METHODS FOR DRUG SCREEN USING ZEBRAFISH MODEL AND THE COMPOUNDS SCREENED THEREFROM

CROSS-REFERENCE TO RELATED APPLICATION(S)

[0001] This application claims priority to U.S. Provisional Patent Application No. 61/649,611, filed on May 21, 2012, the disclosure of which is hereby incorporated by reference in its entirety.

Field of the Invention

[0001] The invention relates to a method for drug screening using zebrafish as a model. The invention particularly relates to a method for identifying candidate compounds for affecting the expression of lumican and collagen fibrillogenesis and for treating a disease ~~medicated~~mediated by expression of lumican and/or collagen fibrillogenesis and the candidate compounds identified therefrom. Specifically, the method of the invention identifies drugs for treating and/or preventing myopia and/or keratoconus disease.

Background of the Invention

[0002] Myopia is the most common eye disorder in the world. In Western countries, the prevalence of myopia is about 16%~27%, whereas in Asian countries it may be even higher, such as an 82% prevalence for the Chinese population in Singapore. A refractive error equal to or below -6 diopters (D), defined as high myopia, is also termed "pathological myopia" since its potential complications, including cataracts, glaucoma, macular degeneration and retinal detachment, might lead to blindness. Genetic and environmental factors may cause myopia. It has been estimated that about half or more of all persons suffering from myopia have axial myopia caused by elongation of the eye along the visual axis. At birth, the human eye is about two-thirds the size of an adult eye and is relatively short in the axial direction. As a consequence, young children tend to be hyperopic. As the eye grows during childhood, compensatory fine tuning of the optical properties of the cornea and lens occurs, increasing the ocular length. Often the entire process takes place virtually flawlessly and the eye becomes emmetropic. When this fine tuning process fails, however, it usually brings about a lengthened eye. As a result, distant images get focused in front of the plane of the retina and axial myopia results. In clinical trials, only anti-cholinergic drugs (such as atropine) have been used to control the progress of myopia. However, the long-term use of atropine needed to control the progress of myopia can cause side effects such as blurred vision, constipation, decreased sweating, difficulty sleeping, dizziness, drowsiness, dry mouth, nose, or skin, headache, loss of appetite, loss of taste, nausea, or nervousness. Therefore, there is a need to develop replacement drugs for controlling, preventing and/or treating myopia.

number of eyes in zebrafish or that of big eyes in control zebrafish that is not contacted with the test compound. Preferably, the test compound can be identified as a candidate compound if the ratio of the number of big eyes is less than 30% relative to the total number of eyes in zebrafish or that of big eyes in control zebrafish that is not contacted with the test compound. Preferably, the ratio is less than 15%. More preferably, the ratio decreases to about 0% to about 30%, about 0% to about 25%, about 0% to about 20%, about 0% to about 15%, about 0% to about 10%, about 1% to about 30%, about 1% to about 25%, about 1% to about 20% or about 1% to about 15%.

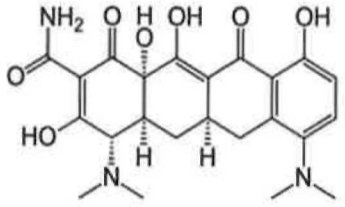
[0049] In a further aspect, screening of test compounds is accomplished by identifying those in a group of test compounds that decrease the ratio of the big eye of zebrafish to less than 30%. Test compounds that decrease the big eye ratio are also referred to herein as "candidate compounds."

[0050] The new screening methods of the invention can be used to identify compounds, e.g., small organic or inorganic molecules (molecular weight less than 1,000 Da), oligopeptides, oligonucleotides, or carbohydrates that decrease the big eye ratio of the lumican knockdown zebrafish. As used herein, a "test compound" can be any chemical compound, for example, a macromolecule (e.g., a polypeptide, a protein complex, glycoprotein, or a nucleic acid) or a small molecule (e.g., an amino acid, a nucleotide, an organic or inorganic compound). A test compound can have a formula weight of less than about 10,000 grams per mole, less than 5,000 grams per mole, less than 1,000 grams per mole, or less than about 500 grams per mole. The test compound can be naturally occurring (e.g., an herb or a natural product), synthetic, or can include both natural and synthetic components. Examples of test compounds include metalloprotease inhibitors, collagenase inhibitors, TGF-β pathway activators, TGF-β inhibitors and Cox inhibitors.

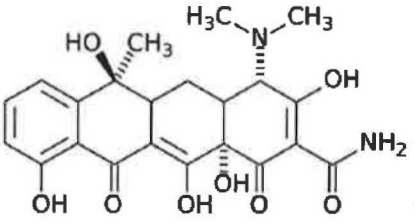
Metalloprotease Inhibitors for Use in A Method for Affecting the Expression of Lumican and/or Collagen Fibrillogenesis, and/or Treating Myopia and/or Keratoconus Disease

[0051] In one embodiment, the invention provides a method for treating a disease ~~medicated~~mediated by expression of lumican and/or collagen fibrillogenesis and/or treating myopia and/or keratoconus disease, comprising administering to the subject a therapeutically effective amount of a MMP inhibitor.

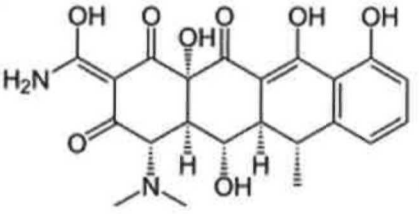
[0052] Metalloproteases (MMPs) are also thought to play a major role on cell behaviors such as cell proliferation, migration (adhesion/dispersion), differentiation, angiogenesis, apoptosis, and host defense. Inhibitors of metalloproteases are known. Examples include natural biochemicals such as tissue inhibitors of metalloproteinases (TIMPs), α2-macroglobulin and their analogs or derivatives. A number of smaller peptide-like compounds that inhibit metalloproteases have been described. Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are known as is shown in, for example, WO95/12389, WO96/11209 and U.S. Pat. No. 4,595,700. Hydroxamate group-containing MMP inhibitors are disclosed in a number of published patent applications such as WO 95/29892, WO



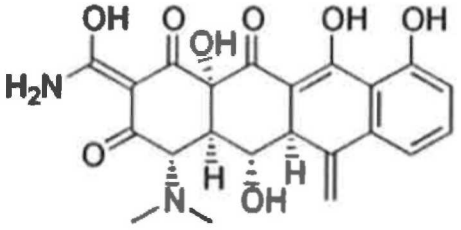
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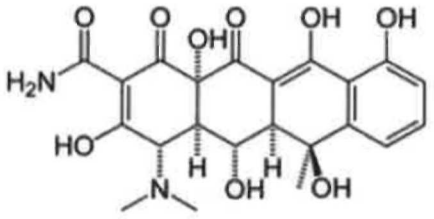
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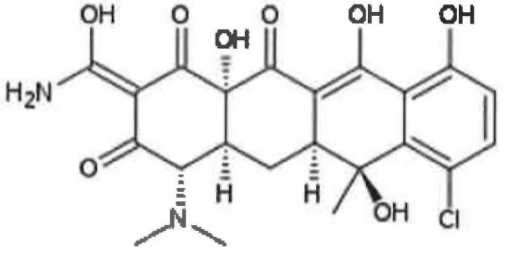
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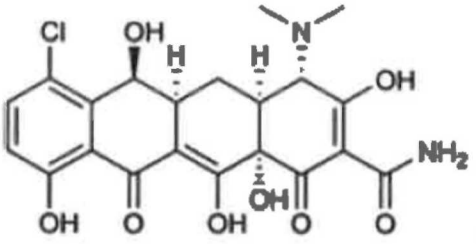
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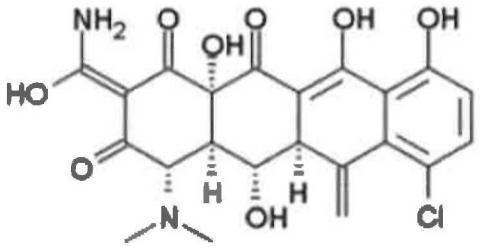
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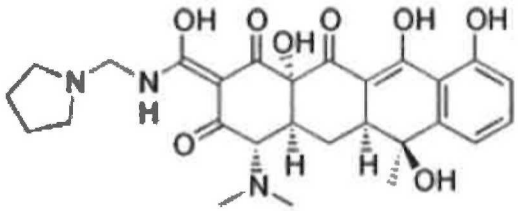
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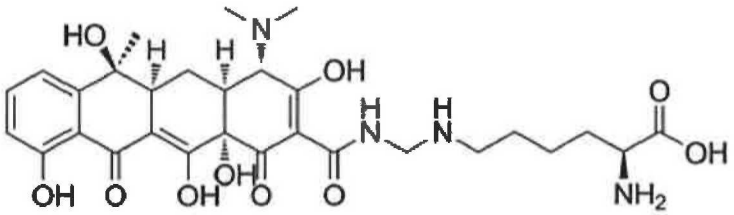
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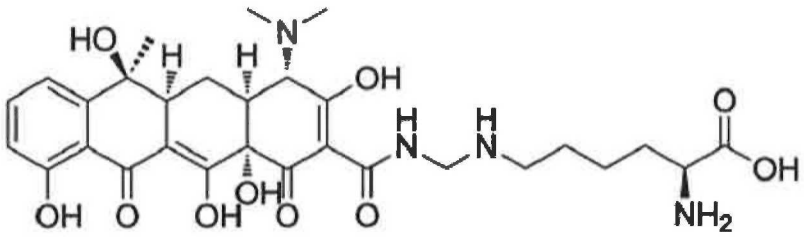
Meclocycline,



Rolitetracycline,



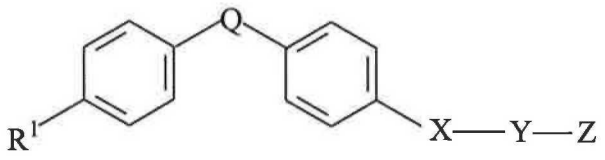
~~Lymecycline~~Lymecycline, and



Tigecycline,

or a tautomer or pharmaceutically acceptable salt, prodrug or solvate thereof.

[0060] According to another embodiment of the invention, the MMP inhibitor is a diaryl ether hydroxamate having the following Formula (III) or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof,



(III)

wherein

R^1 is halogen, OH, NH_2, $OC_{1\text{-}10}$alkyl unsubstituted or substituted by 1-3 halogen, or NH_2;

Q is absent or O;

X is O or $S(O)_2$;

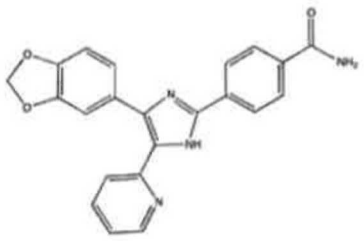
Y is CH_2 or NH;

TGF-beta Inhibitors for Use in A Method for Affecting the Expression of Lumican and/or Collagen Fibrillogenesis, and/or Treating Myopia and/or Keratoconus Disease

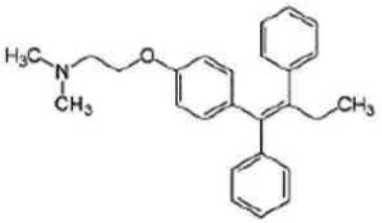
[0067] In an another embodiment, the invention provides a method for treating a disease ~~medicated~~mediated by expression of lumican and/or collagen fibrillogenesis, and/or treating myopia and/or keratoconus disease, comprising administering to the subject a therapeutically effective amount of a TGF-beta inhibitor.

[0068] Transforming growth factor-beta (TGF-beta) belongs to a large super-family of multifunctional polypeptide factors. TGF-beta is a potent inducer of growth arrest in many cell types, including epithelial cells. This activity is the basis of the tumor suppressor role of the TGF-beta signaling system in carcinomas. Other activities, including TGF-beta-induced epithelial-to-mesenchymal differentiation, contribute to cancer progression. PCT patent application WO 02/0948332 describes a genus of dihydropyrrolopyrazole compounds useful for treating disorders associated with enhanced TGF-beta signaling activity or overproduction. US 7,638,537 and US 7,635,702 provide pyrazole compounds and imidazole compounds as potent inhibitors of TGF-signaling pathway.

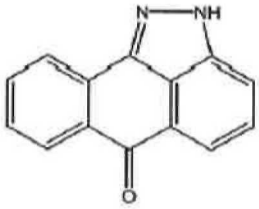
[0069] According to one embodiment of the invention, the TGF-beta inhibitor is selected from the group consisting of:



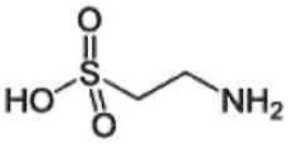
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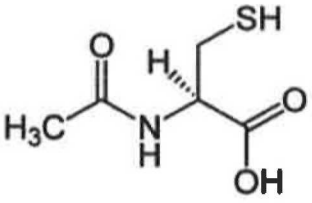
Tamoxifen,



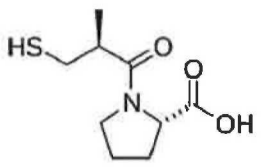
SP600125,



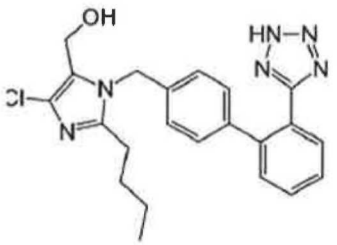
Taurine,



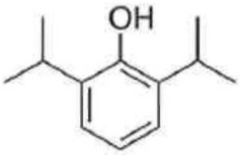
N-acetylcysteine,



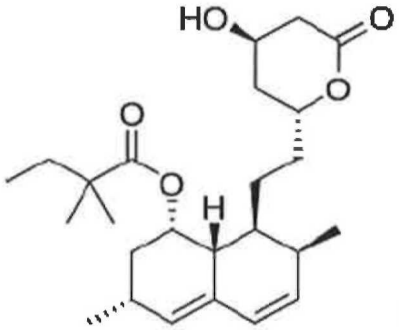
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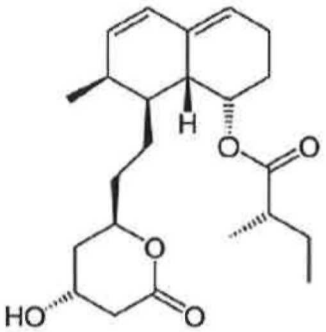
Losartan,



~~Propfol~~Propofol,



Simvastatin, and



Mevastatin.

or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

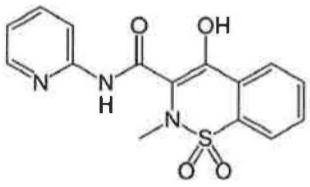
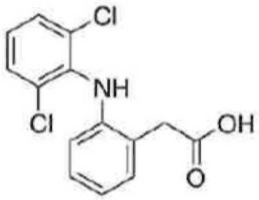
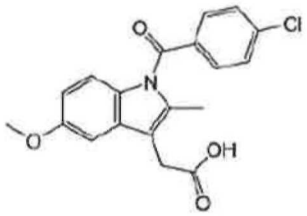
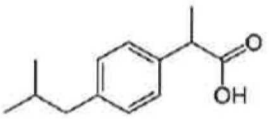
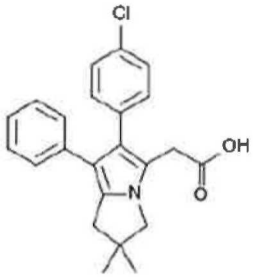
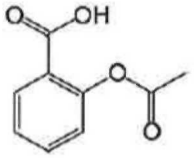
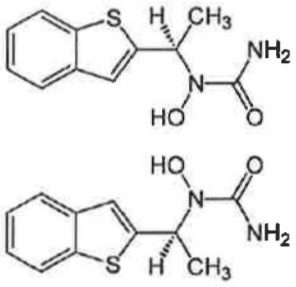
[0070] Preferably, the TGF-beta inhibitor is Losartan, N-acetylcysteine, Propofol and Captopril.

COX/LOX Inhibitors for Use in A Method for Affecting the Expression of Lumican and/or Collagen Fibrillogenesis, and/or Treating Myopia and/or Keratoconus Disease

[0071] In a further embodiment, the invention provides a method for treating a disease ~~medicated~~mediated by expression of lumican and/or collagen fibrillogenesis and/or treating myopia and/or keratoconus disease, comprising administering to the subject a therapeutically effective amount of a COX/LOX inhibitor.

[0072] COX enzymes convert arachidonic acid to the prostaglandin endoperoxide PGH2, from which other prostaglandins are formed. A number of drugs inhibit the action of either the COX or the LOX enzymes.

[0073] According to the invention, the COX/LOX inhibitor is selected from the group consisting of:


Piroxicam,

Voltaren (Diclofenac),

Indomethacin,

Ibuprofen,

Licofelone,

Aspirin, and

and Zileuton;

or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

[0074] Preferably, the COX/LOX inhibitor is Aspirin.

Anticholinergic & Muscarinic Serier Compounds for Use in A Method for Affecting the Expression of Lumican and/or Collagen Fibrillogenesis, and/or Treating Myopia and/or Keratoconus Disease

[0075] Further, in a another embodiment, the invention provides a method for treating a disease ~~medicated~~mediated by expression of lumican and/or collagen fibrillogenesis and/or treating myopia and/or keratoconus disease, comprising administering to the subject a therapeutically effective amount of an anticholinergic or muscarinic compound.

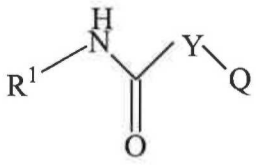
[0076] According to the invention, the anticholinergic or muscarinic compound is selected from the group consisting of:

Claims

What is claimed is:

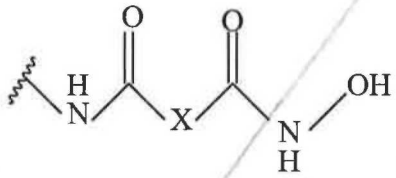
1. The use of MMP inhibitor in the manufacture of a medicament for the treatment of a disease medicated by expression of lumican and/or collagen fibrillogenesis, and/or myopia and/or keratoconus disease.

2. The use as claimed in Claim 1, wherein the MMP inhibitor is a peptidomimetic hydroxamate MMP inhibitor having the following Formula (I) or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof,



(I)

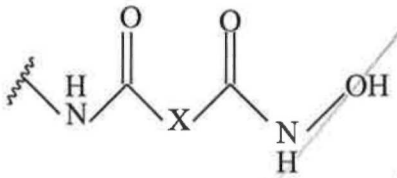
wherein

Q is absent or  ;

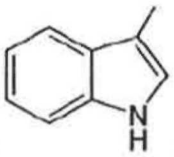
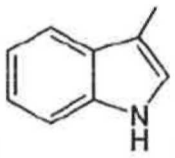
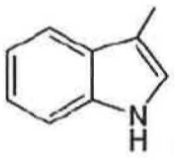
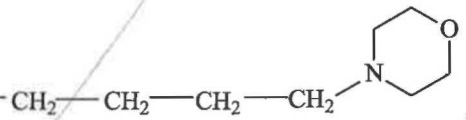
X is C_{1-10}alkylene, C_{2-10} alkenylene or C_{2-10} alkynylene, unsubstituted or substituted by one or more OH, C_{1-10} straight or branched alkyl, C_{2-10} straight or branched alkenyl, C_{1-10}alkylC_{5-15}aryl, C_{1-10}alkenylC_{5-15}aryl, C_{1-10}alkynylC_{5-15}aryl, C_{1-10}alkylsulfanylC_{5-15}aryl, C_{1-10}alkylsulfonylC_{5-15}aryl, C_{1-10}alkylsulfinylC_{5-15}aryl, C_{1-10}alkyloxy or C_{5-15}aryl;

Y is C_{1-10}alkylene, C_{2-10} alkenylene or C_{2-10} alkynylene, unsubstituted or substituted by one or more OH, C_{1-10} straight or branched alkyl, C_{2-10} straight or branched alkenyl, C_{1-10}alkylC_{5-15}aryl, C_{1-10}alkenylC_{5-15}aryl, C_{1-10}alkynylC_{5-15}aryl, C_{1-10}alkylsulfanylC_{5-15}aryl, C_{1-10}alkylsulfonylC_{5-15}aryl, C_{1-10}alkylsulfinylC_{5-15}aryl, C_{1-10}alkyloxy, C_{5-15}aryl, C_{1-10}alkylC_{5-15}aryl, C_{5-14}heteroaryl, C_{1-10}alkylC_{5-14}heteroaryl, or C_{1-10}alkylsulfanylC_{5-14}heteroaryl, provided that when Q is absent, Y is C_{5-14}heteroaryl; wherein the heteroaryl is optionally substituted and has 1 to 3 heteroatoms independently selected from N, O and S; and

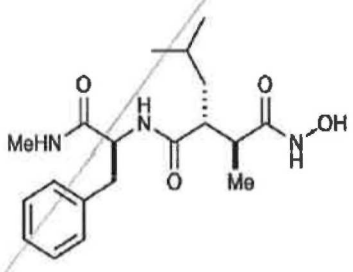
R^1 is H, OH, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{5-15}aryl, C_{1-10}alkylC_{5-15}aryl, C_{5-14}heteroaryl, or C_{1-10}alkylC_{5-14}heteroaryl.



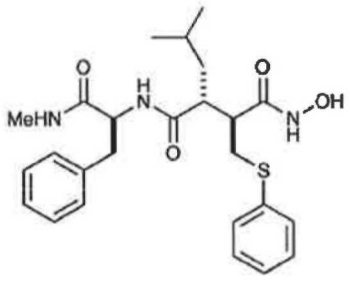
3. The use as claimed in Claim 2, wherein when Q is , X is $-CH_2-$, $-CH(CH_2CH_2(CH_3)_2)-$, or $-CH_2CH_2-$, $-CH(CH_2CH_2(CH_3)_2)CH(CH_3)-$, $-CH(CH_2CH_2(CH_3)_2)CH(CH_2\text{-S-phenyl})-$, $-CH(CH_2CH_2(CH_3)_2)CH(OCH_3)-$, $-CH(CH_2CH_2(CH_3)_2)-$, or $-CH_2CH_2-$, $-CH(CH_2CH_2(CH_3)_2)CH(CH_3)-$, $-CH(CH_2CH_2(CH_3)_2)CH_2-$, $-CH(CH_2CH_2(CH_3)_2)CH(OH)-$, or $-CH(CH_2CH_2(CH_3)_2)CH(CH_2\text{-S-thienyl})-$; Y is $-CH(CH_2\text{-phenyl})-$, $-CH(C(CH_3)_3)-$ or $-CH(CH_2\text{-indolyl})-$; and R_1 is CH_3 or phenyl.

4. The use as claimed in Claim 2, when Q is absent, Y is  ; more preferably, when Q is absent, Y is  and R_1 is $C_{5\text{-}15}$heteroaryl; most preferably, when Q is absent, Y is  and R_1 is .

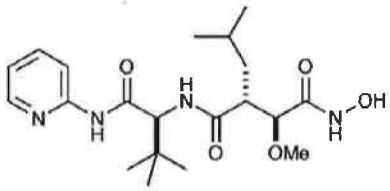
5. The use as claimed in Claim 2, wherein the compound of Formula (I) is selected from the group consisting of:



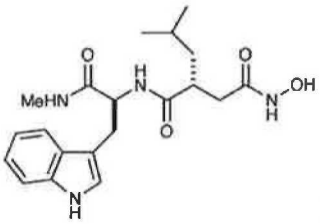
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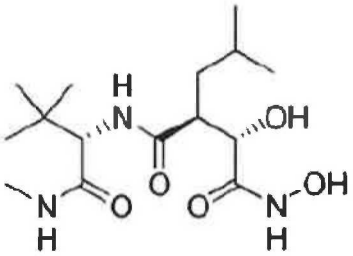
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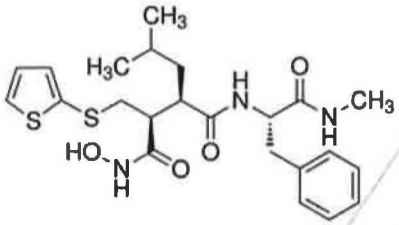
Salimostat,



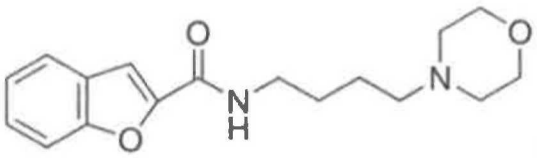
Ilomastat,



Marimastat,



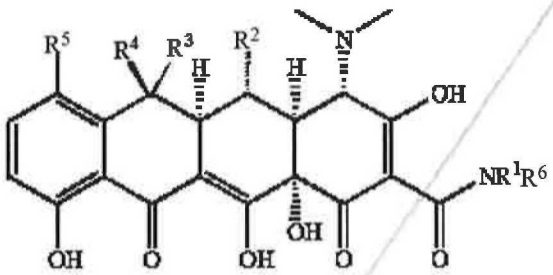
Batimastat, and



CL-82198,

or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

6. The use as claimed in Claim 1, wherein the MMP inhibitor is a tetracyclic-based MMP inhibitor having the following Formula (II) or a tautomer or pharmaceutically acceptable salt, prodrug or solvate thereof,



(II)

wherein

R^1 and R^6 are each independently H, C_{1-10}alkylC_{5-14}heteroaryl, or $C_{1-10}NR^7R^8$;

R^2 is hydrogen or OH;

R^3 and R^4 are each independently H, OH, NH_2, NO, CN, C_{1-10}alkyl, C_{1-10}alkenyl or C_{1-10}alkynyl;

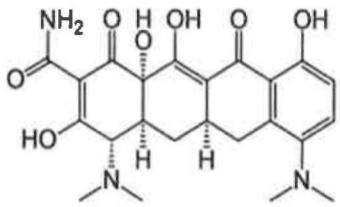
R^5 is hydrogen, halogen, NH_2, OH, NO, CN, C1-10 alkyl, NHC_{1-10}alkyl, $N(C_{1-10}alkyl)_2$, C_{5-15}aryl or C_{5-14}heteroaryl; and

R^7 and R^8 are each independently H, C_{1-10}alkyl C_{1-10}alkylNH_2COOH or taken together with the nitrogen atom to which each is attached form a 3 to 8 membered heteroaryl;

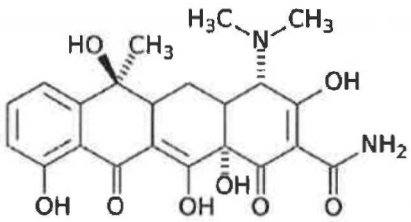
wherein heteroaryl has 1 to 3 heteroatoms independently selected from N, O and S.

7. The use as claimed in Claim 6, wherein R^1 is H; R^6 is H, -CH_2-pyrrolyl, -CH_2-NH-CH_2-CH_2-CH_2-CH_2-CH(NH2)-COOH; R^2 is H or oxo; R3 is H or OH; R4 is H or OH and R^5 is NH_2, $N(CH_3)_2$or halogen.

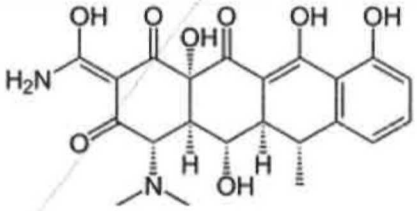
8. The use as claimed in Claim 6, wherein the compound of Formula (II) is selected from the group consisting of:



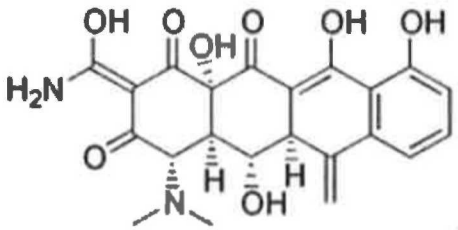
Minocycline hydrochloride,



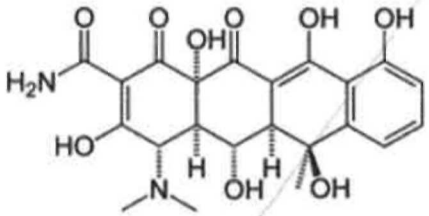
Tetracycline,



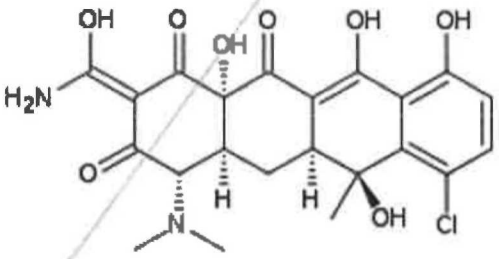
Doxycycline,



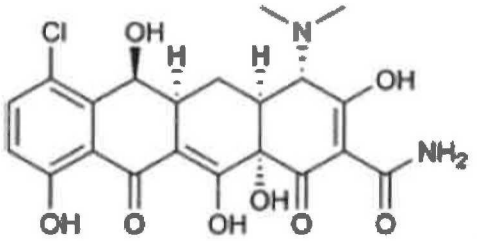
Metacycline,



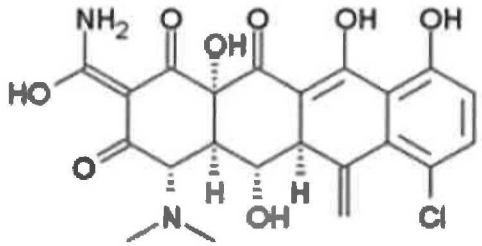
Oxytetracycline,



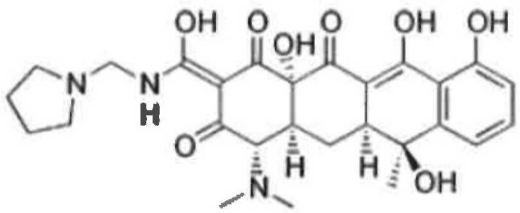
Chlortetracycline,



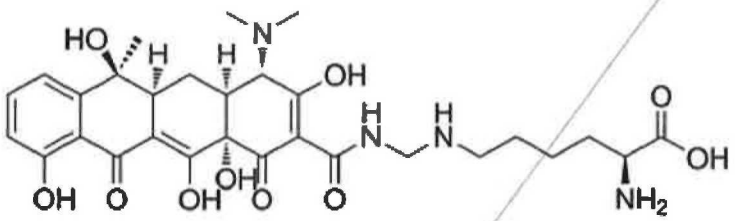
Democlocycline,



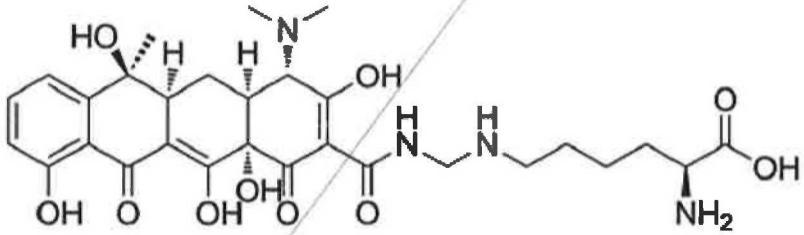
Meclocycline,



Rolitetracycline,



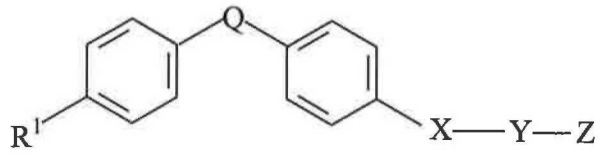
Lymccycline, and



Tigecycline,

or a tautomer or pharmaceutically acceptable salt, prodrug or solvate thereof.

9. The use as claimed in Claim 1, wherein the MMP inhibitor is a diaryl ether hydroxamate having the following Formula (III) or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof,



(III)

wherein

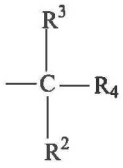
R^1 is halogen, OH, NH_2, OC_{1-10}alkyl unsubstituted or substituted by 1-3 halogen, or NH_2;

Q is absent or O;

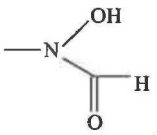
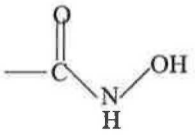
X is O or $S(O)_2$;

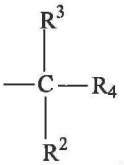
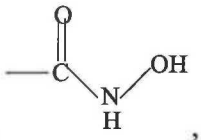
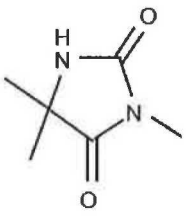
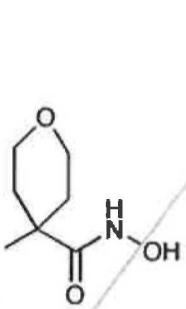
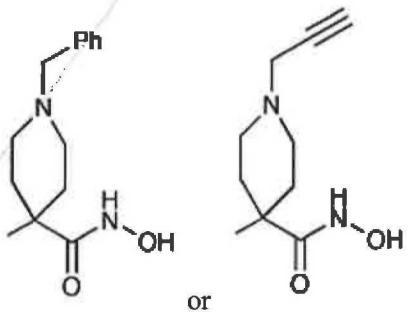
Y is CH_2 or NH;

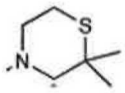
Z is C_{5-14}heteroaryl having 1 to 3 heteroatoms independently selected from N, O and S or

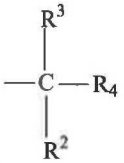
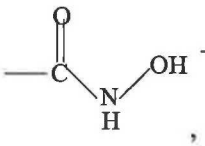
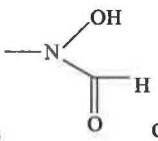
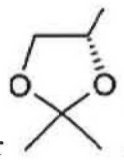


, and

R^2, R^3 and R^4 are each independently H, C_{1-10}alkyl, , ,or unsubstituted or substituted C_{5-14}heteroaryl having 1 to 3 heteroatoms independently selected from N, O and S; or R^2 and R^4 are taken together with the carbon atom to which each is attached form a 5 membered saturated heterocyclyl ring which is unsubstituted or substituted by CN or C_{1-10}alkyl, C_{1-10}alkylC_{5-15}aryl,

provided that when Q is absent, R^1 is $OC(halogen)_3$, X is O, Y is CH_2, Z is , and R^2, R^3 and R^4 are each independently H, , or , or R^2 and R^4 are taken together with the carbon or nitrogen atom to form , or ,

when Q is O; R^1 is halogen or $OC(halogen)_3$, X is $S(O)_2$, and Z is , and

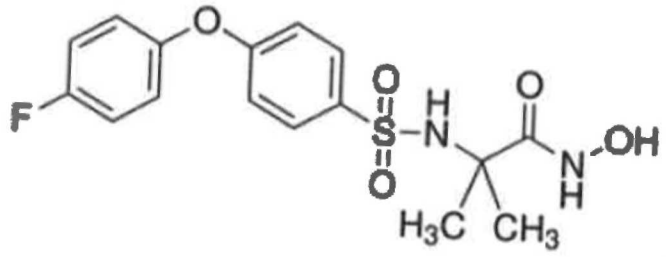
when Q is O; R^1 is halogen or $OC(halogen)_3$, X is $S(O)_2$, Y is NH; Z is ; and R^2, R^3 and R^4 are each independently H, C_{1-10}alkyl, , , or .

.

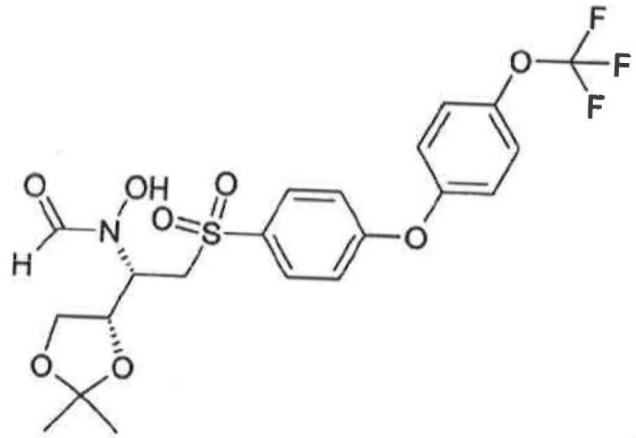
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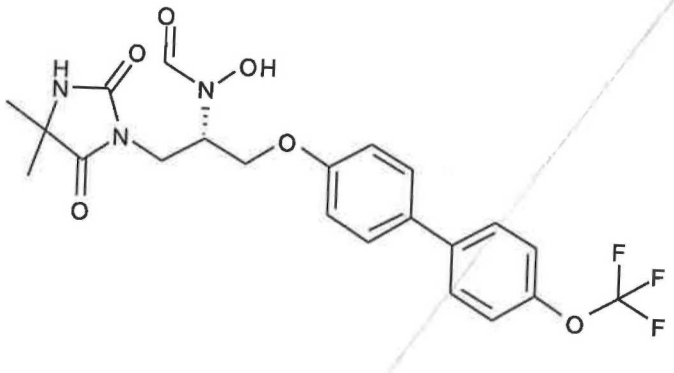
10. The use as claimed in Claim 9, wherein the compound of Formula (III) is selected from the group consisting of:



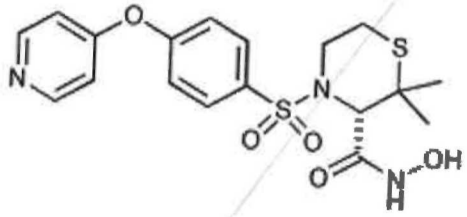
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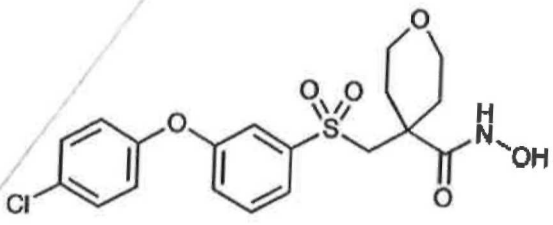
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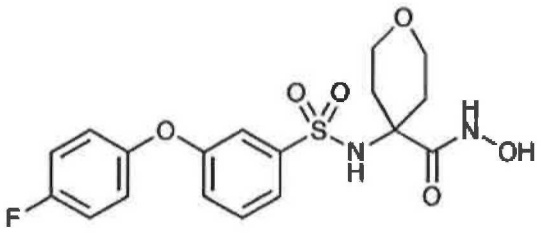
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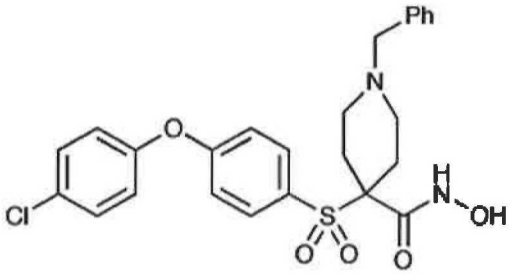
Prinomastat,



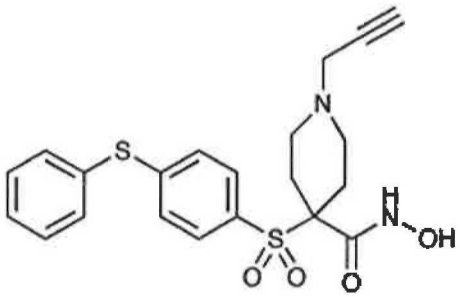
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CAS No. 230954-09-3,



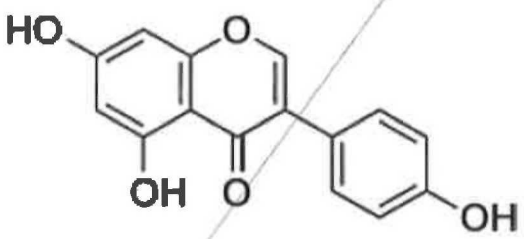
CAS NO. 239796-97-5, and



SC-276,

or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

11. The use as claimed in Claim 1, wherein the MMP inhibitor is a compound having the following formula:

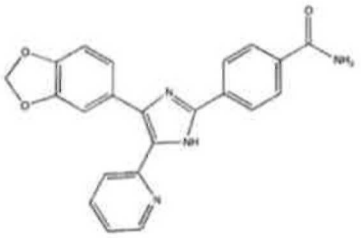


Genistein,

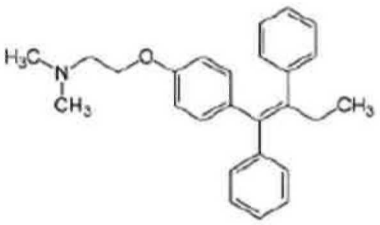
or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

12. The use of TGF-beta inhibitor in the manufacture of a medicament for the treatment of a disease medicated by expression of lumican and/or collagen fibrillogenesis, and/or myopia and/or keratoconus disease.

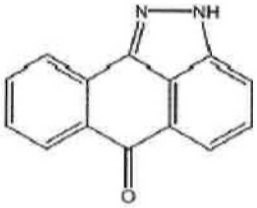
13. The use as claimed in Claim 12, wherein the TGF-beta inhibitor is selected from the group consisting of:



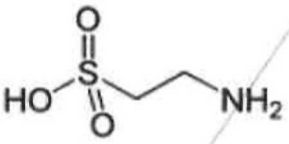
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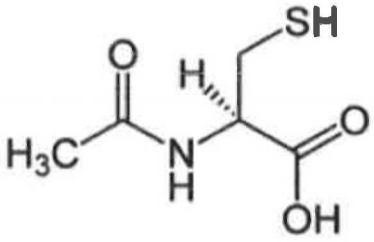
Tamoxifen,



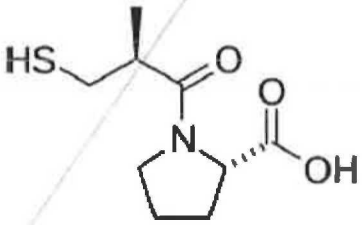
SP600125,



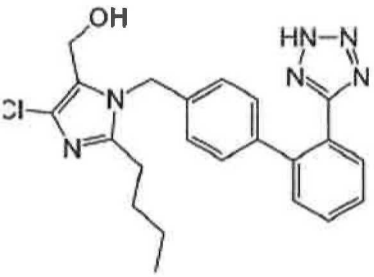
Taurine,



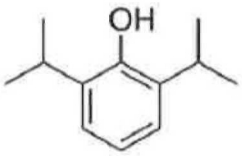
N-acetylcysteine,



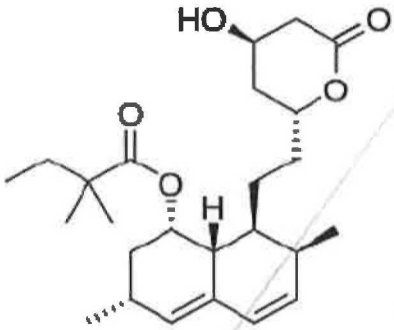
Captopril,



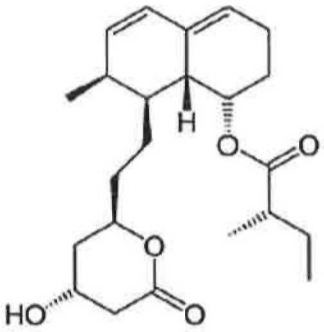
Losartan,



Propfol,



Simvastatin, and

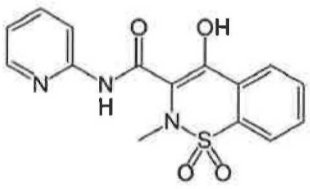


Mevastatin.

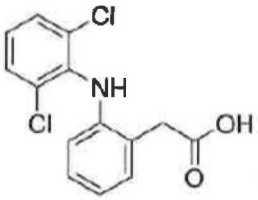
or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

14. The use of COX/LOX inhibitor in the manufacture of a medicament for the treatment of a disease medicated by expression of lumican and/or collagen fibrillogenesis, and/or myopia and/or keratoconus disease.

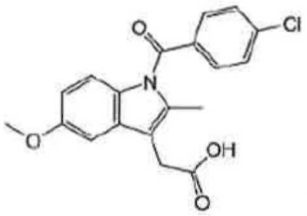
15. The use as claimed in Claim 14, wherein the COX/LOX inhibitor is selected from the group consisting of:



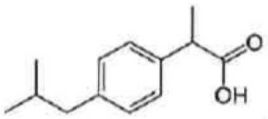
Piroxicam,



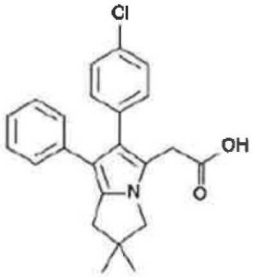
Voltaren (Diclofenac),



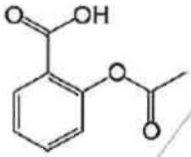
Indomethacin,



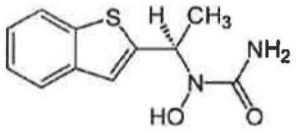
Ibuprofen,

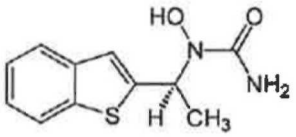


Licofelone,



Aspirin, and





Zileuton;

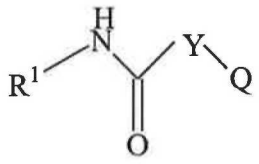
or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

CLAIMS

What is claimed is:

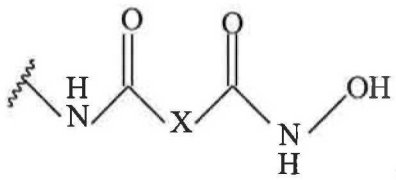
1. The use of a compound in the manufacture of a medicament for the treatment of myopia and/or keratoconus disease, wherein the compound is at least one selected from the group consisting of MMP inhibitor, TGF-beta inhibitor and COX/LOX inhibitor.

2. The use as claimed in Claim 1, wherein the MMP inhibitor is a peptidomimetic hydroxamate MMP inhibitor having the following Formula (I) or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof,

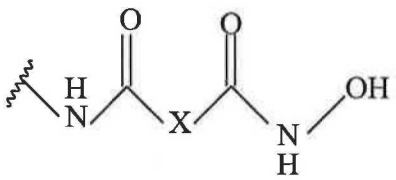


(I)

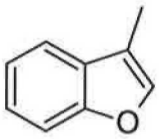
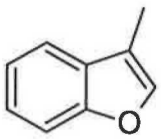
wherein

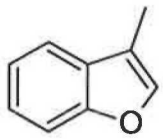


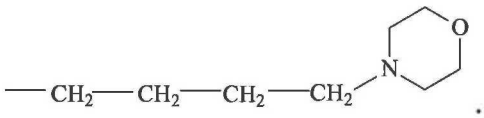
Q is absent or ;



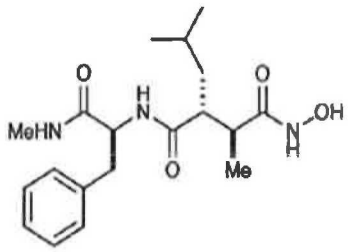
wherein when Q is , X is $-CH_2-$, $-CH(CH_2CH_2(CH_3)_2)-$, or $-CH_2CH_2-$, $-CH(CH_2CH_2(CH_3)_2)CH(CH_3)-$, $-CH(CH_2CH_2(CH_3)_2)CH(CH_2\text{-S-phenyl})-$, $-CH(CH_2CH_2(CH_3)_2)CH(OCH_3)-$, $-CH(CH_2CH_2(CH_3)_2)-$, or $-CH_2CH_2-$, $-CH(CH_2CH_2(CH_3)_2)CH(CH_3)-$, $-CH(CH_2CH_2(CH_3)_2)CH_2-$, $-CH(CH_2CH_2(CH_3)_2)CH(OH)-$, or $-CH(CH_2CH_2(CH_3)_2)CH(CH_2\text{-S-thienyl})-$; Y is $-CH(CH_2\text{-phenyl})-$, $-CH(C(CH_3)_3)-$ or $-CH(CH_2\text{-indolyl})-$; and R_1 is CH_3 or phenyl; and

when Q is absent, Y is  ; more preferably, when Q is absent, Y is  and

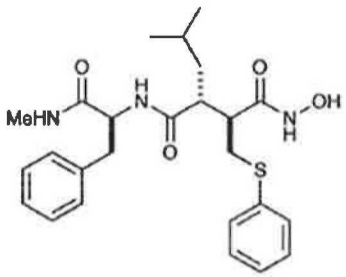
R_1 is C_{5-15}heteroaryl; most preferably, when Q is absent, Y is  and R_1 is



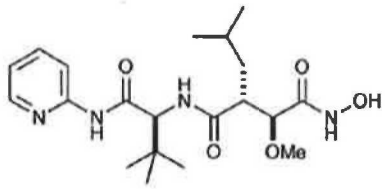
3. The use as claimed in Claim 2, wherein the compound of Formula (I) is selected from the group consisting of:



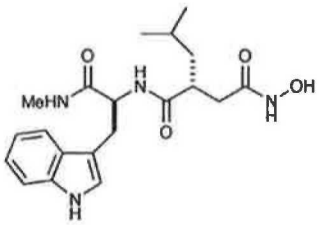
KB-R-7785,



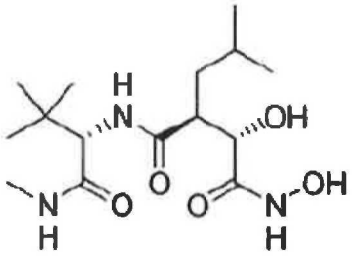
GI-129471,



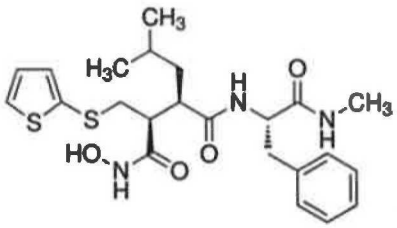
Salimostat,



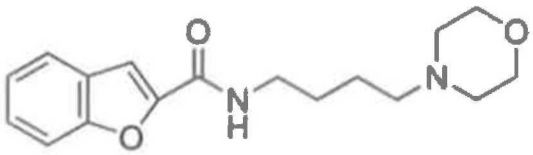
Ilomastat,



Marimastat,



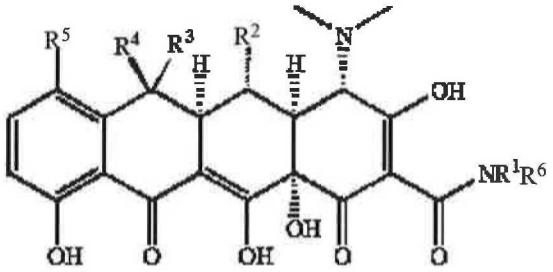
Batimastat, and



CL-82198,

or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

4. The use as claimed in Claim 1, wherein the MMP inhibitor is a tetracyclic-based MMP inhibitor having the following Formula (II) or a tautomer or pharmaceutically acceptable salt, prodrug or solvate thereof,



(II)

wherein

R^1 and R^6 are each independently H, C_{1-10}alkylC_{5-14}heteroaryl, or $C_{1-10}NR^7R^8$;

R^2 is hydrogen or OH;

R^3 and R^4 are each independently H, OH, NH_2, NO, CN, C_{1-10}alkyl, C_{1-10}alkenyl or C_{1-10}alkynyl;

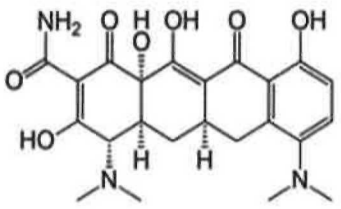
R^5 is hydrogen, halogen, NH_2, OH, NO, CN, C1-10 alkyl, NHC_{1-10}alkyl, $N(C_{1-10}alkyl)_2$, C_{5-15}aryl or C_{5-14}heteroaryl; and

R^7 and R^8 are each independently H, C_{1-10}alkyl C_{1-10}alkylNH_2COOH or taken together with the nitrogen atom to which each is attached form a 3 to 8 membered heteroaryl;

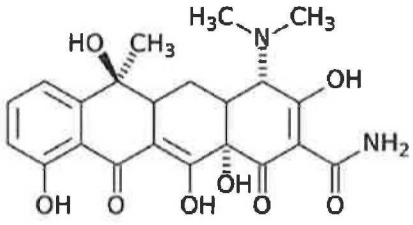
wherein heteroaryl has 1 to 3 heteroatoms independently selected from N, O and S.

5. The use as claimed in Claim 4, wherein R^1 is H; R^6 is H, -CH_2-pyrrolyl, -CH_2-NH-CH_2-CH_2-CH_2-CH_2-CH(NH2)-COOH; R^2 is H or oxo; R3 is H or OH; R4 is H or OH and R^5 is NH_2, $N(CH_3)_2$or halogen.

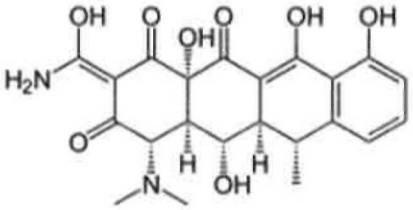
6. The use as claimed in Claim 4, wherein the compound of Formula (II) is selected from the group consisting of:



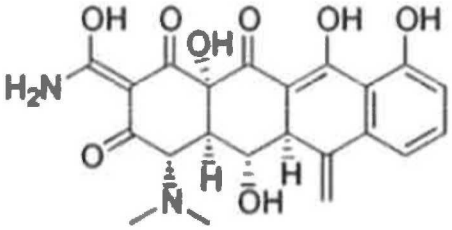
Minocycline hydrochloride,



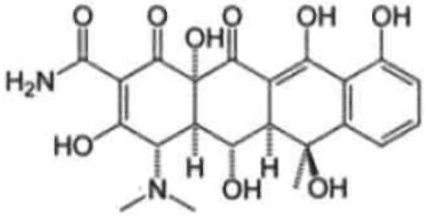
Tetracycline,



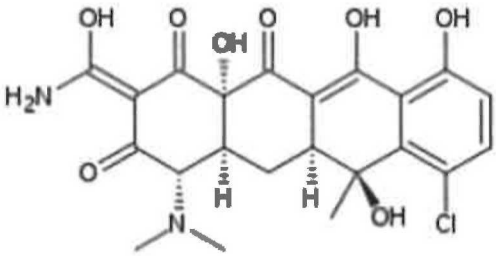
Doxycycline,



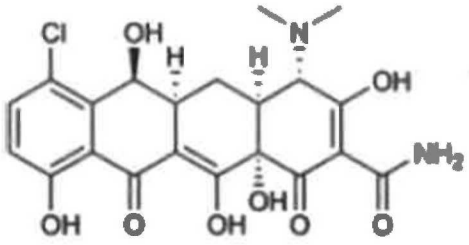
Metacycline,



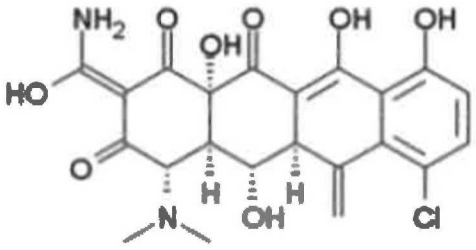
Oxytetracycline,



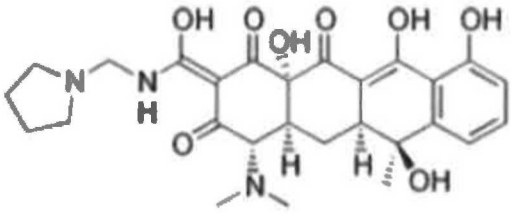
Chlortetracycline,



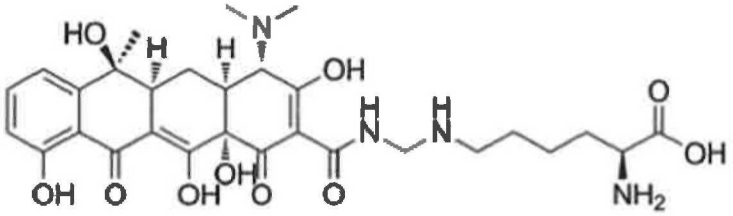
Demeclocycline,



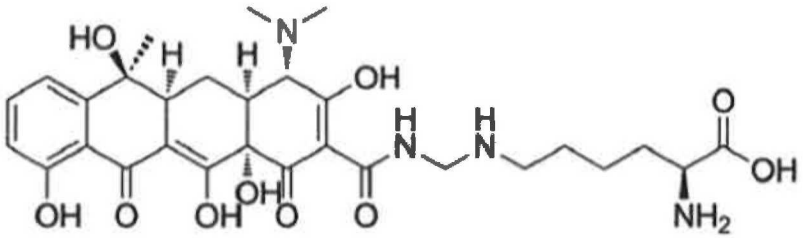
Meclocycline,



Rolitetracycline,



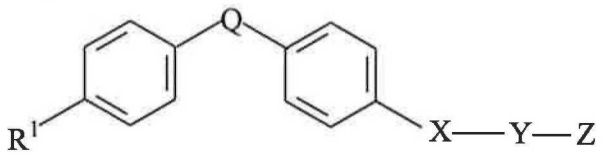
Lymecycline, and



Tigecycline,

or a tautomer or pharmaceutically acceptable salt, prodrug or solvate thereof.

7. The use as claimed in Claim 1, wherein the MMP inhibitor is a diaryl ether hydroxamate having the following Formula (III) or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof,



(III)

wherein

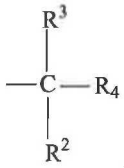
R^1 is halogen, OH, NH_2, $OC_{1\text{-}10}$alkyl unsubstituted or substituted by 1-3 halogen, or NH_2;

Q is absent or O;

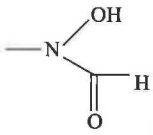
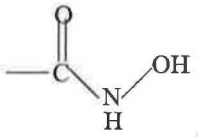
X is O or $S(O)_2$;

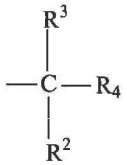
Y is CH_2 or NH;

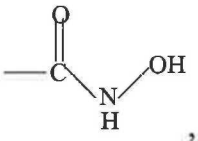
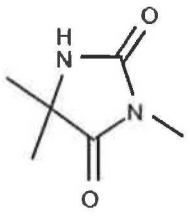
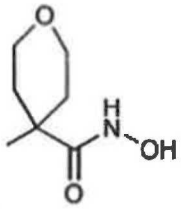
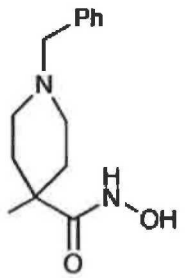
Z is C_{5-14}heteroaryl having 1 to 3 heteroatoms independently selected from N, O and S or

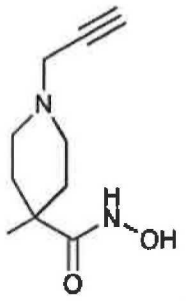


, and

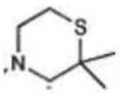
R^2, R^3 and R^4 are each independently H, C_{1-10}alkyl,  ,  ,or unsubstituted or substituted C_{5-14}heteroaryl having 1 to 3 heteroatoms independently selected from N, O and S; or R^2 and R^4 are taken together with the carbon atom to which each is attached form a 5 membered saturated heterocyclyl ring which is unsubstituted or substituted by CN or C_{1-10}alkyl, C_{1-10}alkylC_{5-15}aryl,

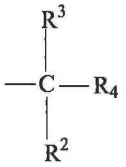
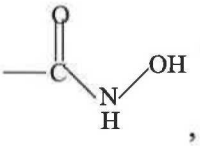
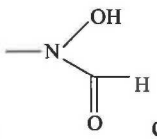
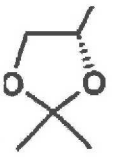
provided that when Q is absent, R^1 is $OC(halogen)_3$, X is O, Y is CH_2, Z is  , and

R^2, R^3 and R^4 are each independently H,  , or  , or R^2 and R^4 are taken together with the carbon or nitrogen atom to form  ,  or

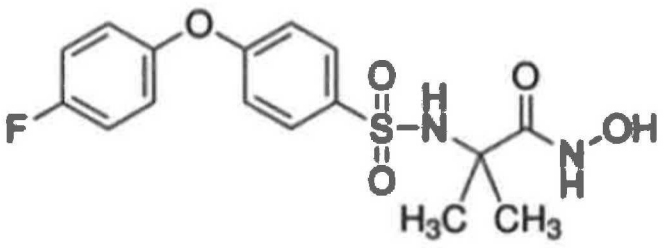


,

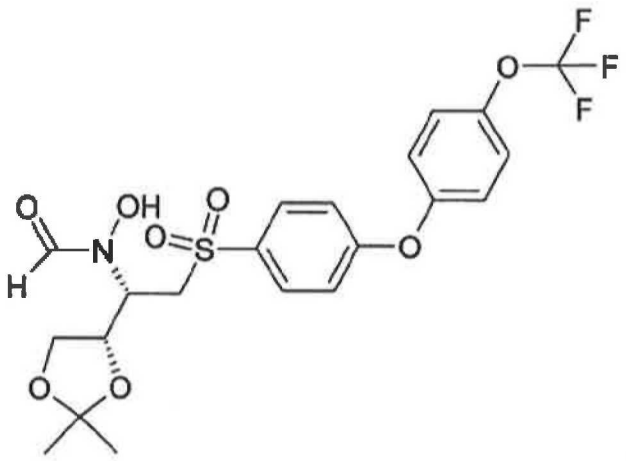
when Q is O; R^1 is halogen or $OC(halogen)_3$, X is $S(O)_2$, and Z is , and

when Q is O; R^1 is halogen or $OC(halogen)_3$, X is $S(O)_2$, Y is NH; Z is  ; and R^2, R^3 and R^4 are each independently H, $C_{1\text{-}10}$alkyl, ,  or .

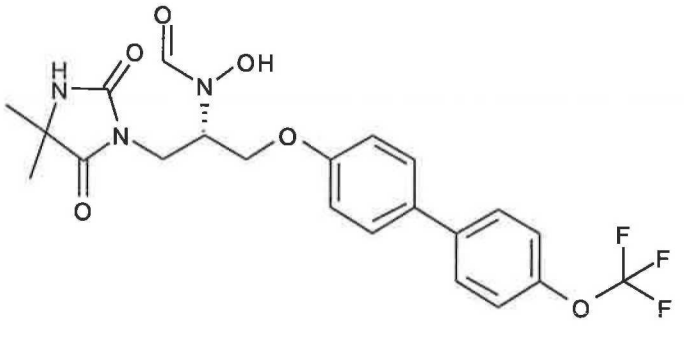
8. The use as claimed in Claim 7, wherein the compound of Formula (III) is selected from the group consisting of:



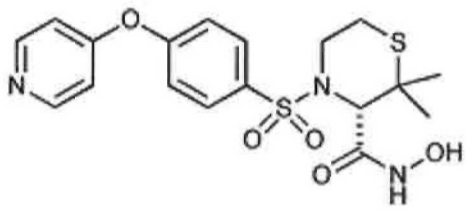
CP471474,



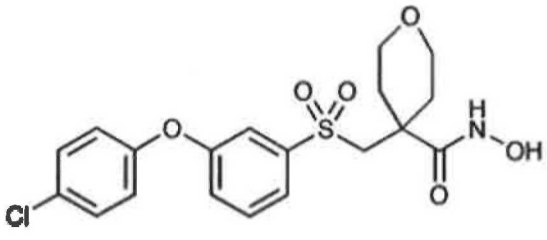
ABT-518,



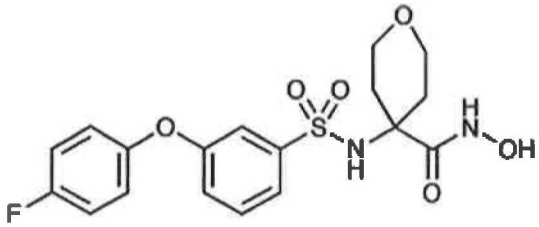
ABT-770,



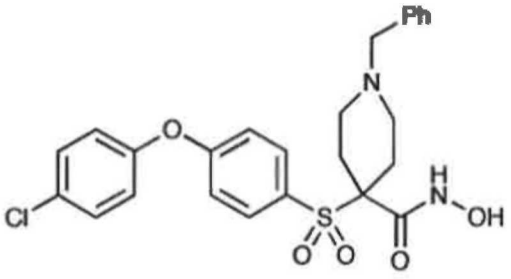
Prinomastat,



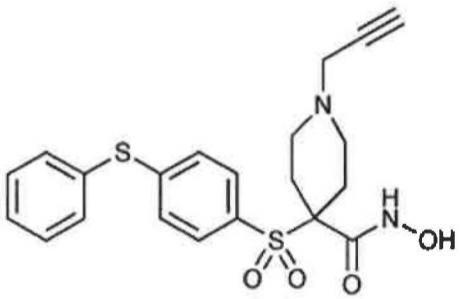
RS-130830,



CAS No. 230954-09-3,



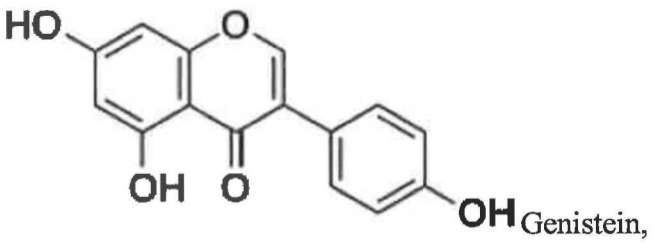
CAS NO. 239796-97-5, and



SC-276,

or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

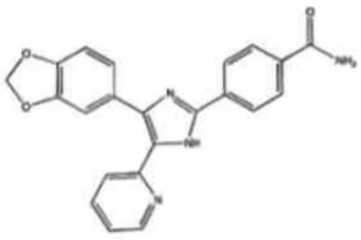
9. The use as claimed in Claim 1, wherein the MMP inhibitor is a compound having the following formula:



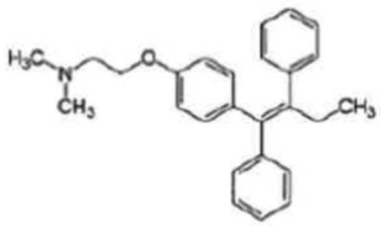
Genistein,

or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

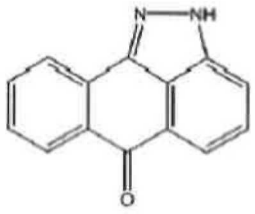
10. The use as claimed in Claim 1, wherein the TGF-beta inhibitor is selected from the group consisting of:



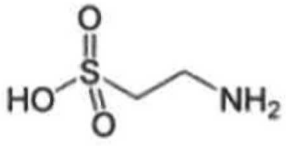
SB-431542,



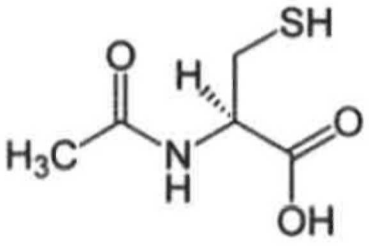
Tamoxifen,



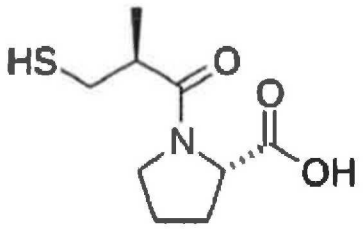
SP600125,



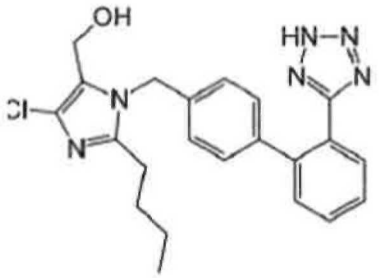
Taurine,



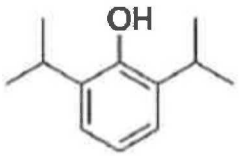
N-acetylcysteine,



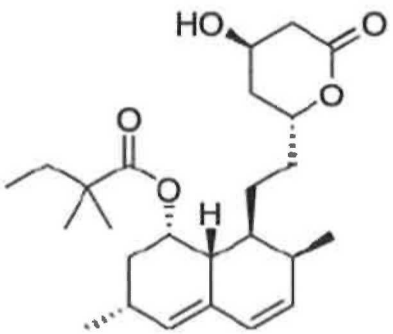
Captopril,



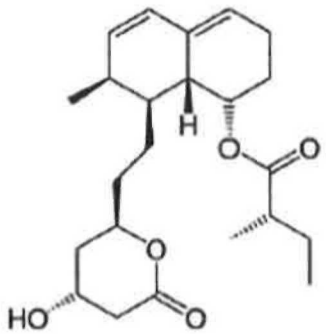
Losartan,



Propofol,



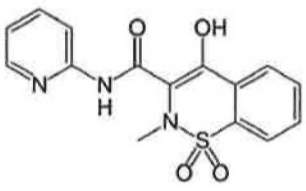
Simvastatin, and



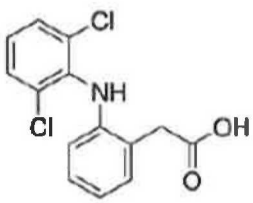
Mevastatin.

or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

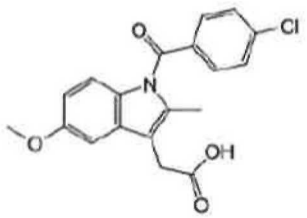
11. The use as claimed in Claim 1, wherein the COX/LOX inhibitor is selected from the group consisting of:



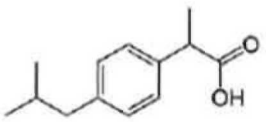
Piroxicam,



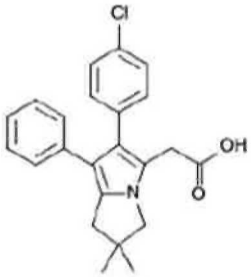
Voltaren (Diclofenac),



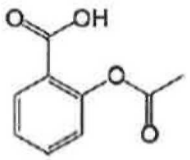
Indomethacin,



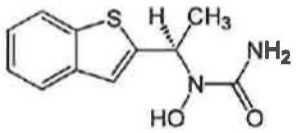
Ibuprofen,

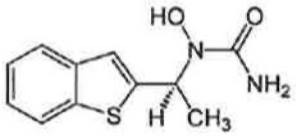


Licofelone,



Aspirin, and





Zileuton;

or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.