CLAIMS

1. The use of an inhibitor of insulin-regulated aminopeptidase (IRAP) for the manufacture of a medicament for the therapeutic treatment of fibrosis.

2. Use according to claim 1, wherein the individual is identified as having fibrosis.

3. Use according to claim 1 or 2, wherein the use reduces progression of, or reverses, at least one clinically or biochemically observable characteristic of fibrosis, thereby treating fibrosis.

4. Use according to claim 3, wherein the clinically or biochemically observable characteristic comprises any one of organ dysfunction, scarring, alteration of normal extracellular matrix balance, increase in collagen deposition, differentiation of fibroblasts to myofibroblasts, reduction in the level of matrix metalloproteinases, increase in the level of tissue Inhibitors of matrix metalloproteinases, increased levels of either N-terminal or C-terminal propeptide of type I procollagen (PINP or PICP), decreased levels of C-terminal telopeptide of Type I Collagen (CTP or CITP), increased collagen deposition or impaired cardiac function measured by various noninvasive imaging techniques, and impaired renal function measured by increased proteinurea and albuminurea, decreased glomerular filtration rate, doubling of plasma creatinine levels, preferably wherein collagen is a precursor or mature forms of collagen α1 Type 1.

5. Use according to any one of claims 1 to 4, wherein the fibrosis is:

(a) age-induced; or

(b) stress-induced or injury-induced.

6. Use according to claim 5, wherein the fibrosis is associated with hypertensive heart disease, hypertensive cardiomyopathy or heart failure, or nephropathy with or without associated diabetes, or other stress-induced or injury-induced cardiovascular sequelae that may involve a fibrotic response, with or without underlying cardiovascular disease.

7. Use according to any one of claims 1 to 6, wherein the fibrosis is selected from the group consisting of cardiac fibrosis, liver fibrosis, kidney fibrosis, vascular fibrosis, lung fibrosis and dermal fibrosis, preferably the liver fibrosis is non-alcoholic steatohepatitis (NASH).

8. Use according to any one of claims 1 to 7, wherein the inhibitor of IRAP directly inhibits the enzymatic activity of IRAP.

9. Use according to claim 8, wherein:

(i) the inhibitor binds to IRAP;

(ii) binds to the active site of IRAP; or

(iii) competes with a substrate of IRAP for binding to IRAP.

10. Use according to any one of claims 1 to 9, wherein the inhibitor of IRAP exhibits a *K*i value of less than 1 mM, as determined by an assay of aminopeptidase activity or substrate degradation,

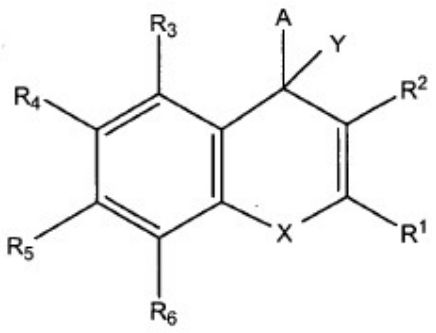
wherein the assay of amino peptidase activity comprises hydrolysis of the synthetic substrate L-Leucine 7-amido-4-methyl coumarin hydrochloride (Leu-MCA) monitored by release of the fluorogenic product MCA;

wherein the assay of substrate degradation is degradation of the peptide substrates CYFQNCPRG or YGGFL.

11. Use according to any one of claims 1 to 10, wherein the inhibitor is selected from the group consisting of a small molecule, an antibody and a peptide.

12. Use according to any one of claims 1 to 10, wherein the inhibitor is an interfering RNA.

13. Use according to any one of claims 1 to 11, wherein the inhibitor has a structure according to Formula (I):



(I)

wherein

A is aryl, heteroaryl carbocyclyl or heterocyclyl, each of which may be optionally substituted, when R^1 is $NHCOR_8$;

or quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridyl, phthalazinyl or pteridinyl, each of which may be optionally substituted, when R^1 is NR_7R_8, $NHCOR_8$, $N(COR_8)_2$, $N(COR_7)(COR_8)$, $N{=}CHOR_8$ or $N{=}CHR_8$;

X is O, NR' or S, wherein R' is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted acyl, optionally substituted heteroaryl, optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R_7 and R_8 are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, or R_7 and R_8, together with the nitrogen atom to which they are attached form a 3-8-membered ring which may be optionally substituted;

R^2 is CN, CO_2R^9, $C(O)O(O)R^9$, $C(O)R^9$ or $C(O)NR^9R^{10}$ wherein R^9 and R^{10} are independently selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, each of which may be optionally substituted, and hydrogen; or R^9 and R^{10} together with the nitrogen atom to which they are attached, form a 3-8-membered ring which may be optionally substituted;

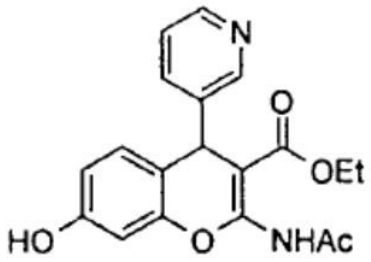
R_3-R_6 are independently selected from hydrogen, halo, nitro, cyano alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, carbocyclyl, hydroxy, alkoxy, alkenyloxy, alkynyloxy, alkynyloxy, aryloxy, heteroaryloxy, heterocyclyloxy, amino, acyl, acyloxy,

carboxy, carboxyester, methylenedioxy, amido, thio, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, carbocyclylthio, acylthio and azido, each of which may be optionally substituted where appropriate, or any two adjacent R^3-R^6, together with the atoms to which they are attached, form a 3-8-membered ring which may be optionally substituted; and

Y is hydrogen or C_{1-10}alkyl,

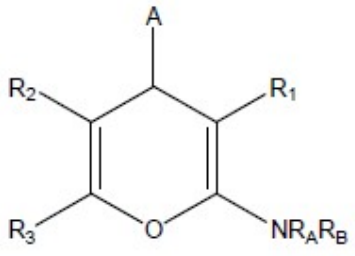
or a pharmaceutically acceptable salt or solvate thereof.

14. Use according to claim 13, wherein the inhibitor has the structure:



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15. Use according to any one of claims 1 to 11, wherein the inhibitor has a structure according to Formula (II):



(II)

wherein

A is selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, carbocyclyl, carbocyclylalkyl, each of which may be optionally substituted;

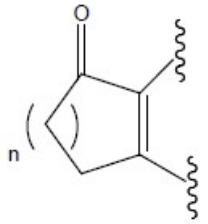
R_A and R_B are independently selected from hydrogen, alkyl and acyl;

R_1 is selected from CN or CO_2R_C;

R_2 is selected from CO_2R_C and acyl;

R_3 is selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, carbocyclyl, carbocyclylalkyl, each of which may be optionally substituted; or

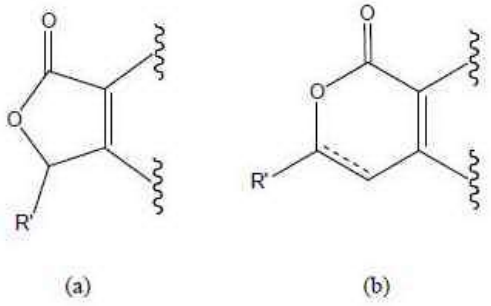
R_2 and R_3 together form a 5-6-membered saturated keto-carbocyclic ring:



wherein n is 1 or 2;

and which ring may be optionally substituted one or more times by C_{1-6}alkyl; or

R_2 and R_3 together form a 5-membered lactone ring (a) or a 6-membered lactone ring (b)

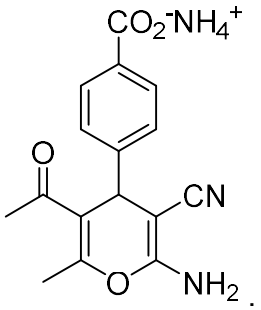


wherein ---- is an optional double bond and R' is alkyl.

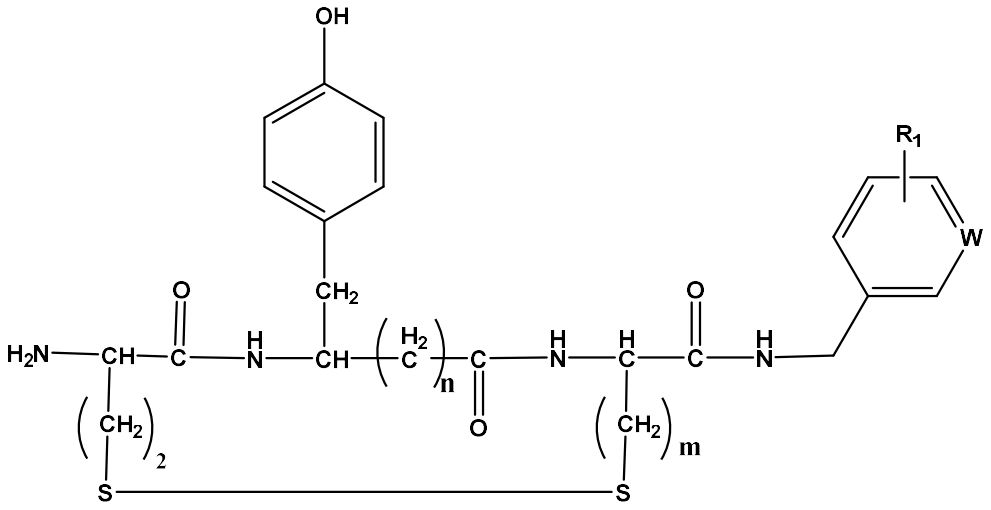
R_C is selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, carbocyclyl, carbocyclylalkyl, each of which may be optionally substituted;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

16. Use according to claim 15, wherein the inhibitor has the structure:



17. Use according to any one of claims 1 to 11, wherein the inhibitor has a structure according to Formula (III):



(III)

wherein

R_1 is H or CH_2COOH; and

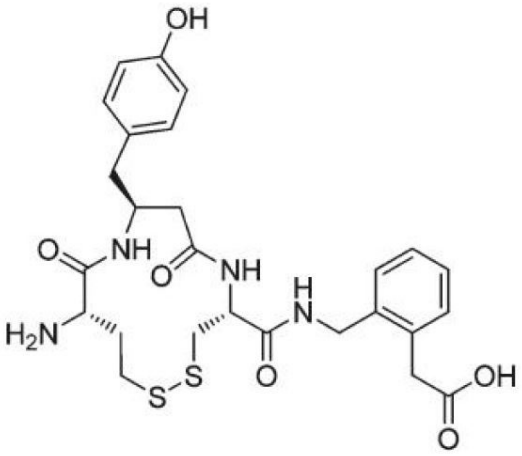
n is 0 or 1; and

m is 1 or 2; and

W is CH or N;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

18. Use according to claim 17, wherein the inhibitor has the structure:



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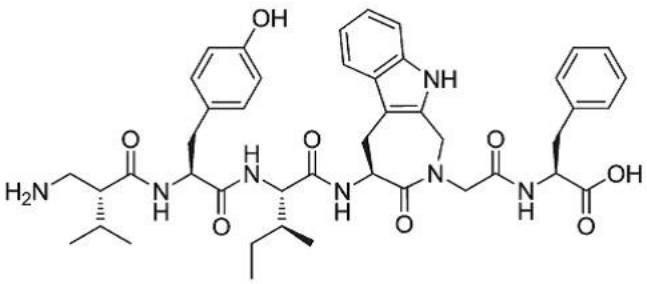
19. Use according to any one of claims 1 to 11, wherein the inhibitor has a structure according to any one of the following sequences:

Val-Tyr-Ile-His-Pro-Phe,

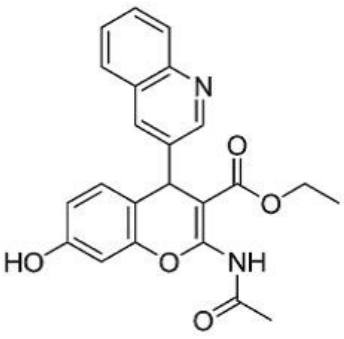
c[Cys-Tyr-Cys]-His-Pro-Phe, and

c[Hcy-Tyr-Hcy]-His-Pro-Phe.

20. Use according to any one of claims 1 to 11, wherein the inhibitor has a structure according to:



or


N
O
O
HO
O
NH
O

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