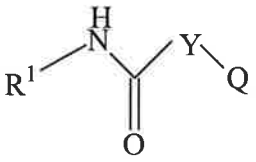
Claims

What is claimed is:

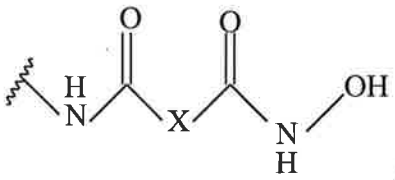
1. The use of MMP inhibitor in the manufacture of a medicament for the treatment of a disease medicated by expression of lumican and/or collagen fibrillogenesis, and/or myopia and/or keratoconus disease.~~A method for treating a disease medicated by expression of lumican and/or collagen fibrillogenesis, and/or treating myopia and/or keratoconus disease, comprising administering to the subject a therapeutically effective amount of a MMP inhibitor.~~

2. The use as claimed in ~~method of~~ 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

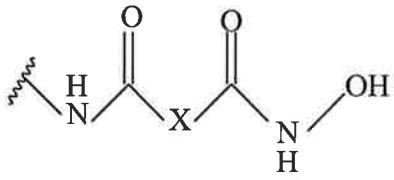


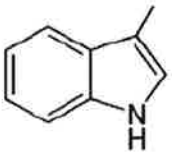
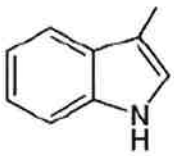
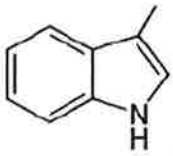
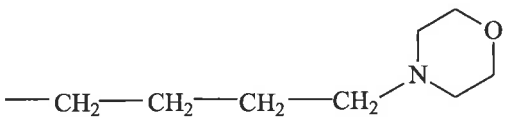
Q is absent or ;

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;

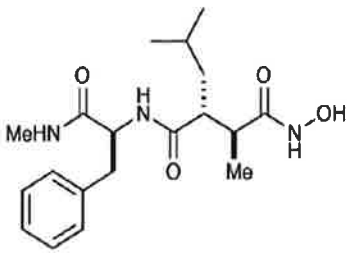
Y is C_{1-10}alkylene, C_{2-10} alkenylene or C_{2-10} alkynylene, unsubstituted or substituted by one or more OH, C_{1-10} straight or branched alkyl, C_{2-10} straight or branched alkenyl, C_{1-10}alkylC_{5-15}aryl, C_{1-10}alkenylC_{5-15}aryl, C_{1-10}alkynylC_{5-15}aryl, C_{1-10}alkylsulfanylC_{5-15}aryl,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

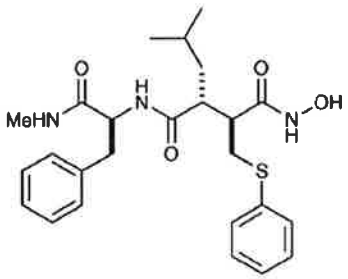
3. The use as claimed in~~method of~~ Claim 2, wherein when Q is , X is $-CH_2-$, $-CH(CH_2CH_2(CH_3)_2)-$, or $-CH_2CH_2-$, $-CH(CH_2CH_2(CH_3)_2)CH(CH_3)-$, $-CH(CH_2CH_2(CH_3)_2)CH(CH_2\text{-S-phenyl})-$, $-CH(CH_2CH_2(CH_3)_2)CH(OCH_3)-$, $-CH(CH_2CH_2(CH_3)_2)-$, or $-CH_2CH_2-$, $-CH(CH_2CH_2(CH_3)_2)CH(CH_3)-$, $-CH(CH_2CH_2(CH_3)_2)CH_2-$, $-CH(CH_2CH_2(CH_3)_2)CH(OH)-$, 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~~method of~~ Claim 2, 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 .

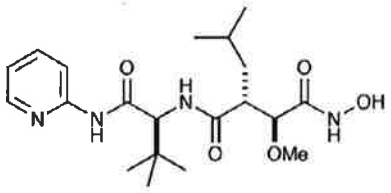
5. The use as claimed in~~method of~~ Claim 2, wherein the compound of Formula (I) is selected from the group consisting of:



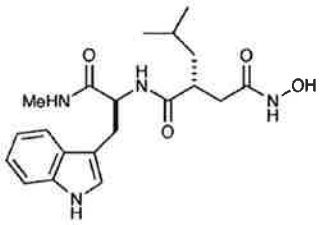
KB-R-7785,



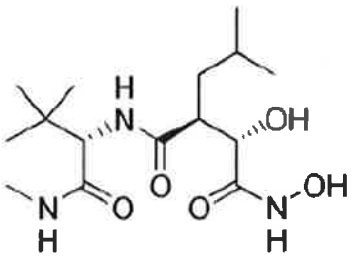
GI-129471,



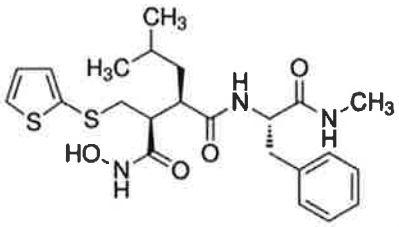
Salimostat,



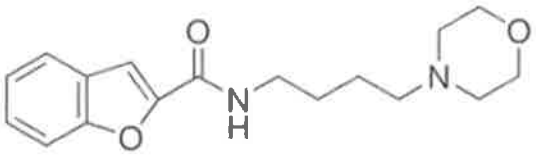
Ilomastat,



Marimastat,



Batimastat, and

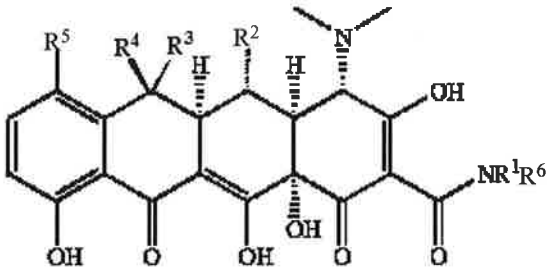


CL-82198,

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

~~6. The method of Claim 5, wherein the the compound is CL-82198, Marimastat, or Batimastat.~~

7. The use as claimed in~~method of~~ 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;

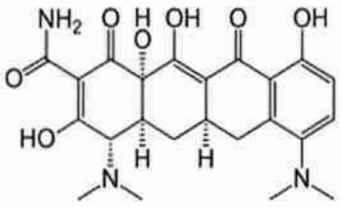
R^5 is hydrogen, halogen, NH_2, OH, NO, CN, C1-10 alkyl, NHC_{1-10}alkyl, $N(C_{1-10}alkyl)_2$, C_{5-15}aryl or C_{5-14}heteroaryl; and

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

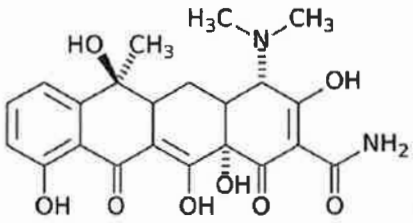
wherein heteroaryl has 1 to 3 heteroatoms independently selected from N, O and S.

87. The use as claimed in~~method of~~ Claim ~~7~~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.

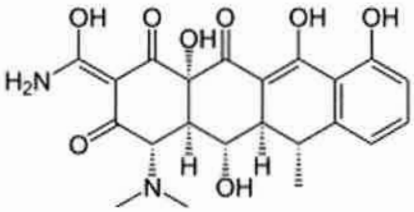
98. The use as claimed in~~method of~~ Claim ~~6~~7, wherein the compound of Formula (II) is selected from the group consisting of:



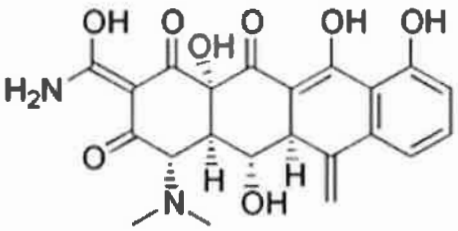
Minocycline hydrochloride,



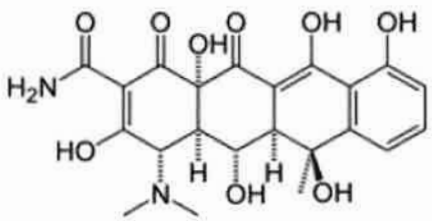
Tetracycline,



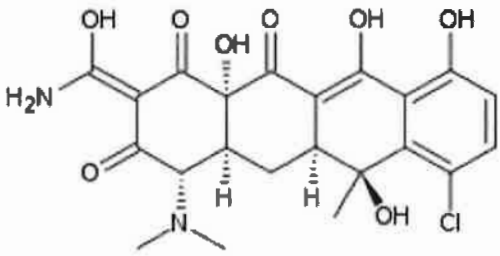
Doxycycline,



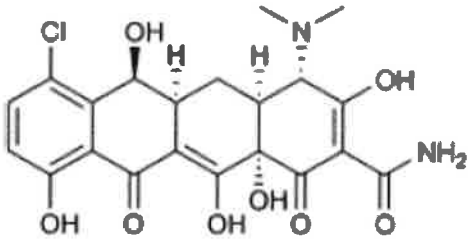
Metacycline,



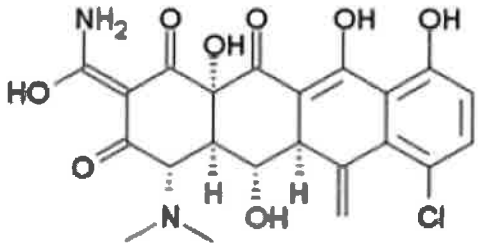
Oxytetracycline,



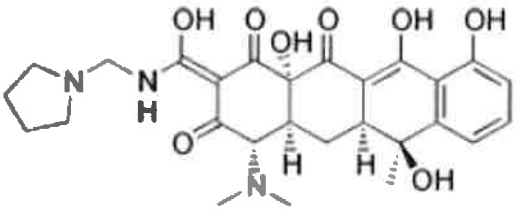
Chlortetracycline,



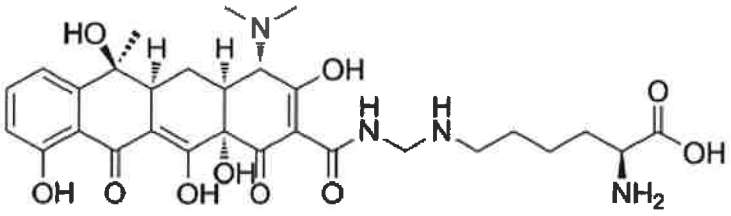
Democlocycline,



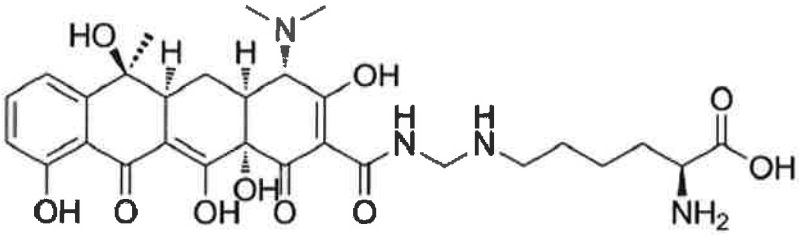
Meclocycline,



Rolitetracycline,



Lymccycline, and

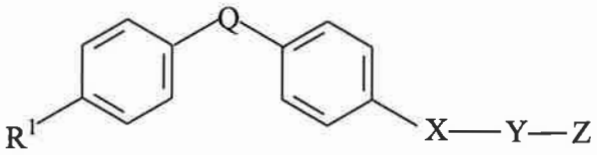


Tigecycline,

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

~~10. The method of Claim 9, wherein the compound is Minocycline, Tetracycline or doxycycline.~~

~~11~~9. The use as claimed in~~method of~~ Claim 1, wherein the ~~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

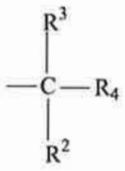
R^1 is halogen, OH, NH_2, OC_{1-10}alkyl unsubstituted or substituted by 1-3 halogen, or NH_2;

Q is absent or O;

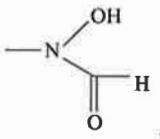
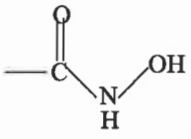
X is O or $S(O)_2$;

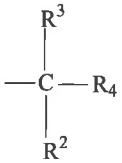
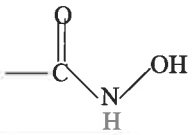
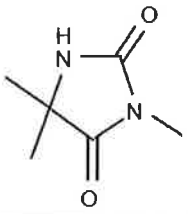
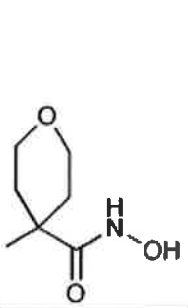
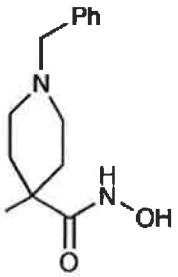
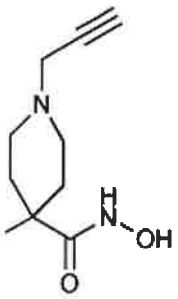
Y is CH_2 or NH;

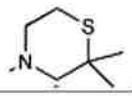
Z is C_{5-14}heteroaryl having 1 to 3 heteroatoms independently selected from N, O and S or

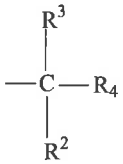
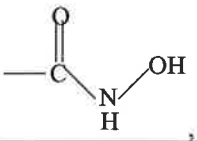
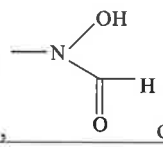
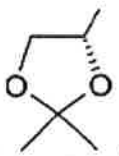


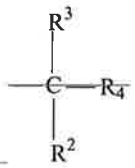
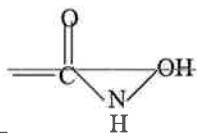
, and

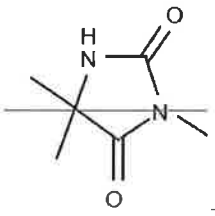
R^2, R^3 and R^4 are each independently H, C_{1-10}alkyl, , ,or unsubstituted or substituted C_{5-14}heteroaryl having 1 to 3 heteroatoms independently selected from N, O and S; or R^2 and R^4 are taken together with the carbon atom to which each is attached form a 5 membered saturated heterocyclyl ring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

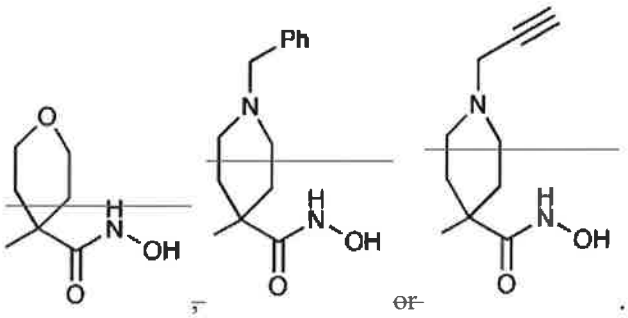
when Q is O; R^1 is halogen or $OC(halogen)_3$, X is $S(O)_2$, and Z is , and

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, $C_{1\text{-}10}$alkyl, , , or .

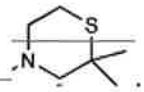
~~12. The method of Claim 11, wherein when Q is absent, R^1 is $OC(halogen)_3$, X is O, Y is CH_2, Z is~~  ~~, and R^2, R^3 and R^4 are each independently H,~~  ~~, or~~

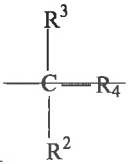


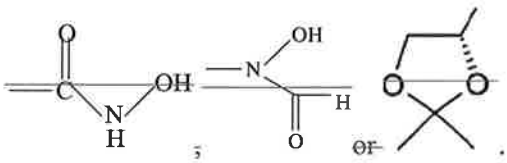
~~, or R^2 and R^4 are taken together with the carbon or nitrogen atom to form~~



~~;~~ ~~or~~ .

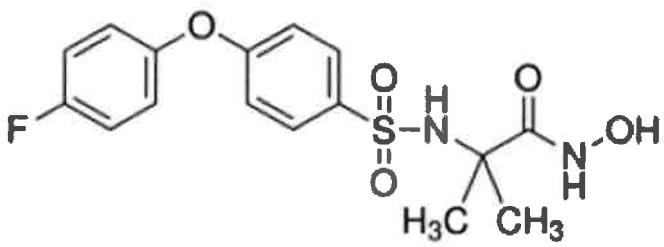
~~13. The method of Claim 11, wherein when Q is O; R^1 is halogen or $OC(halogen)_3$, X is $S(O)_2$, and Z is~~  .

~~14. The method of Claim 11, wherein 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,~~

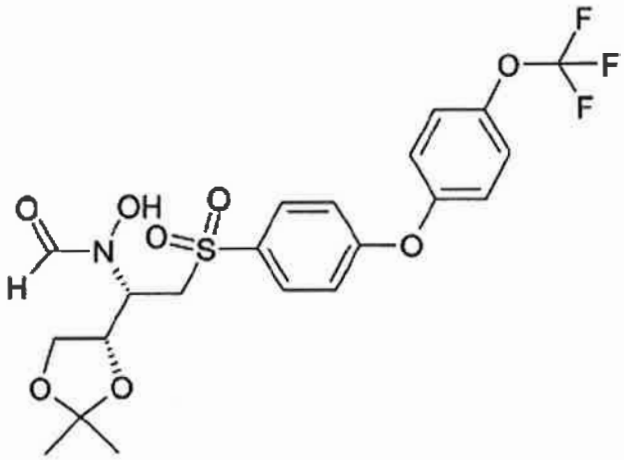


~~;~~ ~~or~~ .

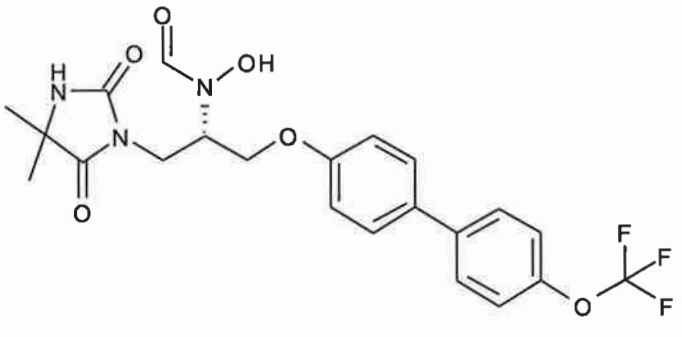
~~15~~10. The use as claimed in~~method of~~ Claim ~~11~~9, wherein the compound of Formula (III) is selected from the group consisting of:



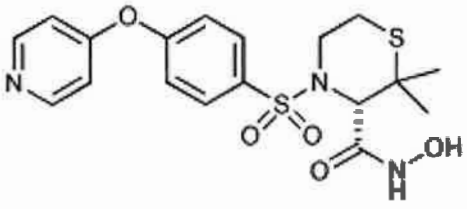
CP471474,



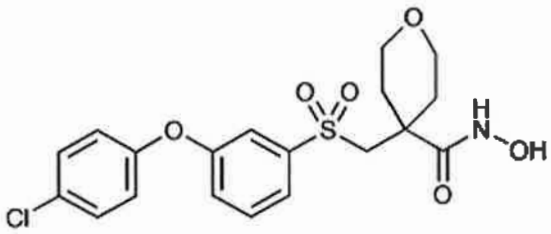
ABT-518,



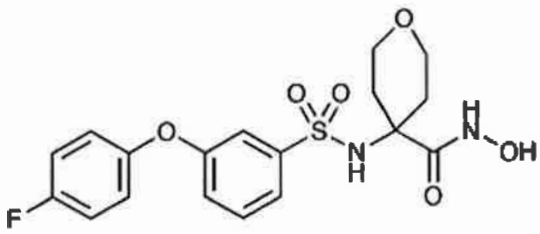
ABT-770,



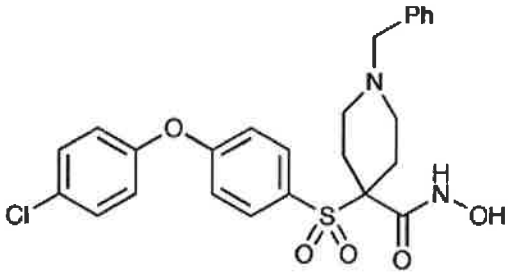
Prinomastat,



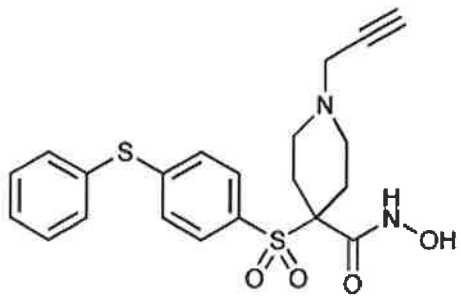
RS-130830,



CAS No. 230954-09-3,



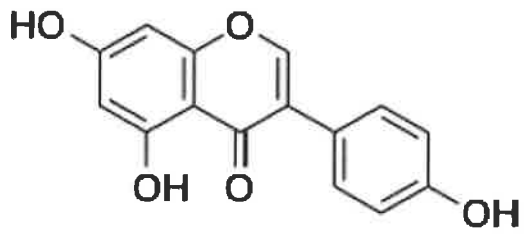
CAS NO. 239796-97-5, and



SC-276,

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

~~16~~11. The use as claimed in~~method of~~ Claim 1, wherein the MMP inhibitor is a compound having the following formula:

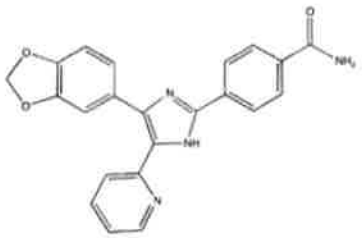


Genistein,

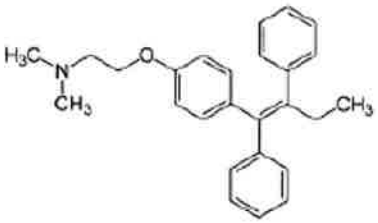
or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

~~17~~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.~~A method for treating a disease medicated 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.~~

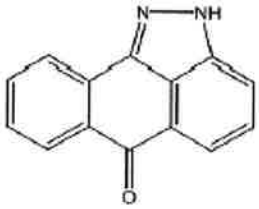
~~18~~13. The use as claimed in~~method of~~ Claim ~~17~~12, wherein the TGF-beta inhibitor is selected from the group consisting of:



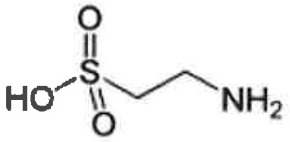
SB-431542,



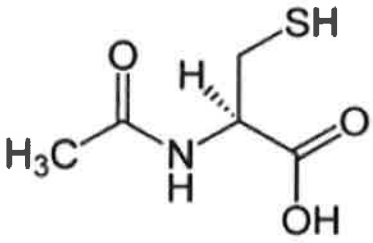
Tamoxifen,



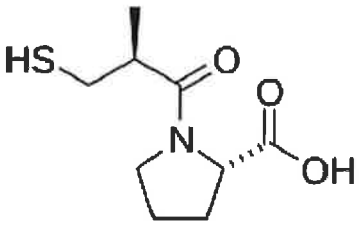
SP600125,



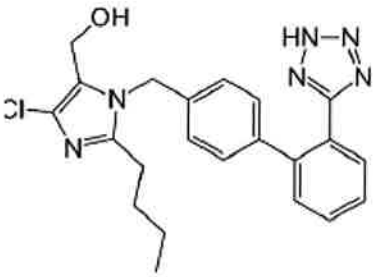
Taurine,



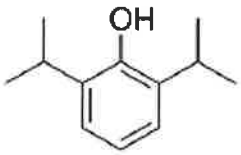
N-acetylcysteine,



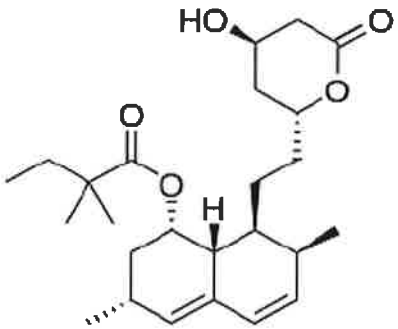
Captopril,



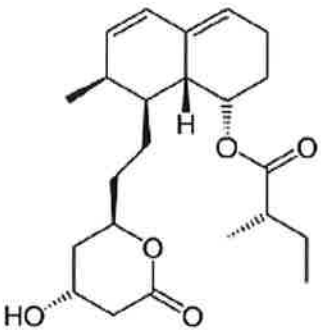
Losartan,



Propfol,



Simvastatin, and



Mevastatin.

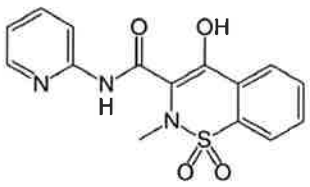
or a pharmaceutically acceptable salt, prodrug, solvate, stereoisomer or enantiomer thereof.

~~19. The method of Claim 18, wherein the TGF-beta inhibitor is Losartan, N-acetylcysteine, Propofol and Captopril.~~

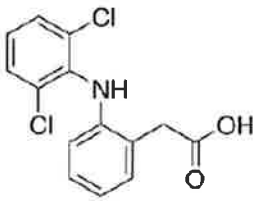
~~20~~14. The use of COX/LOX inhibitor in the manufacture of a medicament for the treatment of a disease medicated by expression of lumican and/or collagen fibrillogenesis, and/or myopia and/or

keratoconus disease.~~A method for treating a disease medicated 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.~~

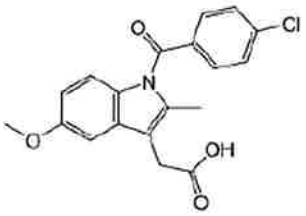
~~21~~15. The use as claimed in~~method of~~ Claim ~~20~~14, wherein the COX/LOX inhibitor is selected from the group consisting of:



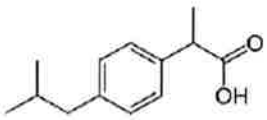
Piroxicam,



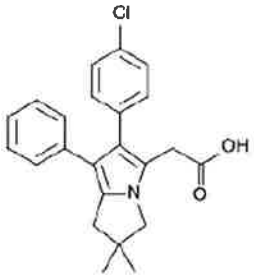
Voltaren (Diclofenac),



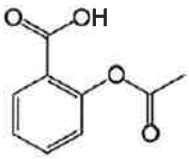
Indomethacin,



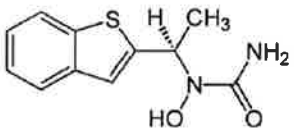
Ibuprofen,

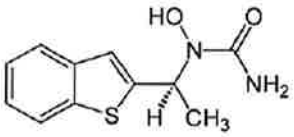


Licofelone,



Aspirin, and





Zileuton;

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

~~22. The method of Claim 1, 17 or 20, wherein the method is for treating myopia.~~

~~23. The method of Claim 1, 17 or 20, wherein the MMP inhibitor, TGF beta inhibitor or COX/LOX inhibitor is in combination with a pharmaceutically acceptable carrier to form an eye drop, ophthalmic gel, ophthalmic ointment or ophthalmic emulsion.~~