dried overnight over P_2O_5 to yield the product (0.030g, 6%) as a yellow powder. ESI-MS: (MH+) = 515. ^1H NMR (300 MHz, CD_3OD) δ 7.53 (1H, d, J = 9Hz), 6.87 (1H, d, J = 9Hz), 4.18 (m, 1H), 4.06 (s, 2H), 3.19 (m, 1H), 3.00 (m, 10H), 2.40 (m, 1H), 2.20 (m, 1H), 1.64 (m, 1H), 1.24 (3H, t, J = 9Hz), 1.13 (m, 3H).

(4S,4aS,5aR,12aS)-4-Dimethylamino-3,10,12,12a-tetrahydroxy-7-(2-methylamino-3,4-dioxo-cyclobut-1-enyl)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydro-naphthacene-2-carboxylic acid amide (Compound AD)

[0113]



[0114] A mixture of 7-iodosancycline (2 mmol), 3-isopropoxy-4-tributylstannanyl-cyclobut-3-ene-1,2-dione (4.4 mmol), tetrakis(triphenylphosphine)palladium (0.4 mmol) and CuI (0.4 mmol) in N,N-dimethylacetamide was microwave irradiated for 50 minutes at 80 °C. The resulting compound was purified using a DVB column to give 7-(2'-isopropoxy-3',4'-dioxo-

cyclobut-1'-enyl)-sancycline as a yellow solid: MS (Mz+1 = 553).

[0115] To a solution of 7-(2'-isopropoxy-3',4'-dioxo-cyclobut-1'-enyl)-sancycline (0.9 mmol) in methanol (20 mL) was added 1 mL of 33% methylamine in absolute ethanol and the reaction mixture was stirred for 40 minutes. The resulting product was purified by prep-HPLC using C18 (linear gradient 10-40% acetonitrile in 20 mM aqueous triethanolamine, pH 7.4) column to give a yellow solid: MS (Mz+1 = 524); ^{1}H NMR (300 MHz, CD_3OD) δ 7.46 (1H, d, J = 8.7 Hz), 6.88 (1H, d, J = 8.7 Hz), 4.01 (s, 1H), 3.27 (s, 3H), 3.07-2.82 (9H), 2.45 (m, 1H), 2.10 (m, 1H), 1.52 (m, 1H). Compound AI
may also be prepared in a similar manner.

Example 2: Anti-Bacterial Activity

[0116] In this example, the gram (+) and gram (-) antibacterial activities of the tetracycline compounds used in the methods of the invention were assessed.

[0117] Gram (-) and gram (+) antibacterial minimum inhibitory concentration (MIC) values (µg/mL) were obtained using CLSI methodology for anti-bacterial susceptibility testing. On each day of testing, serial dilutions of compounds were prepared in microdilution plates using a Tecan robotic workstation. Mueller Hinton broth cultures of representative sensitive and resistant gram negative strains were grown or adjusted to match the turbidity of a 0.5 McFarland standard. 1:200 dilutions were made in an appropriate broth (cation supplemented Mueller Hinton broth) to allow a final inoculum of 1 x 10^5 cfu. Plates were incubated at 35 °C in ambient air for 18-24 hours, were read spectrophotometrically and checked manually for evidence of bacterial growth. The lowest dilution of compound that inhibited growth was recorded as the MIC. Lysed horse blood was used to supplement broth for testing *S. pneumoniae*. The MIC's for each compound were assessed against *S. aureus, S. pneumoniae, P. acnes, E. coli* and *B. theta*. The results are shown in Table 3. Good antibacterial activity *(e.g.,* less than about 4 µg/mL) is indicated by "***," modest antibacterial activity (between about 4 and 8 µg/mL) is indicated by "**," or weak antibacterial activity (greater than about 8 µg/mL) is indicated by "*." The symbol "-" indicates that no data was obtained.

Table 3

Compound Code	*S. aureus* RN450	*S. pneumoniae* 157E - Strep	*P. acnes* ATCC 6919	*P. acnes* ATCC 11827	*E. coli* ATCC 25922	*E. coli* MG 1655	*B. thetaiotaomicron* ATCC 29741
P	***	***	***	***	**	**	**

U	***	***	***	***	***	**	**
Y	***	**	***	***	*	*	*
Z	***	***	***	***	**	**	*
AA	***	***	***	***	**	**	**
AB	***	***	***	***	**	*	**
AD	***	***	***	***	**	**	*
AE	***	***	***	***	**	*	**
AF	***	***	***	***	**	**	***
AM	**	**	***	***	*	*	**
AN	***	***	***	***	**	*	**
AO	***	***	***	***	***	*	**
AR	***	***	***	***	**	**	***
AS	***	**	***	***	*	*	**
AT	***	***	***	***	**	*	***
AU	***	**	***	***	*	*	**
AV	***	***	***	***	**	*	**
AX	***	***	***	***	**	**	***
AY	***	**	***	***	*	*	**
Doxycycline	***	***	***	***	***	***	**
Minocycline	***	***	***	***	***	***	**

Example 3: Toxicity Profile

[0118] In this example, the cytotoxicity of the tetracycline compounds used in the methods of the invention were assessed.

[0119] Mammalian cell cytotoxicity was assessed to evaluate potential *in vivo* risks associated with the tetracycline compounds of the invention. A soluble, non-toxic redox dye ("Resazurin"; Alamar Blue) was used to assess a tetracycline compound's effect on cellular metabolism. At the onset of the experiment, cultures of mammalian COS-1 or CHO cells were washed, trypsinized, and harvested. Cell suspensions were prepared, seeded into 96-well black-walled microtiter plates, and incubated overnight at 37 °C, in 5% CO_2 and approximately 95% humidity. On the next day, serial dilutions of test drug were prepared under sterile conditions and transferred to cell plates. Plates were then incubated under the above conditions for 24 hours. Following the incubation period, the media/drug was aspirated, and 50 µL of resazurin was added. Plates were then incubated under the above conditions for 2 hours and then in the dark at room temperature for an additional 30 minutes. Fluorescence measurements were taken (excitation 535 nm, emission 590 nm) and toxic effects in treated versus control cells were compared based on the degree of fluorescence in each well. The results are shown in Table 4. Minocycline and doxycycline toxicity scores are shown for comparison. Compounds which showed some cytotoxicity (*e.g.*, less than about 35 µg/mL) to are indicated by "***," compounds which showed moderate cytoxicity are indicated by "**" (*e.g.*, between about 35 and 75 µg/mL) and compounds that showed minimal cytoxicity are indicated by "*" (*e.g.*, greater than about 75 µg/mL).

Table 4

Compound	COS-1 Cytotoxicity IC_{50} (µg/mL)	CHO Cytotoxicity IC_{50} (µg/mL)	Compound	COS-1 Cytotoxicity IC_{50} (µg/mL)	CHO Cytotoxicity IC_{50} (µg/mL)
Minocycline	*	*	AR	***	**
Doxycycline	*	*	AS	*	*
P	*	*	AT	***	***
U	*	**	AU	*	*
Y	*	*	AV	**	**
Z	*	*	AX	***	***
AA	*	*			
AB	***	***			
AD	***	***			
AE	*	***			
AF	**	**			
AM	*	*			
AN	***	***			
AO	*	*			

Example 4: Phototoxic Potential

[0120] In this example, the phototoxic potential of the tetracycline compounds used in the methods of the invention was assessed. In particular, 3T3 fibroblast cells were harvested and plated at a concentration of 1 x 10^5 cells/mL and the plates were incubated overnight at 37°C, in 5% CO_2 and approximately 95% humidity. On the following day the medium was removed from the plates and replaced with Hanks' Balanced Salt Solution (HBSS). Drug dilutions were made in HBSS and added to the plates. For each compound tested, a duplicate plate was prepared that was not exposed to light as a control for compound toxicity. Plates were then incubated in a dark drawer (for controls), or under UV light (meter reading of 1.6-1.8 mW/cm^2) for 50 minutes. Cells were then washed with HBSS, fresh medium was added, and plates were incubated overnight as described above. The following day neutral red was added as an indicator of cell viability. The plates were then incubated for an additional 3 hours. Cells were then washed with HBSS and blotted on absorbent paper to remove excess liquid. A solution of 50% EtOH, 10% glacial acetic acid was added and after 20 minutes incubation, and the plate's absorbance at 535 nm was read using a Wallac Victor 5 spectrophotometer. The phototoxicity reflected the difference between the light-treated and control cultures. The results are given in Table 5. Results for the tetracycline derivative COL-3, as well doxycycline and minocycline are shown for comparison. Compounds which showed phototoxicity are indicated by "****" (*e.g.,*

less than 5 µg/mL), compounds which showed moderate phototoxicity are indicated by "***" (*e.g.,* greater than about 5 µg/mL and less than about 25 µg/mL), compounds which showed some phototoxicity are indicated by "**" (*e.g.*, greater than about 25 µg/mL and less than about 75 µg/mL) and compounds that showed minimal or no phototoxicity are indicated by "*" (*e.g.*, greater than about 75 µg/mL).

Table 5

Compound Code	Dark Tox50 (uM)	UV Tox50 (uM)	Compound Code	Dark Tox50 (uM)	UV Tox50 (uM)
Minocycline	*	*	AM	*	*
Doxycycline	*	***	AN	*	**
COL-3	**	****	AO	*	*
P	*	**	AR	*	**
U	*	*	AS	*	*
Y	*	*	AT	*	***
Z	*	*	AU	*	*
AA	*	*	AV	*	*
AB	*	***	AX	*	*
AD	*	*			
AE	*	**			
AF	*	*			

Example 5. Half-life Determination of the Oxidation

[0121] In this example, the half-life of minocycline and a tetracycline compound used in the methods of the invention were assessed under oxidative conditions, as described in Nilges, *et al.* (Nilges M, Enochs W, Swartz H. J. Org. Chem. 1991, 56, 5623-30). Not to be limited by theory, it is believed that the tissue staining may be caused oxidative instability. The tetracycline compounds were subjected to accelerated oxidation in a continuous-flow microreactor using a 15 molar excess of sodium periodate at pH 11 and 22 °C. Aliquots of each reaction mixture were quenched at various time points with ascorbic acid and the disappearance of each compound was determined by RP-HPLC. Pseudo first-order rate constants and $t_{1/2}$ values were obtained from the plots of log (Ao-At/Ao) versus time, where Ao is the HPLC area determined for each compound at time = 0 and At is the HPLC area at time = t. The results indicated that minocycline had a half-life for oxidation of 8.2 seconds, while compound B had a half-life for oxidation of 495 seconds.

Example 6: *In vivo* Anti-bacterial Activity with S. aureus Model

[0122] In this example, the *in vivo* anti-bacterial activity of the tetracycline compounds used in the methods of the invention were assessed.

[0123] Groups of five mice were injected intraperitoneally with a lethal dose of S. *aureus* RN450 in a medium of mucin. Mice were evaluated at 24 hours to determine survival. Untreated animals experienced 100% mortality. Subcutaneous treatment with a single dose of minocycline, doxycycline or the test compound resulted in 100% survival. In some instances, a dose response study was performed with the compound such that a PD_{50} (a dose of compound that protects 50% of the animals) could be calculated. The results are shown in Table 6.

Table 6

Compound	Dose (mg/kg)	Percent Survival	PD50 (mg/kg)
Untreated	-	0(0/5)	--
Minocycline	5	100 (5/5)	0.72
Doxycycline	5	100 (5/5)	0.13
P	5	100 (5/5)	0.13
AA	5	100 (5/5)	--
AD			4.54
AN			1.1
AF			0.23
AO			0.48
AR		0.58	0.58
AT			1.11

Example 7: *In vivo* Anti-Inflammatory Activity with Rat Carrageenan-Induced Paw Edema Inflammatory Model

[0124] To asses the anti-inflammatory potential of the tetracycline compounds used in the methods of the invention, the tetracycline compounds were assessed in a model of carrageenan induced rat paw inflammation. The model used a sub-plantar injection of carrageenan in the rat to induce an inflammatory response. The test compound or saline (control) was administered IP 30 minutes before a subplantar injection of carrageenan (1.5 mg/0.1 mL). Paw volume was measured (mm^2) before subplantar injection and again 3 hours after the injection of carrageenan using a plethysmometer. The results are shown in **Figure 1.** Significant differences as deteremined by a Kruskal-Wallis One Way ANOVA are noted between the inflammation of the untreated controls versus treated animals ($p = 0.5$)

[0125] Figure 1 compares the modulation of carregeenan induced inflammation of minocycline

compared with various doses of compound P. Minocycline exhibited an EC_{50} at approximately 50 mg/kg, while compound P exhibited similar or improved activity.

REFERENCES CITED IN THE DESCRIPTION

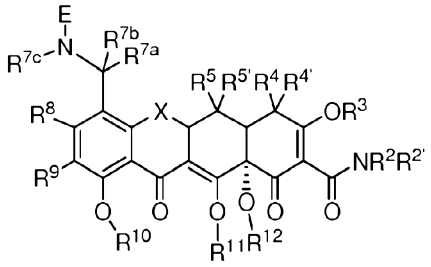
This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Non-patent literature cited in the description

- **NILGES MENOCHS WSWARTZ H.**J. Org. Chem., 1991, vol. 56, 5623-30 [0121]

Patentkrav

1. Forbindelse til anvendelse til behandling af en inflammatorisk hudlidelse hos en person, hvor forbindelsen er en forbindelse med formel I eller et farmaceutisk acceptabelt salt deraf:



(I)

hvor

X er CHC(R^{13}Y'Y), CR^6'R^6, C=CR^6'R^6, S, NR^6 eller O;

E er N$R^{7d}R^{7e}$ eller OR^{7f};

R^2, R^2', R^4', R^{4a} og R^{4b} hver for sig er hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, en heterocyklisk eller heteroaromatisk gruppe;

R^3, R^{10}, R^{11} og R^{12} hver er hydrogen;

R^4 er N$R^{4a}R^{4b}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen eller hydrogen;

R^5 og R^5' hver for sig er hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, en heteroaromatisk gruppe, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkylcarbonyloxy eller arylcarbonyloxy;

R^6 og R^6' hver for sig er hydrogen, methylen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino eller arylalkyl;

R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e} og R^{7f} hver for sig er hydrogen, allyl, alkyl, alkenyl, alkynyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, alkylamino, aminoalkyl, acyl, aryl, arylalkyl, alkylcarbonyloxy eller arylcarbonyloxy, eller R^{7c} og R^{7d} eller R^{7c} og R^{7f} er koblet til frembringelse af en ring;

R^8 er hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino eller arylalkyl;

R^9 er hydrogen, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, aminoalkyl, amido, arylalkenyl, arylalkynyl, thionitroso eller $-(CH_2)_{0-3}(NR^{9c})_{0-1}C(=Z')ZR^{9a}$;

Z er $CR^{9d}R^{9e}$, S, NR^{9b} eller O;

Z' er O, S eller NR^{9f};

R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e} og R^{9f} hver for sig er hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, en heterocyklisk eller heteroaromatisk gruppe;

R^{13} er hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino eller arylalkyl; og

Y' og Y hver for sig er hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, amido, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino eller arylalkyl;

hvor betegnelsen "alkyl" indbefatter både usubstituerede alkyldele og substituerede alkyldele, der har substituenter, der erstatter et hydrogen på et eller flere carbonatomer i carbonhydridrygraden, hvor substituenterne er valgt blandt alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylat, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphat, phosphonato, phosphinato, cyano, amino, acylamino, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylat, sulfater, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluormethyl, cyano, azido, heterocyclyl, alkylaryl, en aromatisk og heteroaromatisk gruppe;

hvor betegnelsen "alkenyl" indbefatter både usubstituerede alkenyldele og substituerede alkenyldele, der har substituenter, der erstatter et hydrogen på et eller flere carbonatomer i carbonhydridrygraden, hvor substituenterne er valgt blandt alkylgrupper, alkynylgrupper, halogener, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylat,

alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphat, phosphonato, phosphinato, cyano, amino, acylamino, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylat, sulfater, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluormethyl, cyano, azido, heterocyclyl, alkylaryl, en aromatisk og heteroaromatisk gruppe;

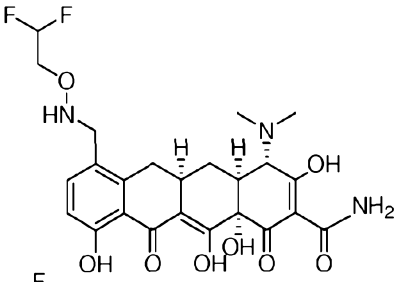
hvor betegnelsen "alkynyl" indbefatter både usubstituerede alkynyldele og substituerede alkynyldele, der har substituenter, der erstatter et hydrogen på et eller flere carbonatomer i carbonhydridrygraden, hvor substituenterne er valgt blandt alkylgrupper, alkynylgrupper, halogener, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylat, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphat, phosphonato, phosphinato, cyano, amino, acylamino, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylat, sulfater, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluormethyl, cyano, azido, heterocyclyl, alkylaryl, en aromatisk og heteroaromatisk gruppe;

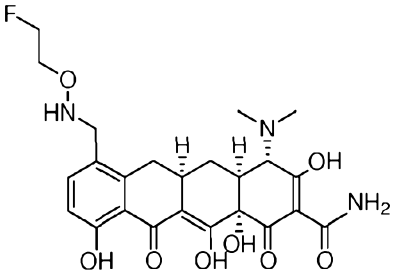
hvor betegnelsen "aryl" indbefatter 5- og 6-leddede enkeltrings-aromatiske grupper, der kan indbefatte fra nul til fire heteroatomer, der eventuelt er substitueret i en eller flere ringpositioner med en substituent valgt blandt halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylat, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphat, phosphonato, phosphinato, cyano, amino, acylamino, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylat, sulfater, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluormethyl, cyano, azido, heterocyclyl og alkylaryl;

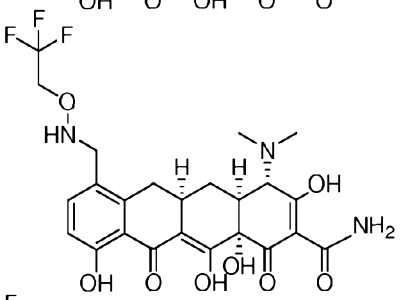
hvor betegnelsen "acyl" indbefatter acyl, der er substitueret

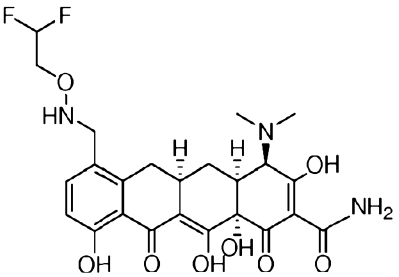
med alkyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylat, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphat, phosphonato, phosphinato, cyano, amino, acylamino, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylat, sulfater, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluormethyl, cyano, azido, heterocyclyl, alkylaryl eller en aromatisk eller heteroaromatisk gruppe; og
hvor betegnelsen "alkoxy" indbefatter substituerede og usubstituerede alkyl-, alkenyl- og alkynylgrupper, der er kovalent koblet til et oxygenatom og eventuelt substitueret med alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylat, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphat, phosphonato, phosphinato, cyano, amino (herunder alkylamino, dialkylamino, arylamino, diarylamino og alkylarylamino), acylamino (herunder alkylcarbonylamino, arylcarbonylamino, carbamoyl og ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylat, sulfater, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluormethyl, cyano, azido, heterocyclyl, alkylaryl eller en aromatisk eller heteroaromatisk gruppe.

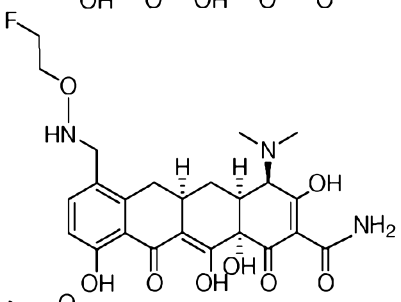
2. Forbindelse til anvendelse ifølge krav 1, hvor forbindelsen er:

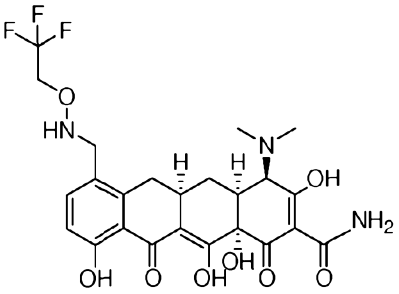


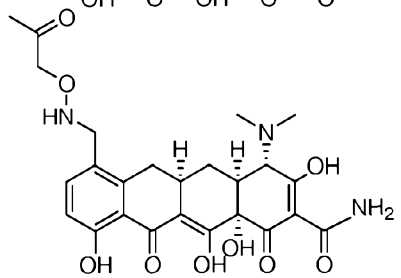


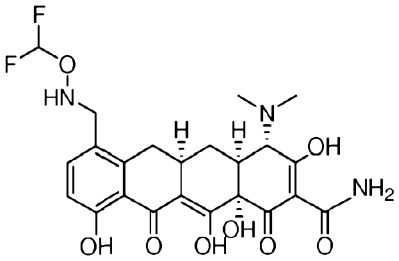


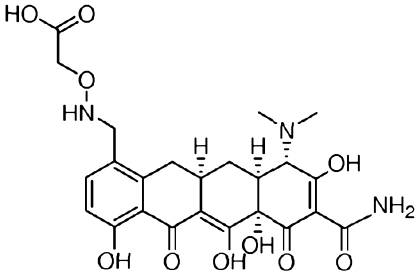


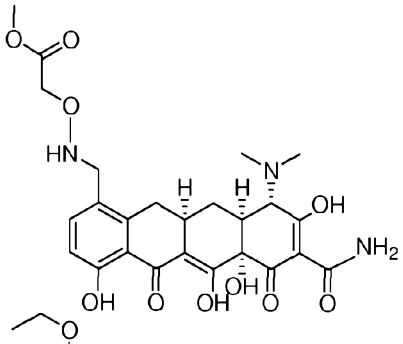


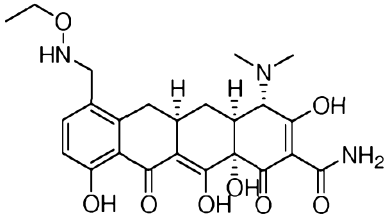


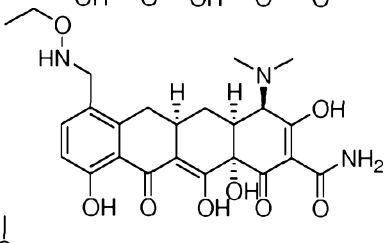


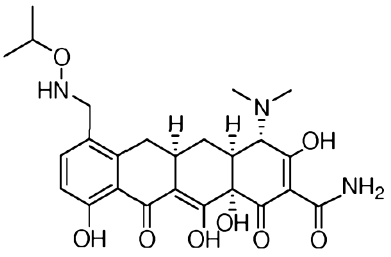


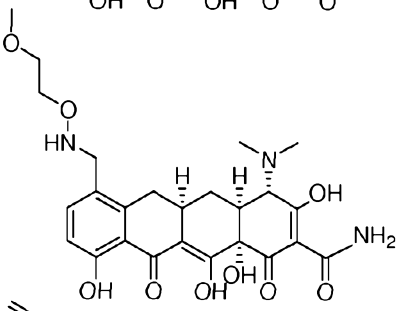


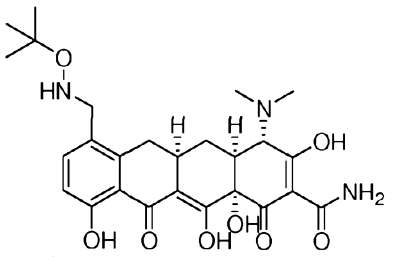


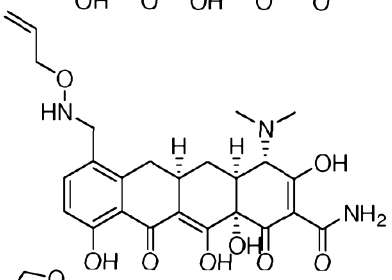


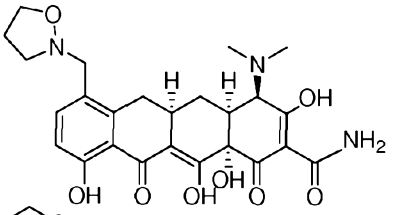


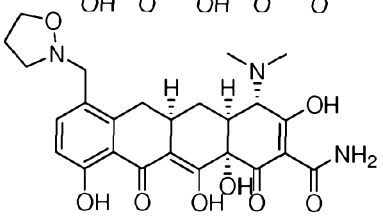


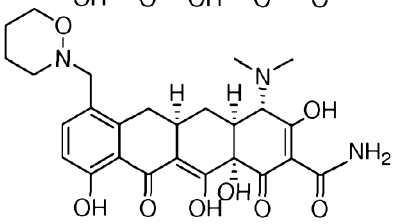


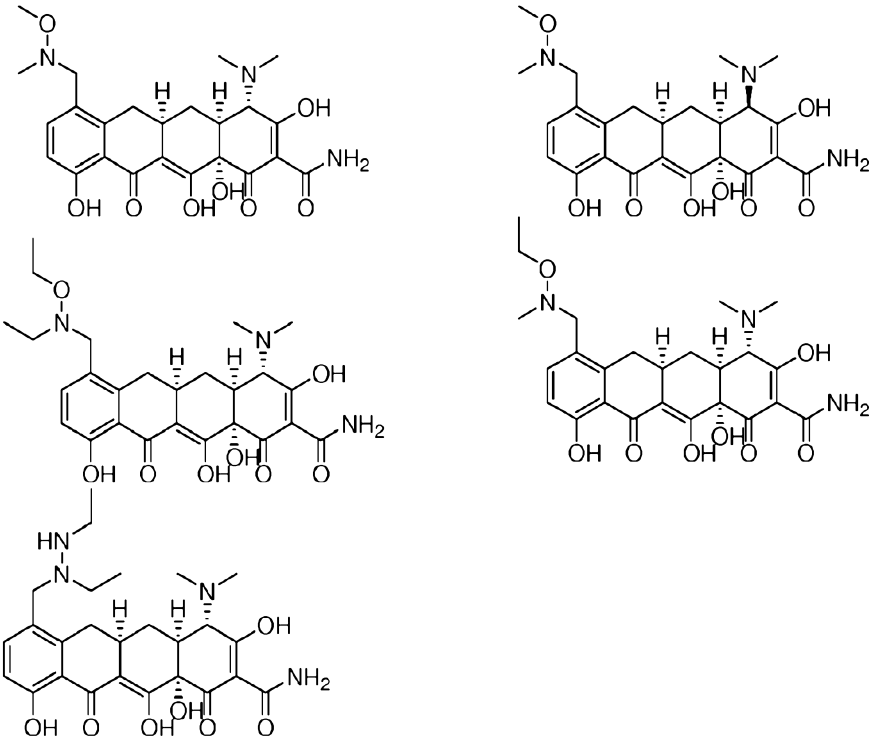






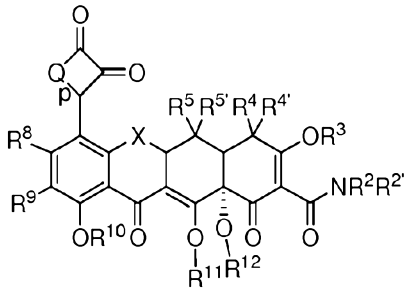






eller et farmaceutisk acceptabelt salt deraf.

3. Forbindelse til anvendelse til behandling af en inflammatorisk hudlidelse hos en person, hvor forbindelsen er en forbindelse med formel VI eller et farmaceutisk acceptabelt salt deraf:



(VI)

hvor

X er $CHC(R^{13}Y'Y)$, $CR^6'R^6$, $C=CR^6'R^6$, S, NR^6 eller O;

p er en enkeltbinding eller en dobbeltbinding;

Q er CR^{7s}, når p er en dobbeltbinding, eller Q er $CR^{7s}'R^{7s}"$, når p er en enkeltbinding;

R^2, R^2', R^4', R^{4a} og R^{4b} hver for sig er hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, en heterocyklisk eller heteroaromatisk gruppe;

R^3, R^{10}, R^{11} og R^{12} hver er hydrogen;

R^4 er $NR^{4a}R^{4b}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen eller

hydrogen;

R^5 og $R^{5'}$ hver for sig er hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, en heteroaromatisk gruppe, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkylcarbonyloxy eller arylcarbonyloxy;

R^6 og $R^{6'}$ hver for sig er hydrogen, methylen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino eller arylalkyl;

R^{7s}, $R^{7s'}$ og $R^{7s''}$ hver er hydrogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, aminoalkyl, alkylamino, aryl, acyl, arylalkyl, alkylcarbonyloxy eller arylcarbonyloxy;

R^8 er hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino eller arylalkyl;

R^9 er hydrogen, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, aminoalkyl, amido, arylalkenyl, arylalkynyl, thionitroso eller $-(CH_2)_{0-3}(NR^{9c})_{0-1}C(=Z')ZR^{9a}$;

Z er $CR^{9d}R^{9e}$, S, NR^{9b} eller O;

Z' er O, S eller NR^{9f};

R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e} og R^{9f} hver for sig er hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, en heterocyklisk eller heteroaromatisk gruppe;

R^{13} er hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino eller arylalkyl; og

Y' og Y hver for sig er hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, amido, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino eller arylalkyl;

hvor betegnelsen "alkyl" indbefatter både usubstituerede alkyldele og substituerede alkyldele, der har substituenter, der erstatter et hydrogen på et eller flere carbonatomer i carbonhydridrygraden, hvor substituenterne er valgt blandt

alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylat, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphat, phosphonato, phosphinato, cyano, amino, acylamino, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylat, sulfater, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluormethyl, cyano, azido, heterocyclyl, alkylaryl, en aromatisk og heteroaromatisk gruppe;

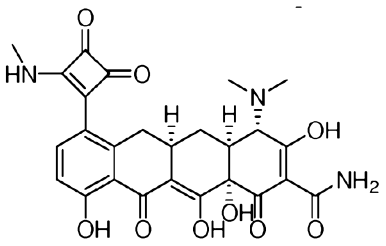
hvor betegnelsen "alkenyl" indbefatter både usubstituerede alkenyldele og substituerede alkenyldele, der har substituenter, der erstatter et hydrogen på et eller flere carbonatomer i carbonhydridrygraden, hvor substituenterne er valgt blandt alkylgrupper, alkynylgrupper, halogener, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylat, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphat, phosphonato, phosphinato, cyano, amino, acylamino, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylat, sulfater, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluormethyl, cyano, azido, heterocyclyl, alkylaryl, en aromatisk og heteroaromatisk gruppe;

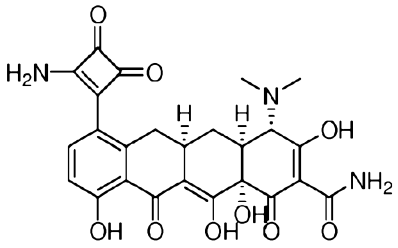
hvor betegnelsen "alkynyl" indbefatter både usubstituerede alkynyldele og substituerede alkynyldele, der har substituenter, der erstatter et hydrogen på et eller flere carbonatomer i carbonhydridrygraden, hvor substituenterne er valgt blandt alkylgrupper, alkynylgrupper, halogener, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylat, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphat, phosphonato, phosphinato, cyano, amino, acylamino, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylat, sulfater, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluormethyl, cyano, azido,

heterocyclyl, alkylaryl, en aromatisk og heteroaromatisk gruppe;
hvor betegnelsen "aryl" indbefatter 5- og 6-leddede enkeltrings-aromatiske grupper, der kan indbefatte fra nul til fire heteroatomer, der eventuelt er substitueret i en eller flere ringpositioner med en substituent valgt blandt halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylat, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphat, phosphonato, phosphinato, cyano, amino, acylamino, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylat, sulfater, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluormethyl, cyano, azido, heterocyclyl og alkylaryl;
hvor betegnelsen "acyl" indbefatter acyl substituerede med alkyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylat, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphat, phosphonato, phosphinato, cyano, amino, acylamino, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylat, sulfater, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluormethyl, cyano, azido, heterocyclyl, alkylaryl eller en aromatisk eller heteroaromatisk gruppe; og
hvor betegnelsen "alkoxy" indbefatter substituerede og usubstituerede alkyl-, alkenyl- og alkynylgrupper, der er kovalent koblet til et oxygenatom og eventuelt substitueret med alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylat, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphat, phosphonato, phosphinato, cyano, amino (herunder alkylamino, dialkylamino, arylamino, diarylamino og alkylarylamino), acylamino (herunder alkylcarbonylamino, arylcarbonylamino, carbamoyl og ureido),

amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylat, sulfater, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluormethyl, cyano, azido, heterocyclyl, alkylaryl eller en aromatisk eller heteroaromatisk gruppe..

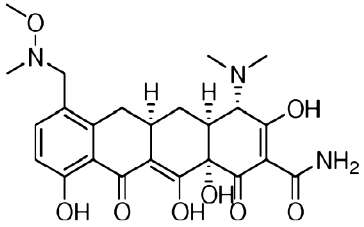
4. Forbindelse til anvendelse ifølge krav 3, hvor forbindelsen er:





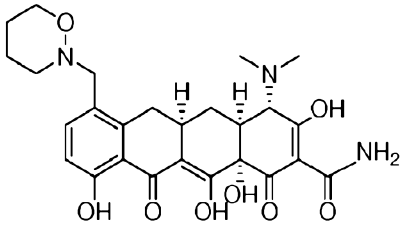
eller et farmaceutisk acceptabelt salt deraf.

5. Forbindelse til anvendelse ifølge krav 1 eller 2, hvor forbindelsen er:



eller et farmaceutisk acceptabelt salt deraf.

6. Forbindelse til anvendelse ifølge krav 1 eller 2, hvor forbindelsen er:



eller et farmaceutisk acceptabelt salt deraf.

7. Forbindelse til anvendelse ifølge krav 1, hvor X er $CR^{6'}R^{6}$, R^{4} er $NR^{4a}R^{4b}$, R^{4a} og R^{4b} hver er alkyl, og R^{2}, R^{2}, R^{3}, $R^{4'}$ R^{5}, $R^{5'}$ R^{6}, R^{6}, R^{8}, R^{9}, R^{10}, R^{11} og R^{12} hver er hydrogen.

8. Forbindelse til anvendelse ifølge krav 7, hvor R^{7a} og R^{7b} er hydrogen.

9. Forbindelse til anvendelse ifølge krav 8, hvor E er OR^{7f}.

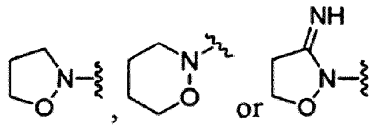
10. Forbindelse til anvendelse ifølge krav 9, hvor R^{7c} er hydrogen.

11. Forbindelse til anvendelse ifølge krav 10, hvor R^{7f} er alkyl.

12. Forbindelse til anvendelse ifølge krav 9, hvor R^{7c} og R^{7f} er koblet til frembringelse af en ring.

13. Forbindelse til anvendelse ifølge krav 12, hvor ringen er en 5- eller 6-leddet ring.

14. Forbindelse til anvendelse ifølge krav 13, hvor ringen er



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15. Forbindelse til anvendelse ifølge krav 8, hvor R^{7c} er alkyl.

16. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1 til 15, hvor forbindelsen er formuleret som et medikament, der omfatter et farmaceutisk acceptabelt bæremateriale og en effektiv mængden af den substituerede tetracyklinforbindelse.

17. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1 til 15, hvor forbindelsen har en MIC, der er mindre end MIC for doxycyklin eller minocyklin i forhold til S. aureus, P. acnes eller S. pneumoniae.

18. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1 til 15, hvor forbindelsen har en MIC, der er mindre end 32 µg/ml i forhold til S. aureus, P. acnes eller S. pneumoniae.

19. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1 til 15, hvor den inflammatoriske hudlidelse er valgt fra gruppen, der består af eksem, dermatitis, psoriasis, pyoderma gangrenosum, akne og rosacea.

20. Forbindelse til anvendelse ifølge krav 19, hvor den inflammatoriske hudlidelse er akne.

21. Forbindelse til anvendelse ifølge krav 19, hvor den inflammatoriske hudlidelse er rosacea.

DRAWINGS

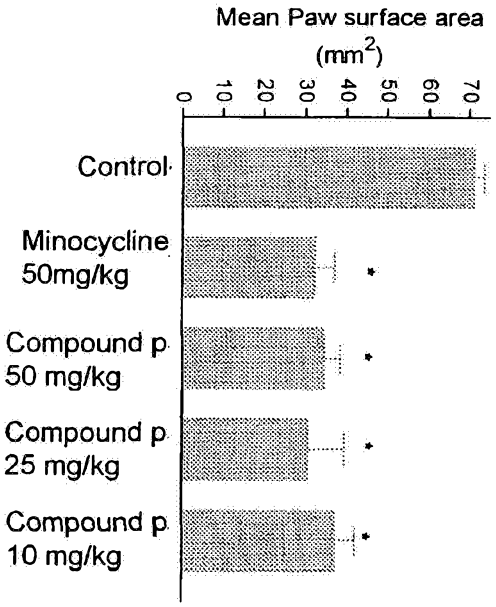

Figure 1