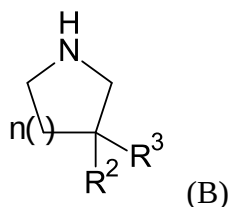


in the presence of a compound of formula (B)



and a base, wherein R^1 to R^4 and n are as defined herein.

In another aspect, there is provided a compound as defined herein for use as
5 therapeutically active substance.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a therapeutically inert carrier.

In another aspect, there is provided use of a compound as defined herein for the preparation of medicaments for the treatment or prophylaxis of pain, neuropathic pain,
10 atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft rejection, chronic allograft nephropathy, diabetic nephropathy, glomerulonephropathy, cardiomyopathy, heart failure, myocardial ischemia/infarction, systemic sclerosis, thermal
15 injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, stroke, transient ischemic attack, uveitis, asthma, osteoporosis, psychiatric diseases, psychosis, encephalitis, malaria, immunological disorders, arthritis, gastrointestinal disorders, rheumatoid arthritis or allergy.

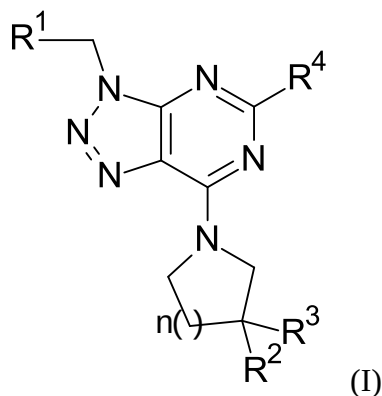
In another aspect, there is provided a compound as defined herein for use in the
20 treatment or prophylaxis of pain, neuropathic pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft rejection, chronic allograft nephropathy, diabetic nephropathy, glomerulonephropathy, cardiomyopathy, heart failure,
25 myocardial ischemia/infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, stroke, transient ischemic attack, uveitis, asthma, osteoporosis,

psychiatric diseases, psychosis, encephalitis, malaria, immunological disorders, arthritis, gastrointestinal disorders, rheumatoid arthritis or allergy.

In the present description the term “alkyl”, alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, particularly a
5 straight or branched-chain alkyl group with 1 to 6 carbon atoms and more particularly a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched-chain C₁-C₈ alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the

Claims

1. A compound of formula (I)



wherein

- 5 R¹ is a ring selected from phenyl and [1,2,5]oxadiazolyl wherein said ring is substituted with one substituent selected from halosulfonyl, halosulfonylalkyl, isothiocyanatoalkyl, isothiocyanato, aminoalkyldisulfanylalkyl, hydroxyalkyldisulfanylalkyl, hydroxyalkyldisulfanyl, aminoalkyldisulfanyl, halogen, alkyl, pyridinyldisulfanylalkyl, benzotriazolylsulfonylalkyl, dihydroxyalkyldisulfanylalkyl and pyridinyldisulfanyl and optionally further substituted with cyano;

R² and R³ are independently selected from hydrogen, hydroxyl, halogen, thiohydroxyl, thiohydroxyazetidiny, azido, isothiocyanato and alkyldisulfanyl;

- 15 provided that at least one of R¹, R² and R³ is a group comprising sulfonyl, isothiocyanato, disulfanyl, thiohydroxyl or azido;

R⁴ is alkyl or phenylhaloalkyl; and

n is 0 or 1;

or a pharmaceutically acceptable salt or ester thereof.

2. A compound according to claim 1, wherein R¹ is a ring selected from phenyl and [1,2,5]oxadiazolyl wherein said ring is substituted with one substituent selected from halosulfonyl, halosulfonylalkyl, isothiocyanatoalkyl, isothiocyanato, halogen, alkyl, hydroxyalkyldisulfanylalkyl, pyridinyldisulfanylalkyl, dihydroxyalkyldisulfanylalkyl and optionally further substituted with cyano.

3. A compound according to claim 1 or 2, wherein R¹ is a ring selected from phenyl and [1,2,5]oxadiazolyl wherein said ring is substituted with one substituent selected from fluorosulfonyl, fluorosulfonylmethyl, isothiocyanatomethyl, isothiocyanato, chloro, methyl, hydroxyethyl disulfanylethyl, fluorosulfonylethyl, pyridinyldisulfanylethyl, dihydroxyethyl disulfanylethyl and optionally further substituted with cyano.
4. A compound according to any one of claims 1 to 3, wherein R¹ is fluorosulfonylphenyl, fluorosulfonylmethylphenyl, isothiocyanatomethylphenyl, isothiocyanatophenyl, chlorophenyl, methyl[1,2,5]oxadiazolyl, hydroxyethyl disulfanylethylphenyl, fluorosulfonylethylphenyl, pyridinyldisulfanylethylphenyl, dihydroxyethyl disulfanylethylphenyl or (fluorosulfonyl)(cyano)phenyl.
5. A compound according to any one of claims 1 to 4, wherein R² is hydrogen and R³ is hydroxyl, thiohydroxyl, azido, isothiocyanato or methyl disulfanyl, or R² and R³ are both fluoro at the same time.
6. A compound according to any one of claims 1 to 5, wherein R⁴ is tert.-butyl or phenyldifluoromethyl.
7. A compound according to any one of claims 1 to 6, wherein n is 1.
8. A compound according to any one of claims 1 to 7 selected from
2-({5-tert-butyl-7-[(3S)-3-hydroxypyrrolidin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}methyl)benzene-1-sulfonyl fluoride;
(2-{[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]methyl}phenyl)methanesulfonyl fluoride;
[2-({5-tert-butyl-7-[(3S)-3-hydroxypyrrolidin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}methyl)phenyl)methanesulfonyl fluoride;
5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3-{{2-(isothiocyanatomethyl)phenyl}methyl}-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
(3S)-1-(5-tert-butyl-3-{{2-(isothiocyanatomethyl)phenyl}methyl}-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)pyrrolidin-3-ol;
5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3-[(2-isothiocyanatophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

- 2-{{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}benzene-1-sulfonyl fluoride;
- 2-{{(2-{{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl)methyl}disulfanyl}ethan-1-amine;
- 5 2-{{(2-{{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl)methyl}disulfanyl}ethan-1-ol;
- 2-{{(2-{{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl)disulfanyl}ethan-1-ol;
- 10 2-{{(2-{{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl)disulfanyl}ethan-1-amine;
- 2-{{2-({5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl)disulfanyl}ethan-1-amine;
- 2-{{2-({5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl)methyl}disulfanyl}ethan-1-amine;
- 15 2-{{5-[difluoro(phenyl)methyl]-7-[(3S)-3-hydroxypyrrolidin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}benzene-1-sulfonyl fluoride;
- 2-{{5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}benzene-1-sulfonyl fluoride;
- 20 [2-{{5-[difluoro(phenyl)methyl]-7-[(3S)-3-hydroxypyrrolidin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl]methanesulfonyl fluoride;
- [2-{{5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl]methanesulfonyl fluoride;
- (3S)-1-(5-[difluoro(phenyl)methyl]-3-{{2-(isothiocyanatomethyl)phenyl)methyl}-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)pyrrolidin-3-ol;
- 25 5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3-{{2-(isothiocyanatomethyl)phenyl)methyl}-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3-{{2-(isothiocyanatophenyl)methyl}-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

- 1-{5-tert-butyl-3-[(2-chlorophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol;
- 1-{5-tert-butyl-3-[(2-chlorophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}azetidine-3-thiol;
- 5 (3S)-1-{5-tert-butyl-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol;
- (3R)-1-{5-tert-butyl-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol;
- 10 (3S)-1-{5-tert-butyl-3-[(2-chlorophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol;
- (3R)-1-{5-tert-butyl-3-[(2-chlorophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol
- 7-(3-azidopyrrolidin-1-yl)-5-tert-butyl-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 15 5-tert-butyl-3-[(2-chlorophenyl)methyl]-7-(3-isothiocyanatopyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 5-tert-butyl-7-(3-isothiocyanatopyrrolidin-1-yl)-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 20 7-(3-azidopyrrolidin-1-yl)-5-tert-butyl-3-[(2-chlorophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 5-[difluoro(phenyl)methyl]-7-[3-(methyldisulfanyl)pyrrolidin-1-yl]-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 3-[(2-chlorophenyl)methyl]-5-[difluoro(phenyl)methyl]-7-[3-(methyldisulfanyl)pyrrolidin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 25 7-(3-azidopyrrolidin-1-yl)-5-[difluoro(phenyl)methyl]-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 7-(3-azidopyrrolidin-1-yl)-3-[(2-chlorophenyl)methyl]-5-[difluoro(phenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

- 3-[(2-chlorophenyl)methyl]-5-[difluoro(phenyl)methyl]-7-(3-isothiocyanatopyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 5-[(difluoro(phenyl)methyl)-7-(3-isothiocyanatopyrrolidin-1-yl)-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 5 2-[[5-[difluoro(phenyl)methyl]-7-[(3S)-3-hydroxypyrrolidin-1-yl]triazolo[4,5-d]pyrimidin-3-yl]methyl]benzenesulfonyl fluoride;
- 2-[[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]methyldisulfanyl]ethanol;
- 10 2-[[5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]benzenesulfonyl fluoride;
- 5-[(difluoro(phenyl)methyl)-7-(3,3-difluoropyrrolidin-1-yl)-3-[[2-[2-(pyridin-2-yl)disulfanyl]ethyl]phenyl]methyl]triazolo[4,5-d]pyrimidine;
- 2-[2-[2-[[5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyldisulfanyl]ethanol;
- 15 2-[2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyldisulfanyl]ethanol;
- 3-[[2-[2-(benzotriazol-1-yl)sulfonyl]ethyl]phenyl]methyl]-5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidine;
- 20 2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethanesulfonyl fluoride;
- 5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3-[[2-[2-(pyridin-2-yl)disulfanyl]ethyl]phenyl]methyl]triazolo[4,5-d]pyrimidine;
- 2-[2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyldisulfanyl]ethanamine;
- 25 2-[2-[2-[[5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyldisulfanyl]ethanamine;
- 3-[2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyldisulfanyl]propane-1,2-diol;

- 2-[[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl)methyl]phenyl]disulfanyl]ethanol;
- 5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3-[[2-(pyridin-2-yl)disulfanyl]phenyl)methyl]triazolo[4,5-d]pyrimidine; and
- 5 2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl)methyl]-3-ethynylbenzenesulfonyl fluoride.
9. A compound according to any one of claims 1 to 8 selected from
- 2-({5-tert-butyl-7-[(3S)-3-hydroxypyrrolidin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}benzene-1-sulfonyl fluoride;
- 10 (2-{[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl)methanesulfonyl fluoride;
- 5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3-{[2-(isothiocyanatomethyl)phenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 15 (3S)-1-(5-tert-butyl-3-{[2-(isothiocyanatomethyl)phenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)pyrrolidin-3-ol;
- 5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3-[(2-isothiocyanatophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 2-{{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}benzene-1-sulfonyl fluoride;
- 20 1-{5-tert-butyl-3-[(2-chlorophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol;
- (3S)-1-{5-tert-butyl-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol;
- 25 7-(3-azidopyrrolidin-1-yl)-5-tert-butyl-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 5-tert-butyl-7-(3-isothiocyanatopyrrolidin-1-yl)-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 5-[difluoro(phenyl)methyl]-7-[3-(methyl)disulfanyl]pyrrolidin-1-yl)-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

7-(3-azidopyrrolidin-1-yl)-3-[(2-chlorophenyl)methyl]-5-[difluoro(phenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

2-[[5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]benzenesulfonyl fluoride;

5 2-[2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyl]disulfanyl]ethanol;

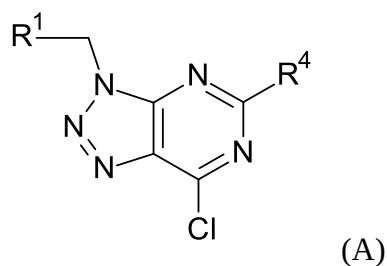
2-[2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethanesulfonyl fluoride;

10 5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3-[[2-[2-(pyridin-2-yl]disulfanyl)ethyl]phenyl]methyl]triazolo[4,5-d]pyrimidine;

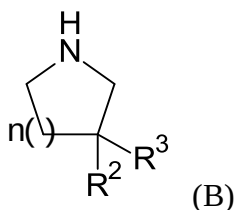
3-[2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyl]disulfanyl]propane-1,2-diol; and

2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]-3-ethynylbenzenesulfonyl fluoride.

15 10. A process for the manufacture of a compound according to any one of claims 1 to 9 comprising the reaction of a compound of formula (A)



in the presence of a compound of formula (B)



20 and a base, wherein R¹ to R⁴ and n are as defined in any one of claims 1 to 9.

11. A compound according to any one of claims 1 to 9 for use as therapeutically active substance.

12. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 9 and a therapeutically inert carrier.
13. The use of a compound according to any one of claims 1 to 9 for the preparation of medicaments for the treatment or prophylaxis of pain, neuropathic pain,
5 atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft rejection, chronic allograft nephropathy, diabetic nephropathy, glomerulonephropathy, cardiomyopathy, heart failure, myocardial
10 ischemia/infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, stroke, transient ischemic attack, uveitis, asthma, osteoporosis, psychiatric diseases, psychosis, encephalitis, malaria, immunological disorders, arthritis, gastrointestinal disorders, rheumatoid arthritis or allergy.
14. A compound according to any one of claims 1 to 9 for use in the treatment or prophylaxis of pain, neuropathic pain, atherosclerosis, age-related macular
15 degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft rejection,
20 chronic allograft nephropathy, diabetic nephropathy, glomerulonephropathy, cardiomyopathy, heart failure, myocardial ischemia/infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, stroke, transient ischemic
25 attack, uveitis, asthma, osteoporosis, psychiatric diseases, psychosis, encephalitis, malaria, immunological disorders, arthritis, gastrointestinal disorders, rheumatoid arthritis or allergy.
