Title: USE OF EP4 RECEPTOR ANTAGONISTS IN THE TREATMENT OF CARTILAGE DISEASE

Abstract: This invention relates to a compound with EP4 antagonistic activity, or a pharmaceutically acceptable salt with EP4 receptor antagonistic activities, which is useful in the treatment of cartilage disease. This invention also relates to a compound of formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof with EP4 receptor antagonistic activities, which is useful in the treatment of cartilage disease. This invention also relates to a pharmaceutical composition for the treatment of cartilage disease which comprises a therapeutically effective amount of a compound of formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof. Further this invention relates to a method for the treatment of cartilage disease in an animal subject including a mammalian subject, which comprises administering to the animal subject including a mammalian subject a compound of the formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof.
Description

Title of Invention: USE OF EP4 RECEPTOR ANTAGONISTS IN THE TREATMENT OF CARTILAGE DISEASE

Technical Field

[0001] This invention relates to compounds for use in therapeutic treatment of the human body. In particular, it relates to compounds with selective EP4 receptor antagonism which are useful for treating cartilage disease, or preventing or delaying the onset or the progression of the said disease.

[0002] This invention also relates to a pharmaceutical composition for the treatment of cartilage disease which comprises a therapeutically effective amount of a compound of formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof. This invention relates to a method for the treatment of cartilage disease in an animal subject including a mammalian subject, which comprises administering to the animal subject including a mammalian subject a compound of the formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof. Further this invention relates to a method for the treatment of cartilage disease in an animal subject including a mammalian subject, which comprises administering to the animal subject including a mammalian subject in need a therapeutically effective amount of a compound of the formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof.

Background Art

[0003] An articular disorder is a disease whose major lesion is a degeneration of an articular cartilage. Cartilage is the organization composed by collagen and proteoglycan. Due to various causes, the synthesizing ability of proteoglycan in this cartilage organization declines, and proteoglycan starts to be released from the organization. The release of type-I collagenase (metalloprotease I) is simultaneously increased, and collagen of the cartilage organization is resolved. The destruction of the cartilage organization proceeds due to a series of these responses. And it undergoes, depending on the stage of the lesion, a hyperplasia of a synovial membrane, a destruction of a subcartilaginous bone, a hyperplasia or a neoplasia of a circumarticular cartilage, which are followed by a deformation of the cartilage, which may lead to dysfunction in a serious case. While the articular disorder occurs most frequently in a knee joint, it occurs also in the joints of elbows, thighs, legs and fingers. Among the articular diseases, the disease which is observed in the largest number of patients is an osteoarthritis, and it is considered to occur increasingly in an elderlies-dominating society in near future, since one of its causes is considered to be the aging of a human. For treating this, an analgesic anti-inflammatory agent or a hyaluronic acid formulation is employed to remedy the pain due
to cartilage degeneration or subcartilaginous bone destruction. However, all therapeutic methods are only nosotropic, and exhibit no sufficient effects. Suppression of cartilage destruction, promotion of chondrogenesis and induction of cartilage cell differentiation are considered to be effective in prevention and treatment of a cartilage disease.

[0004] In the field of therapeutic and prophylactic agents against cartilage diseases which are no more than nosotropic currently, a novel cartilage disease preventing and/or treating agent which is rather radical and excellent in terms of the characteristics required in a useful pharmaceutical (e.g., such as stability, absorption, bioavailability) is demanded.

[0005] Prostaglandin E2 (PGE2) is a potent modulator involved in the pathogenesis of a variety of diseases such as inflammation, pain, arthritis, and cancer. PGE2 binds to at least four subtypes of PGE receptor, designated EP1, EP2, EP3, and EP4. Molecular pharmacology studies have revealed that all subtypes are 7-transmembrane spanning receptors that belong to the G-protein coupled receptor superfamily. EP1 activation stimulates the release of intracellular calcium; EP2 and EP4 stimulation both activate adenylate cyclase but differ in their response to certain ligands; and EP3 stimulation inhibits adenylate cyclase via inhibitory G-proteins (NPL 1).

[0006] Many compounds which show EP4 receptor antagonism have been reported. However it has never been reported that compounds with selective EP4 receptor antagonism which are useful for treating cartilage disease.

Citation List

Non Patent Literature


Summary of Invention

Technical Problem

[0008] As mentioned above, for treating cartilage disease, all therapeutic methods are only nosotropic, and exhibit no sufficient effects. Therefore the compounds which are truly effective for cartilage disease are strongly desired.

[0009] In particular, an object of the present invention is to provide compounds with selective EP4 receptor antagonism which are useful for treating cartilage disease, or preventing or delaying the onset or the progression of cartilage disease.

[0010] An object of the present invention is to provide a pharmaceutical composition for the treatment of cartilage disease which comprises a therapeutically effective amount of a compound of formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof. An object of the present invention is to provide a method for the treatment of cartilage disease in an animal subject including a mammalian subject,
which comprises administering to the animal subject including a mammalian subject a compound of the formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof. Further an object of the present invention is to provide a method for the treatment of cartilage disease in an animal subject including a mammalian subject, which comprises administering to the animal subject including a mammalian subject in need a therapeutically effective amount of a compound of the formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof.

**Solution to Problem**

[0011] The present inventors made much effort to develop a pharmaceutical capable of exerting a direct effect on a cartilage cell to suppress a cartilage destruction and also capable of promoting cartilaginous osteoanagenesis, and finally discovered that a compound of formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof guarantees beneficial effects on cytokine-induced cartilage calcification in a full-depth articular explants model, rat mono-iodoacetate and/or meniscal transection model, rat meniscal transection and/or ovariectomised model, which clearly are useful for prevention and/or treatment of a cartilage disease.

[0012] Specifically, the gist of the present invention is as follows:

1. Use of a compound with EP4 antagonistic activity, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cartilage diseases in an animal subject including a mammalian subject;

2. Use of a compound of the formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cartilage diseases in an animal subject including a mammalian subject:
wherein $Y_1$, $Y_2$, $Y_3$, and $Y_4$ are independently selected from N, CH and C(L);
$R_1$ is H, Ci$_8$ alkyl, C$_2$ alkyl, C$_2$ alkenyl, C$_2$ alkynyl, C$_3$ cycloalkyl, Ci$_8$ alkoxy, halo-substituted Ci$_8$ alkoxy, Ci$_8$ alkenyl-S(0)m-, Q$^1$, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, amino, mono- or di-(Ci$_8$ alkyl)amino, C$_{1-4}$ alkyl-C(=0)-N(R$_3$) or C$_{1-4}$ alkyl-S(0)m-N(R$_3$), wherein said Ci$_8$ alkyl, C$_2$ alkenyl and C$_2$ alkynyl are optionally substituted with halo, Ci$_3$ alkyl, hydroxy, oxo, C$_{1-4}$ alkoxy-, C$_{1-4}$ alkyl-S(0)m-, C$_3$ cycloalkyl-, cyano, indanyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q$^1$, Q$^1$-C(=0)-, Q$^1$-O-, Q$^1$-S(0)m-, Q$^1$-Ci$_4$ alkyl-O-, Q$^1$-Ci$_4$ alkyl-S(0)m-, Q$^1$-Ci$_4$ alkyl-C(=0)-N(R$_3$), Q$^1$-Ci$_4$ alkyl-N(R$_3$) or Q$^1$-Ci$_4$ alkyl-N(R$_3$);
Q$^1$ is a 5 to 12 membered monocyclic or bicyclic aromatic ring optionally containing up to 4 heteroatoms selected from O, N and S, and is optionally substituted with halo, Ci$_{1-4}$ alkyl, halo-substituted Ci$_{1-4}$ alkyl, hydroxy, Ci$_{1-4}$ alkoxy, halo-substituted Ci$_{1-4}$ alkoxy, C$_{1-4}$ alkylthio, nitro, amino, mono- or di-(Ci$_{1-4}$ alkyl)amino, cyano, HO-Ci$_4$ alkyl, Ci$_{1-4}$ alkoxy-Ci$_{1-4}$ alkyl, C$_{1-4}$ alkylosulfonyl, aminosulfonyl, C$_{1-4}$ alkyl(C(=0)=)-, HO(0)=C$_{1-4}$, C$_M$ alkyl-0(0)=C$_{1-4}$, R$^1$N (R$^2$)C(=0)=, C$_{14}$ alkylsulfonylamino, C$_3$ cycloalkyl, R$^3$ C(=0)N(R$_4$)- or NH$_2$(HN=)C$_{1-4}$;
A is a 5 or 6 membered monocyclic aromatic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with up to 3 substituents selected from halo, C$_M$ alkyl, halo-substituted C$_M$ alkyl, hydroxy, C$_M$ alkoxy, halo-substituted C$_{1-4}$ alkoxy, C$_{1-4}$ alkylthio, nitro, amino, mono- or di-(Ci$_{1-4}$ alkyl)amino, cyano, HO-C$_M$ alkyl, d$_{1-4}$
alkoxy-Ci_4 alkyl, C_{1-4} alkylsulfonyl, aminosulfonyl, acetyl, R\^3N(R \^4)C(=0)-, H_O(O=)C-, C_{1-4} alkyl-0(0=)C-, C_{14} alkylsulfonylamino, C_{3-7} cycloalkyl, R \^3C(=0)N(R \^4)- and NH\_2(NH=)C-;

B is halo-substituted Ci_{-4} alkylene, C_{3-2} cycloalkylene, C_{2-6} alkenylene, C_{2-6} alkyne, -0-Ci_{-5} alkylene, C_{1-2} alkylene-0-Ci_{-2} alkylene or Ci_{-6} alkylene optionally substituted with an oxo group or Ci_{-3} alkyl;

W is NH, N-Ci_{-4} alkyl, O, S, N-OR \^5 or a covalent bond;

R\^2 is H, C_{1-4} alkyl, OH or C_{1-4} alkoxy;

Z is a 5 tol2 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5 tol2 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, d \_d alkyl, halo-substituted Ci_{-4} alkyl, d \_d alkényl, Ci_{-4} alkynyl, hydroxy, C_{1-4} alkoxy, halo-substituted C_{1-4} alkoxy, Ci_{-4} alkylthio, nitro, amino, mono- or di-(Ci_{-4} alkyl)amino, cyano, H_O-Ci_{-4} alkyl, C_{1-4} alkoxy-Ci_{-4} alkyl, C_{1-4} alkylsulfonyl, aminosulfonyl, C_{1-4} alkylC(=0)-, H_O(O=)C-, C_{1-4} alkyl-0(0=)C-, C_{14} alkylsulfonylamino, C_{3-7} cycloalkyl, NH\_2(OH=)C-, Q^2-S(0)m-, Q^2-0-, Q^2-N(\^R^2)- or Q^2-;

L is halo, Ci_{-4} alkyl, halo-substituted Ci_{-4} alkyl, hydroxy, Ci_{-4} alkoxy, Ci_{-4} alkylthio, nitro, amino, mono- or di-(Ci_{-4} alkyl)amino, halo-substituted Ci_{-4} alkyl, cyano, H_O-Ci_{-4} alkyl, Ci_{-4} alkoxy-Ci_{-4} alkyl, Ci_{-4} alkylsulfonyl, aminosulfonyl, Ci_{-4} alkylC(=0)-, H_O(O=)C-, C_{1-4} alkyl-0(0=)C-, C_{1-4} alkylsulfonylamino, C_{3-7} cycloalkyl, R \^3C(=0)N(R \^4)-, NH\_2(OH=)C-, R \^3N(R \^4)C(=0)-, R \^3N(R \^4)S(0)m-, Q^2-, Q^2-C(=0)-, Q^2-0-, Q^2-C_{1-4} alkyl-O-, or two adjacent L groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;

m is 0, 1 or 2;

R\^3 and R\^4 are independently selected from H and Ci_{-4} alkyl;

R\^5 is H, C_{1-4} alkyl, C_{1-4} alkyl-0(0=)C- or C_{1-4} alkyl-0(0=)C-; and

Q^2 is a 5 tol2 membered monocyclic or bicyclic aromatic ring, optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5 tol2 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{1-4} alkényl, C_{1-4} alkynyl, hydroxy, C_{1-4} alkoxy, halo-substituted C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, amino, mono- or di-(Ci_{-4} alkyl)amino, cyano, H_O-Ci_{-4} alkyl, C_{1-4} alkoxy-Ci_{-4} alkyl, Ci_{-4} alkylsulfonyl, aminosulfonyl, C_{1-4} alkyl(0(0=)C-, R \^3R \^4C(=0)N-, H_O(O=)C-, C_{1-4} alkyl-0(0=)C-, C_{1-4} alkylsulfonylamino, C_{3-2} cycloalkyl, C_{1-4} alkyl-C(=0)NH- or NH\_2(OH=)C-;
wherein A represents a phenyl group or a pyridyl group;
B represents an aryl group or a heteroaryl group;
E represents a 1,4-phenylene group;
R₁ and R₂ independently represent a hydrogen atom, a halogen atom, an alkyl group 
having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms, a 
haloalkyl group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 
4 carbon atoms, a cyano group or an aminocarbonyl group;
R₃ and R₄ independently represent a hydrogen atom or an alkyl group having from 1 to 
4 carbon atoms; or R₃ and R₄ may be joined together to form an alkylene chain having
2 to 6 carbon atoms;
R₅ represents -C₉H₂, C₀₂W,
[Chem.3]
R⁶ represents an alkyl group having from 1 to 6 carbon atoms, a cycloalkyl group 
having from 3 to 7 ring atoms, an aryl group or a heteroaryl group;
X represents a methylene group, an oxygen atom or a sulfur atom;
said aryl groups have from 6 to 10 carbon atoms;
said heteroaryl groups are 5 to 10-membered aromatic heterocyclic groups containing 
from 1 to 3 heteroatoms selected from the group consisting of sulfur atom, oxygen 
atom and nitrogen atom;
said aryl groups and said heteroaryl groups referred to in the definitions of \( B \) are unsubstituted or are substituted by at least one substituent selected from the group consisting of substituents alpha;
said 1,4-phenylene group referred to in the definition of \( E \) is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents beta;
said aryl groups and said heteroaryl groups referred to in the definitions of \( R^6 \) and alpha are unsubstituted or are substituted by at least one substituent selected from the group consisting of substituents beta;
said substituents alpha are selected from the group consisting of halogen atoms, alkyl groups having from 1 to 4 carbon atoms, alkoxy groups having from 1 to 4 carbon atoms, haloalkyl groups having from 1 to 4 carbon atoms, haloalkoxy groups having from 1 to 4 carbon atoms, cyano groups, alkylnyl groups having from 2 to 6 carbon atoms, alkanoyl groups having from 1 to 5 carbon atoms, cycloalkyl groups having from 3 to 7 ring atoms, heteroaryl groups, aryl groups, aralkoxy groups having from 7 to 10 carbon atoms, arylcarbonyl groups, two adjacent alpha groups are optionally joined together to form an alkylene or an alkenylene chain having 3 or 4 carbon atoms, aminocarbonyl groups, alkenyl groups having from 2 to 5 carbon atoms, alkylthio groups having from 1 to 4 carbon atoms, aminosulfanyl groups, aminosulfonyl groups, hydroxy groups, hydroxyalkyl groups having from 1 to 4 carbon atoms, nitro groups, amino groups, carboxy groups, alkoxy carbonyl groups having from 2 to 5 carbon atoms, alkoxyalkyl groups having from 1 to 4 carbon atoms, alkylsulfanyl groups having from 1 to 4 carbon atoms, alkanoylamino groups having from 1 to 4 carbon atoms, alkanoyl (alkyl) amino groups having from 1 to 6 carbon atoms, alkanoylaminoaalkyl groups having from 1 to 6 carbon atoms in both the alkanoyl and alkyl part, alkanoyl (alkyl) aminoalkyl groups having from 1 to 6 carbon atoms in both the alkanoyl and each alkyl part, alkylsulfonlamino groups having from 1 to 4 carbon atoms, mono- or di-alkylaminocarbonyl groups having from 1 to 6 carbon atoms, mono- or di-alkylaminosulfynyl groups having from 1 to 6 carbon atoms, mono- or di-alkylaminosulfonfyl groups having from 1 to 6 carbon atoms, aminocarbonyl groups having from 1 to 4 carbon atoms, mono- or di-alkylamino groups having from 1 to 6 carbon atoms, mono- or di-alkylaminoalkyl groups having from 1 to 6 carbon atoms in each alkyl part, aralkyl groups having from 7 to 10 carbon atoms, heteroaarylalkyl groups having from 1 to 4 carbon atoms in the alkyl part, heteroaarylalkoxy groups having from 1 to 4 carbon atoms in the alkoxy part and alkylsulfonlamino groups having from 1 to 4 carbon atoms;
said substituents beta are selected from the group consisting of halogen atoms, alkyl groups having from 1 to 4 carbon atoms, alkoxy groups having from 1 to 4 carbon
atoms, haloalkyl groups having from 1 to 4 carbon atoms, haloalkoxy groups having from 1 to 4 carbon atoms and cyano groups;
W is a pharmaceutically acceptable ester prodrug group; with the proviso \( R^1 \) and \( R^2 \) do not represent a hydrogen atom simultaneously;

[Chem.4]

wherein \( X \) represents -CH- or a nitrogen atom;
\( Y \) represents -NR\(^4\), an oxygen atom or a sulfur atom;
\( R^4 \) represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms;
\( Z \) represents a hydrogen atom or a halogen atom;
\( R^1 \) represents an alkyl group having from 1 to 6 carbon atoms optionally substituted with an alkoxy group having from 1 to 6 carbon atoms or a cycloalkyl group having from 3 to 7 carbon atoms; a cycloalkyl group having from 3 to 7 carbon atoms optionally substituted with an alkyl group having from 1 to 3 carbon atoms; a phenyl group optionally substituted with one or more substituents alpha; or a group \( \text{Het}^1 \) optionally substituted with one or more substituents alpha;
\( \text{Het}^1 \) represents a heterocyclic group having from 4 to 7 ring atoms which contains either from 1 to 4 nitrogen ring heteroatoms or from 0 to 2 nitrogen ring heteroatoms and 1 oxygen or 1 sulfur ring heteroatom;
\( R^2 \) and \( R^3 \) independently represent a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms; or \( R^2 \) and \( R^3 \) together form an alkylene chain having from 3 to 6 carbon atoms; and
said substituent alpha is selected from the group consisting of halogen atoms, alkyl groups having from 1 to 4 carbon atoms, haloalkyl groups having from 1 to 4 carbon atoms, hydroxy groups, alkoxy groups having from 1 to 4 carbon atoms, haloalkoxy groups having from 1 to 4 carbon atoms, cyano groups, hydroxy alkyl groups having from 1 to 4 carbon atoms, alkoxyalkyl groups having from 1 to 4 carbon atoms in alkoxy and alky groups, alkylsulfonyl groups having from 1 to 4 carbon atoms, alkanoyl groups having from 2 to 5 carbon atoms, alkenyl groups having from 2 to 4...
carbon atoms, alkynyl groups having from 2 to 4 carbon atoms, alkylthio groups having from 1 to 4 carbon atoms, nitro groups, amino groups, mono- or di-alkylamino groups having from 1 to 4 carbon atoms, aminosulfonyl groups, alkoxy carbonyl groups having from 1 to 4 carbon atoms, alkylsulfonylamino groups having from 1 to 4 carbon atoms, cycloalkyl groups having from 3 to 7 carbon atoms and a mono- or di-alkylaminocarbonyl groups having from 1 to 6 carbon atoms; or a pharmaceutically acceptable ester of such compound;

(IV)

(Va)
wherein X and Y are independently selected from the group consisting of: N and C(R^{11}), wherein each R^{11} is independently selected from the group consisting of: hydrogen, halo and C_{i-4}alkyl;
B is selected from the group consisting of: -C(R^5)(R^6), -0-, -S-, -S(O)-, -S0 \gamma, -C(R^5)(R^6)-C(R^7)(R^8), -0-C(R^5)(R^6), -S-C(R^5)(R^6), -S(0)-C(R^5)(R^6) and -S0 \gamma-C(R^5)(R^6); 
C is selected from the group consisting of aryl and heteroaryl, or a fused analog of aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from R^{10};
E is selected from the group consisting of: -C(0)OH, -C(0)OC_{i-4}alkyl, tetrazolyl and 
wherein R is selected from the group consisting of: C_{i-4}alkyl, aryl and heteroaryl, or a fused analog of aryl or heteroaryl, wherein aryl and heteroaryl or the fused analogs thereof are optionally substituted with one to three substituents independently selected from R^{10};
R^1 to R^8 are independently selected from the group consisting of: H, halo, -O-R^{12}, C_{i-6}alkyl and C_{3,6}cycloalkyl, and one or more pairs of R^1 and R^2, R^5 and R^6, and R^7 and R^8 may be joined together with the carbon atom to which they are attached to form a 3- to 5-membered monocyclic cycloalkyl ring, and R^5 and R^6 or R^7 and R^8 may be joined together to form carbonyl;
R is independently selected from the group consisting of: halo, hydroxyl and Ci$_4$ alkyl;
R$^{10}$ is selected from the group consisting of: halo, cyano, Ci$_4$ alkyl, Ci$_4$ fluoroalkyl, C$_{1-4}$ alkoxy, CI$_4$ thiaoalkoxy and CI$_4$ fluoroalkoxy; and
each R$^{12}$ is selected from the group consisting of: H, CI$_4$ alkyl, C$_{3-6}$ cycloalkyl and heterocyclyl;

[3] The use of of [2], wherein the compound of (I), (II), (III), (IV), (Va) or (Vb) is selected from:

3-[2-].[ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl]phenyl)ethyl]-l-[(4-methylene)sulfonyl]urea;
1- [2-[(5-acetyl-2-ethyl-1H,3-benzodiazol-1-yl]phenyl]ethyl ]-3-[(4-methylbenzene)sulfonyl]urea;
3- [2-[(2-ethyl-5-methoxy-1H,3-benzodiazol-1-yl]phenyl]ethyl ]-1-[(4-methylbenzene)sulfonyl]urea;
2- [4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H,3-benzodiazol-1-yl]phenyl]ethyl N-[(4-methylbenzene)sulfonyl]carbamate;
3- [2-[4-[(6-chloro-5-cyano-2-ethyl-1H,3-benzodiazol-1-yl]phenyl]ethyl ]-1-[(4-methylbenzene)sulfonyl]urea;
2-[4-[5-carbamoyl-6-chloro-2-ethyl-1H,3-benzodiazol-1-yl]phenyl]ethyl N-[(4-methylbenzene)sulfonyl]carbamate;
1-[2-[(2-ethyl-5-(1-hydroxyethyl)-1H,3-benzodiazol-1-yl]phenyl]ethyl ]-3-[(4-methylbenzene)sulfonyl]urea;
1- [2-[(4-6-chloro-2-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)-1H,3-benzodiazol-1-yl]phenyl]ethyl ]-3-[(4-methylbenzene)sulfonyl]urea;
2- [4-[6-chloro-2-(pyridin-2-yl)-5-(trifluoromethyl)-1H,3-benzodiazol-1-yl]phenyl]ethyl N-[(4-methylbenzene)sulfonyl]carbamate;
3- [2-[5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H,3-benzodiazol-1-yl]pyridin-2-yl]ethyl]-1-[(4-methylbenzene)sulfonyl]urea;
2- [4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H,3-benzodiazol-1-yl]phenyl]ethyl N-[(2-chlorobenzene)sulfonyl]carbamate;
3- [2-[4-[5,7-dimethyl-2-(methylamino)-3H-imidazo[4,5-b]pyridin-3-yl]phenyl]ethyl ]-1-[(4-methylbenzene) sulfonyl]urea;
4- ([1S]-l-[(5-chloro-2-(4-fluorophenoxy)benzoylamino]ethyl)benzoic acid;
4-[(1S)-1-({[5-chloro-2-(4-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
4-[(1S)-1-({[5-chloro-2-(3-cyanophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
4-[(1S)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
4-[(1S)-1-({[5-chloro-2-(3-chlorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
4-((1S)-1-{{5-chloro-2-(3-fluorophenoxy)benzoyl}amino}ethyl)benzoic acid;
4-((1S)-1-{{5-chloro-2-(3-chlorophenoxy)benzoyl}amino}ethyl)benzoic acid;
4-[(1S)-1-({[5-chloro-2-(2-chloro-4-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
4-[(1S)-1-({[5-chloro-2-(3,4-difluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
4-[(1S)-1-({[5-chloro-2-(2,3-difluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
4-((1S)-1-{{5-chloro-2-(3,4-difluorophenoxy)benzoyl}amino}ethyl)benzoic acid;
4-[(1S)-1-({[5-chloro-2-(3-chloro-5-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
4-[[1S)-1-({[5-chloro-2-(4-chlorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[[1S)-1-({[5-chloro-2-(3-chlorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[[1S)-1-({[5-chloro-2-(4-fluorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[[1S)-1-({[5-chloro-2-(3,4-difluorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[[1S)-1-({[5-chloro-2-(2,4-difluorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[[1S)-1-({[5-chloro-2-(3-fluorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-((4-(5-methoxypyridin-2-yl)phenoxy)methyl)-5-methyl-N-(o-tolylsulfonyl)furan-2-carboxamide,
5-chloro-3-[(3-chlorophenyl)methyl]-N-[l-[4-(2H-tetrazol-5-yl)phenyl]ethyl]-2-thiophene carboxamide,
2,5-dimethyl-N-[l-[4-[[[(methylsulfonyl)amino]carbonyl]phenyl]ethyl]-4-[[4-(trifluoromethyl)phenyl]methyl]-3-thiophene carboxamide,
2,5-dimethyl-N-[l-[4-[[[(phenylsulfonyl)amino]carbonyl]phenyl]ethyl]-4-[[4-(trifluoromethyl)phenyl]methyl]-3-thiophene carboxamide,
2,5-dimethyl-N-[l-[4-[(2H-tetrazol-5-yl)phenyl]cyclopropyl]-4-[[3-(trifluoromethyl)phenyl]methyl]-3-thiophene carboxamide,
2,5-dimethyl-N-[l-[4-[(2H-tetrazol-5-yl)phenyl]cyclopropyl]-4-[[4-(trifluoromethyl)phenyl]methyl]-3-thiophene carboxamide,
2-chloro-4-[[4-[(3-chlorophenyl)methyl]-2,5-dimethyl-3-thienyl]carbonyl]amino]methyl]-benzoic acid,
4-[(lR)-l-[[2,5-dichloro-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-l-[[2,5-dibromo-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-l-[[2,5-dichloro-4-[(3-chlorobenzoyl)-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-l-[[2,5-dichloro-4-[(3-chlorophenyl)hydroxymethyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
zoic acid,
4-[[[2,5-dichloro-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino][methyl]-benzolic acid,
4-[l-[[[2,5-dimethyl-4-[[3-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]cyclopropyl]-benzoic acid,
4-[l-[[[5-chloro-3-[[3-chlorophenyl]methyl]-2-thienyl]carbonyl]amino]ethyl]-benzoic acid, and
4- {[1-((2,5-dimethyl-4-[(4-trifluoromethyl)benzyl]-3-thienyl]carbonyl)amino]cyclopropyl} benzoic acid,
or a pharmaceutically acceptable salt thereof;
[4] The use of [2] or [3], wherein the compound of (I), (II), (III), (IV), (Va) or (Vb) is selected from:
3-[2-(4-[[2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl]phenyl]ethyl]-1-[(4-methylbenzene)sulfonyl]urea;
4-{{(IS)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl}benzoic acid;
4-{{(IS)-1-([5-chloro-2-[(3-chlorophenyl)methyl]pyridin-3-yl]carbonyl)amino}ethyl}benzoic acid;
4-((4-(5-methoxypyridin-2-yl)phenoxy)methyl)-5-methyl-N-(o-tolylsulfonyl)furan-2-carboxamide;
4- {[1-((2,5-dimethyl-4-[(4-trifluoromethyl)benzyl]-3-thienyl]carbonyl)amino]cyclopropyl} benzoic acid,
or a pharmaceutically acceptable salt thereof;
[5] The use of [4], wherein the compound of (I), (II), (III) or (IV) is selected from:
3-[2-(4-[[2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl]phenyl]ethyl]-1-[(4-methylbenzene)sulfonyl]urea;
4-{{(IS)-1-([5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl}benzoic acid;
4-{{(IS)-1-([5-chloro-2-[(3-chlorophenyl)methyl]pyridin-3-yl]carbonyl)amino}ethyl}benzoic acid; and
4-((4-(5-methoxypyridin-2-yl)phenoxy)methyl)-5-methyl-N-(o-tolylsulfonyl)furan-2-carboxamide,
or a pharmaceutically acceptable salt thereof;
[6] The use of any one of [2] to [5], wherein the compound of the formula (I), (II), (III), (IV), (Va) or (Vb), or the pharmaceutically acceptable salt is used in combination with one or more additional compounds known to be useful in the treatment or prevention of cartilage disease or the symptoms thereof;
[7] The use of [6], wherein the one or more additional compounds known to be useful
in the treatment or prevention of cartilage disease or the symptoms thereof are selected from
NSAIDs, COX-2 inhibitors, steroids, matrix metalloproteinase inhibitors and
hyaluronic acid;

[8] A pharmaceutical composition for the treatment of cartilage disease which
comprises a therapeutically effective amount of a compound of the formula (I), (II),
(III), (IV), (Va) or (Vb) in [2] or a pharmaceutically acceptable salt thereof;

[9] The pharmaceutical composition of [8], which further comprises a therapeutically
effective amount of one or more additional compounds known to be useful in the
treatment or prevention of cartilage disease or the symptoms thereof;

[10] A method for the treatment of cartilage disease in an animal subject including a
mammalian subject, which comprises administering to the animal subject including a
mammalian subject a compound of the formula (I), (II), (III), (IV), (Va) or (Vb) in [2]
or a pharmaceutically acceptable salt thereof;

[II] The method of [10], which further comprises administering a therapeutically
effective amount of one or more additional compounds known to be useful in the
treatment or prevention of cartilage disease thereof;

[12] A method for the treatment of cartilage diseases, which comprises administering
to an animal subject including a mammalian subject in need a therapeutically effective
amount of a compound of the formula (I), (II), (III), (IV), (Va) or (Vb) in [2] or a pharma-
caceutically acceptable salt thereof;

[13] The method of [12], which further comprises administering a therapeutically
effective amount of one or more additional compounds known to be useful in the
treatment or prevention of cartilage disease thereof; and

[14] A compound of the formula (I), (II), (III), (IV), (Va) or (Vb) in [2] or a pharma-
caceutically acceptable salt thereof for use in the treatment of cartilage diseases in an
animal subject including a mammalian subject.

**Advantageous Effects of Invention**

[0013] Namely, the present inventors have discovered that a compound of formula (I), (II),
(III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof shows: 1) dose-
dependent inhibition of cartilage destruction in ex vivo bovine cartilage explant model,
2) dose-dependent inhibition of cartilage destruction and serum biochemical markers
associated with cartilage degradation in the rat mono-iodoacetate and/or meniscal
transection model, and 3) inhibition of cartilage destruction and serum biochemical
markers associated with cartilage degradation in a dose-dependent manner in the rat
meniscal transection and/or ovariectomised model.

These results clearly show that a compound of formula (I), (II), (III), (IV), (Va) or
(Vb), or a pharmaceutically acceptable salt thereof is useful for the treatment and/or
prevention of cartilage disease.

**Brief Description of Drawings**

[0014] In the section "Brief Description of Drawings", the sign "+/-" represents "plus or minus".

[fig.1] Fig. 1 is a graph showing that accumulated release of the C2M to the conditioned medium. P-value of the ANOVA test is shown in the right-hand corner.**** p<0.0001. Mean +/- SEM. O: oncostatin M, T: TNF-alpha

[fig.2] Fig. 2 is a graph showing that accumulated release of the AGNx2 to the conditioned medium. P-value of the ANOVA test is shown in the right-hand corner.**** p<0.0001. Mean +/- SEM. O: oncostatin M, T: TNF-alpha

**Description of Embodiments**

[0015] The present invention features the use of an EP4 receptor antagonist in the manufacture of a medicament for the treatment of cartilage diseases.

[0016] In a further aspect the invention features a method of treating cartilage diseases in an animal subject including a mammalian subject, for example, a mammal, including man, comprising administration of an effective amount of an EP4 receptor antagonist.

[0017] The term "animal subject," as used herein, includes a mammalian subject or a non-mammalian subject. Examples of suitable mammalian subject may include, without limit, human, rodents, companion animals, livestock, and primates. Suitable rodents may include, but are not limited to, mice, rats, hamsters, gerbils, and guinea pigs. Suitable companion animals may include, but are not limited to, cats, dogs, rabbits, and ferrets. Suitable livestock may include, but are not limited to, horses, goats, sheep, swine, cattle, llamas, and alpacas. Suitable primates may include, but are not limited to, chimpanzees, lemurs, macaques, marmosets, spider monkeys, squirrel monkeys, and vervet monkeys. Examples of suitable non-mammalian subject may include, without limit, birds, reptiles, amphibians, and fish. Non-limiting examples of birds include chickens, turkeys, ducks, and geese.

[0018] In a further aspect the invention features a pharmaceutical composition comprising an EP4 receptor antagonist for use in the treatment of cartilage diseases.

[0019] Preferably, the EP4 receptor antagonist used in this invention is a selective EP4 receptor antagonist.

[0020] In another preferred aspect, the EP4 receptor ligand (antagonist), which is disclosed in WO 02/32900, is an aryl or heteroaryl fused imidazole compound of the following Formula (I)
or a pharmaceutically acceptable salt thereof,
wherein
Y 1 , Y 2 , Y 3 , and Y 4 are preferably independently selected from N, CH and C(L);
R 1 is H, C i-8 alkyl, C 2-8 alkenyl, C 2-8 alkynyl, C 3-7 cycloalkyl, C i-8 alkoxy, halo-
substituted C i-8 alkoxy, C i-8 alkyl-S(0)m- , Q 1 -pyrrolidinyl, piperidyl, oxopyrrolidinyl,
oxopiperidyl, amino, mono- or di- (C i-4 alkyl)amino, C i-4 alkyl-C(=0)-N(R 3 )- or C 1-4
alkyl-S(0)m-N(R 3 )-, wherein said C i-8 alkyl, C 2-8 alkenyl and C 2-8 alkynyl are op-
tionally substituted with halo, C i-3 alkyl, hydroxy, oxo, C i-4 alkoxy-, C i-4 alkyl-S(0)m-,
C 3-7 cycloalkyl-, cyano, indanyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl,
pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q 1 - , Q'-C(=0)- , Q'-O- , Q 1 -
S(0)m- , Q 1 -C i-4 alkyl-O- , Q 1 -C i-4 alkyl-S(0)m- , Q 1 -C 1-4 alkyl-C(0)-N(R 3 )- , Q 1 -C A
alkyl-N(R 3 )- or C 1-4 alkyl-C(0)-N(R 3 )- ;
Q 1 is a 5 to 2 membered monocyclic or bicyclic aromatic ring optionally containing up
to 4 heteroatoms selected from O, N and S, and is optionally substituted with halo, C 1-4
alkyl, halo-substituted C 1-4 alkyl, hydroxy, C 1-4 alkoxy, halo-substituted C 1-4 alkoxy, C
1-4 alkylthio, nitro, amino, mono- or di- (C i-4 alkyl)amino, cyano, HO-C i-4 alkyl, C 1-4
alkoxy-C i-4 alkyl, C i-4 alkylsulfonyl, aminosulfonyl, C i-4 alkylC(=0)- , HO(0=)C- , C 1-4
alkyl-0(0=)C- , R 1 N (R 5 )C(=0)- , C 1-4 alkylsulfonylamino, C 3-7 cycloalkyl, R 3
C(=0)N(R 4 )- or NH 2 (HN=)C- ;
A is a 5 or 6 membered monocyclic aromatic ring optionally containing up to 3 het-
teroatoms selected from O, N and S, wherein said 5 or 6 membered monocyclic
aromatic ring is optionally substituted with up to 3 substituents selected from halo, C i-4
alkyl, halo-substituted C\(_{1-4}\) alkyl, hydroxy, C\(_{4}\) alkxy, halo-substituted C\(_{1-4}\) alkoxy, C\(_{1-4}\) alkylthio, nitro, amino, mono- or di-(C\(_{4}\) alkyl)amino, cyano, H-O-C\(_{4}\) alkyl, C\(_{1-4}\) alkoxy-C\(_{4}\) alkyl, C\(_{1-4}\) alkylsulfonyl, aminosulfonyl, acetylb, R \(\neq\) N(R \(\neq\) C\(_{4}\) alkyl)-, H-O(0=)=C\(\neq\), C\(_{1-4}\) alkyl-0(0=)=C\(\neq\), C\(_{1-4}\) alkylsulfonylaminol, C\(_{3}\) cycloalkyl, R \(\neq\) C(0)=N(R \(\neq\)$)

B is halo-substituted Ci\(_{4}\) alkylene, C\(_{3}\) cycloalkylene, C\(_{2}\) alkynylene, -0-Ci\(_{4}\) alkylene, C\(_{1}\) alkylene-0-Ci\(_{2}\) alkylene or Ci\(_{6}\) alkylene optionally substituted with an oxo group or Ci\(_{3}\) alkyl;

W is NH, N-Ci\(_{4}\) alkyl, O, S, N-OR

or a covalent bond;

R\(^2\) is H, C\(_{1-4}\) alkyl, OH or C\(_{4}\) alkoxy;

Z is a 5 to 2 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5 to 2 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C\(_{1-4}\) alkyl, halo-substituted Ci\(_{4}\) alkyl, Ci\(_{4}\) alkynyl, C\(_{1-4}\) alkynyl, hydroxy, Ci\(_{4}\) alkoxy, halo-substituted Ci\(_{4}\) alkoxy, Ci\(_{4}\) alkylthio, nitro, amino, mono- or di-(Ci\(_{4}\) alkyl)amino, cyano, H-O-Ci\(_{4}\) alkyl, C\(_{1-4}\) alkoxy-Ci\(_{4}\) alkyl, Ci\(_{4}\) alkylsulfonyl, aminosulfonyl, C\(_{1-4}\) alkylC(0)=, H-O(0=)=C\(\neq\), C\(_{1-4}\) alkyl-0(0=)=C\(\neq\), C\(_{1-4}\) alkylsulfonylaminol, C\(_{3}\) cycloalkyl, NH\(_2\)

(HN =C\(\neq\), Q\(^2\)-S(0)m\(-\), Q\(^2\)-O\(-\), Q\(^2\)-N (R \(\neq\)) or Q\(^2\);)

L is halo, C\(_{1-4}\) alkyl, halo-substituted C\(_{4}\) M alkyl, hydroxy, C\(_{4}\) M alkoxy, C\(_{4}\) M alkylthio, nitro, amino, mono- or di-(Ci\(_{4}\) alkyl)amino, halo-substituted Ci\(_{4}\) alkyl, cyano, H-O-C\(_{4}\) alkyl, Ci\(_{4}\) alkoxy-Ci\(_{4}\) alkyl, Ci\(_{4}\) alkylsulfonyl, aminosulfonyl, C\(_{1-4}\) alkylC(0)=, H-O(0=)=C\(\neq\), C\(_{1-4}\) alkyl-0(0=)=C\(\neq\), C\(_{1-4}\) alkylsulfonylaminol, C\(_{3}\) cycloalkyl, R \(\neq\) C(0)=N(R \(\neq\)$)

NH\(_2\)(HN =C\(\neq\), R \(\neq\) N(R \(\neq\))C(0)=, R \(\neq\) N(R \(\neq\))S(0)m\(-\), Q\(^2\)-, Q\(^2\)-C(0)=, Q\(^2\)-O\(-\), Q\(^2\)-C\(_{4}\) alkyl-O\(-\), or two adjacent L groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;

m is 0, 1 or 2;

R\(^3\) and R\(^4\) are independently selected from H and C\(_{1-4}\) alkyl;

R\(^5\) is H, C\(_{1-4}\) alkyl, C\(_{4}\) alkyl-0(0=)=C\(\neq\) or C\(_{4}\) alkyl-0(0=)=C\(\neq\); and

Q\(^2\) is a 5 to 2 membered monocyclic or bicyclic aromatic ring, optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5 to 2 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C\(_{1-4}\) alkyl, halo-substituted C\(_{1-4}\) alkyl, C\(_{1-4}\) alkylthio, C\(_{1-4}\) alkynyl, hydroxy, C\(_{1-4}\) alkoxy, halo-substituted Ci\(_{4}\) alkoxy, Ci\(_{4}\) alkylthio, nitro, amino, mono- or di-(Ci\(_{4}\) alkyl)amino, cyano, H-O-Ci\(_{4}\) alkyl, Ci\(_{4}\) alkoxy-Ci\(_{4}\) alkyl, Ci\(_{4}\) alkylsulfonyl, aminosulfonyl, Ci\(_{4}\) alkyl-(0=)=C\(\neq\), R \(\neq\) (R \(\neq\))C(0)=N\(-\), H-O(0=)=C\(\neq\), C\(_{1-4}\) alkyl-0(0=)=C\(\neq\), C\(_{1-4}\) alkylsulfonylaminol, C\(_{3}\) cycloalkyl, C\(_{4}\) alkyl-C(0)=NH or NH\(_2\)(HN =C\(\neq\).

In the compounds of formula (I),
Y¹, Y², Y³, and Y⁴ are preferably independently selected from N, CH and C(L);
L is halo, C₁₄ alkyl, halo-substituted C₁₄ alkyl, hydroxy, Cᵢ₋₄ alkoxy, mono- or di-(Cᵢ₋₄ alkyl)amino, halo-substituted C₁₄ alkoxy, cyano, HO-Ci₄ alkyl, Ci₄ alkoxy-Ci₄ alkyl, C₁₄ alkylsulfonyl, aminosulfonyl, C₁₄ alkylC(=0)-, HO(0=)C-, C₁₄ alkyl-0(0=)C-, C₁₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, R⁻C(=0)N(R¹)C(=0)-, R⁻N(R⁴)C(=0)-, R⁻N(R⁴)S(0)m-, Q²-, Q²-Cⁱ₋₄ alkyl-0-, or two adjacent L groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;
m is 0, 1 or 2;
R³ and R⁴ are independently selected from H and C₁₄ alkyl; and
Q² is a 5 to 2 membered monocyclic or bicyclic aromatic ring, optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5 to 2 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C₁₄ alkyl, halo-substituted Ci₄ alkyl, C₁₄ alkynyl, Ci₄ alkynyl, hydroxy, Ci₄ alkoxy, halo-substituted Ci₄ alkoxy, Ci₄ alkythio, mono- or di-(Ci₄ alkyl)amino, cyano, HO-Ci₄ alkyl, C₁₄ alkyl-Ci₄ alkyl, C₁₄ alkylsulfonyl, aminosulfonyl, C₃₋₇ alkyl-(0=)C-, R⁻(R⁴)⁻C(=0)N-, HO(0=)C-, C⁻¹₄ alkyl-0(0=)C-, C₁₄ alkylsulfonylamino, C₃₋₇ cycloalkyl or C₁₄ alkyl-C(=0)NH-.

More preferably Y¹, Y², Y³, and Y⁴ are independently selected from N, CH and C(L);
L is halo, C₇ M alkyl, halo-substituted C₇ M alkyl, hydroxy, C₇ M alkyl, mono- or di-(Cᵢ₋₄ alkyl)amino, halo-substituted C₇ M alkoxy, cyano, HO-C₇ M alkyl, C₇ M alkylsulfonyl, aminosulfonyl, C₁₄ alkylC(=0)-, HO(0=)C-, C₁₄ alkyl-0(0=)C-, C₁₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, R⁻C(=0)N(R⁴)C(=0)-, R⁻N(R⁴)C(=0)-, R⁻N(R⁴)S(0)m-, Q²-, Q²-Cⁱ₋₄ alkyl-0-, or two adjacent L groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;
m is 0, 1 or 2;
R³ and R⁴ are independently selected from H and C₁₄ alkyl; and
Q² is a 5 or 6 membered monocyclic aromatic ring, containing up to 3 heteroatoms selected from N and S, wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with halo,

more preferably Y¹, Y², Y³, and Y⁴ are independently selected from N, CH and C(L);
L is halo, C₁₄ alkyl, halo-substituted C₁₄ alkyl, hydroxy, C₁₄ alkoxy, mono- or di-(Cᵢ₋₄ alkyl)amino, halo-substituted Cᵢ₋₄ alkoxy, cyano, HO-Cᵢ₋₄ alkyl, Cᵢ₋₄ alkoxy-Cᵢ₋₄ alkyl, aminosulfonyl, C₁₄ alkylC(=0)-, HO(0=)C-, C₁₄ alkyl-0(0=)C-, C₁₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, R⁻C(=0)N(R⁴)C(=0)-, R⁻N(R⁴)C(=0)-, R⁻N(R⁴)S(0)m-, Q²-, Q²-Cⁱ₋₄ alkyl-0-, or two adjacent L groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two
(non-adjacent) carbon atoms are optionally replaced by oxygen atoms; m is 0, 1 or 2;
R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and Q² is a 5 or 6 membered monocyclic aromatic ring, optionally containing 1 sulfur atom wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with halo,

[0024] more preferably Y¹, Y², Y³, and Y⁴ are independently selected from N, CH and C(L);
L is halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, hydroxy, d₋₄ alkoxy, halo-substituted C₁₋₄ alkoxy, cyano, HO-d₋₄ alkyl, acetyl, R²N(R⁴)C(=0)-, R³N(R⁴)S(0)m-, Q²-, Q²-C(=0)-, Q²-0-, Q²-Ci₋₄ alkyl-0-, or two adjacent L groups are joined together to form a methylenedioxy group;
m is 0, 1 or 2
R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and Q² is a 5 or 6 membered monocyclic aromatic ring system,

[0025] more preferably Y¹, Y², Y³, and Y⁴ are independently selected from N, CH and C(L);
L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, -C(=0)NH₂, trifluoromethyloxy, methanesulfonyl, or 1-hydroxy-1-methyl-ethyl, or two adjacent L groups are joined together to form a methylenedioxy group,

[0026] more preferably Y¹, Y², Y³ and Y⁴ are selected from the group consisting of
a) Y¹ and Y³ are C(L), Y² is CH and Y⁴ is N;
b) Y¹ is CH, Y² and Y³ are C(L) and Y⁴ is N;
c) Y¹, Y² and Y³ are C(L) and Y⁴ is N;
d) Y¹ and Y³ are C(L), Y² is N and Y⁴ is CH;
e) Y¹ is C(L) and Y², Y³ and Y⁴ are CH;
f) Y¹, Y³ and Y⁴ are CH, and Y² is C(L);
g) Y¹, Y² and Y³ are CH, and Y⁴ is C(L);
h) Y¹ and Y² are C(L), and Y³ and Y⁴ are CH;
i) Y¹ and Y³ are C(L), and Y² and Y⁴ are CH;
j) Y¹ and Y⁴ are CH, and Y² and Y³ are C(L);
k) Y¹ and Y² are CH, Y³ is C(L) and Y⁴ is N;
l) Y¹ and Y³ are CH, Y² is C(L) and Y⁴ is N;
m) Y¹, Y², Y³ and Y⁴ are CH;
n) Y¹ and Y² are C(L), Y³ is CH and Y⁴ is N;
o) Y¹, Y² and Y⁴ are CH, and Y³ is C(L);
p) Y¹ and Y² are C(L), Y³ is N and Y⁴ is CH;
q) Y¹ and Y³ are C(L), and Y² and Y⁴ are N;
r) Y¹ is C(L), Y² and Y³ are CH, and Y⁴ is N;
s) Y² is C(L), Y¹ and Y³ are CH, and Y⁴ is N; and
t) Y\(^1\), Y\(^2\) and Y\(^3\) are C(L), and Y\(^4\) is CH
L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, \(-\text{C}(=\text{O})\text{NH}_2\), trifluoromethoxy, methanesulfonyl, or 1-hydroxy-1-methyl-ethyl, or two adjacent L groups are joined together to form a methylenedioxy group.

[0027] most preferably Y\(^1\), Y\(^2\), Y\(^3\) and Y\(^4\) are selected from the group consisting of
a) Y\(^1\) and Y\(^3\) are C(L), Y\(^2\) is CH and Y\(^4\) is N;
b) Y\(^1\) is CH, Y\(^2\) and Y\(^3\) are C(L) and Y\(^4\) is N;
c) Y\(^1\), Y\(^2\) and Y\(^3\) are C(L) and Y\(^4\) is N;
d) Y\(^1\) and Y\(^3\) are C(L), Y\(^2\) is N and Y\(^4\) is CH;
e) Y\(^1\) is C(L) and Y\(^2\), Y\(^3\) and Y\(^4\) are CH;
f) Y\(^1\), Y\(^3\) and Y\(^4\) are CH, and Y\(^2\) is C(L);
g) Y\(^1\), Y\(^2\) and Y\(^3\) are CH, and Y\(^4\) is C(L);
h) Y\(^1\) and Y\(^2\) are C(L), and Y\(^3\) and Y\(^4\) are CH;
i) Y\(^1\) and Y\(^3\) are C(L), and Y\(^2\) and Y\(^4\) are CH;
j) Y\(^1\) and Y\(^4\) are CH, and Y\(^2\) and Y\(^3\) are C(L); and
k) Y\(^1\), Y\(^2\) and Y\(^3\) are C(L), and Y\(^4\) is CH
L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, \(-\text{C}(=\text{O})\text{NH}_2\), trifluoromethoxy, methanesulfonyl, or 1-hydroxy-1-methyl-ethyl, or two adjacent L groups are joined together to form a methylenedioxy group.

[0028] In the compounds of Formula (I),
R\(^1\) is preferably H, Ci\(_{\text{r}}\) alkyl, C\(_{2}\) alklenyl, C\(_{2}\) alkynyl, C\(_{3}\) cycloalkyl, C\(_{i}\) alkoxy, halo-substituted C\(_{i}\) alkoxy, C\(_{i}\) alkyl-S(0)m-, Q\(^1\), pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, amino, mono- or di-(Ci\(_{\text{r}}\) alkyl)amino, Ci\(_{\text{r}}\) alkyl-C(=O)-N(R\(^4\))- or Ci\(_{\text{i}}\) alkyl-S(0)m-N(R\(^3\))- wherein said Ci\(_{\text{i}}\) alkyl, C\(_{2}\) alklenyl and C\(_{2}\) alkynyl are optionally substituted with halo, Ci\(_{\text{i}}\) alkyl, hydroxy, oxo, Ci\(_{1}\) alkoxy-, Ci\(_{1}\) alkyl(S)(0)m-, C\(_{3}\) cycloalkyl-, cyano, indanyl, 1,2,3,4-tetrahydroanaphthyl, 1,2-dihydronaphthyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q\(^1\), Q\(^2\)-C(=O)-, Q\(^1\)-O-, Q\(^1\)-S(0)m-, Q\(^1\)-Ci\(_{\text{i}}\) alkyl-O-, Q\(^1\)-Ci\(_{\text{i}}\) alkyl-S(0)m-, Q\(^1\)-Ci\(_{1}\) alkyl-C(=O)-N(R\(^3\))-; Q\(^1\)-Ci\(_{1}\) alkyl-N(R\(^3\))- or Ci\(_{1}\) alkyl-C(=O)-N(R\(^3\))-;
Q\(^1\) is a 5 to 2 membered monocyclic or bicyclic aromatic ring optionally containing up to 4 heteroatoms selected from O, N and S, and is optionally substituted with halo, Ci\(_{1}\) alkyl, halo-substituted Ci\(_{1}\) alkyl, hydroxy, d-alkoxy, halo-substituted Ci\(_{1}\) alkoxy, Ci\(_{1}\) alkylthio, nitro, amino, mono- or di-(Ci\(_{1}\) alkyl) amino, cyano, HO-Ci\(_{4}\) alkyl, Ci\(_{4}\) alkoxy-Ci\(_{4}\) alkyl, Ci\(_{4}\) alkylsulfonyl, Ci\(_{4}\) alkoxy, Ci\(_{1}\) alkyl(C(=O)N(R\(^3\))-), HO(O)\(_{\text{r}}\)C\(_{\text{i}}\)-, Ci\(_{1}\) alkyl-0(0)C\(_{\text{i}}\)-, R\(^3\)N(R\(^4\))C(=O)-, Ci\(_{1}\) alkylsulfonylamino, Ci\(_{3}\) cycloalkyl, R\(^3\)C(=O)N(R\(^4\))- or NH\(_{2}\)(HN=)C-;
m is 0, 1 or 2; and
R\(^3\) and R\(^4\) are independently selected from H and Ci\(_{1}\) alkyl,
In the compounds of Formula (I), more preferably R₁ is H, Cᵢ₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₇ cycloalkyl, Q¹-, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, amino, mono- or di-(Cᵢ₋₈ alkyl)amino, wherein said Cᵢ₋₈ alkyl is optionally substituted with halo, Cᵢ₋₃ alkyl, hydroxy, oxo, C₁₋₄ alkoxy-, C₁₋₄ alkyl-S(0)m-, C₃₋₇ cycloalkyl-, cyano, indanyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q¹-, Q¹-C(O)-, Q¹-O-, Q¹-S- or Q¹-C₁₋₄ alkyl-O-, or C₁₋₄ alkyl-C(0)-N(R³)²; Q¹ is a 5 to 2 membered monocyclic aromatic ring optionally containing up to 4 heteroatoms selected from N and S, and is optionally substituted with halo, d₋₄ alkyl, C₁₋₄ alkylsulfonyl and C₁₋₄ alkylic(=0)-; m is 0, 1 or 2; and R³ is H or C₁₋₄ alkyl,

In the compounds of Formula (I), more preferably R₁ is H, Cᵢ₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₇ cycloalkyl, Q¹-, or mono- or di-(Cᵢ₋₈ alkyl)amino wherein said Cᵢ₋₈ alkyl is optionally substituted with halo, Cᵢ₋₃ alkyl, hydroxy, oxo, C₁₋₄ alkoxy-, C₁₋₄ alkyl-S(0)m-, C₃₋₇ cycloalkyl-, cyano, indanyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q¹, Q¹-C(=0)-, Q¹-O-, Q¹-S-, Q¹-d₋₄ alkyl-O-, or C₁₋₄ alkyl-C(0)-N(H)-; Q¹ is a 5 or 6 membered monocyclic aromatic ring optionally containing up to 4 heteroatoms selected from N and S; and m is 0, 1 or 2,

In the compounds of Formula (I), more preferably R₁ is Cᵢ₋₅ alkyl, C₃₋₇ cycloalkyl, or Q¹-, mono- or di-(Cᵢ₋₈ alkyl)amino wherein said Cᵢ₋₅ alkyl is optionally substituted with Cᵢ₋₃ alkyl, hydroxy, oxo, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q¹, or Cᵢ₋₅ alkyl-C(0)-N(H)-; and Q¹ is a 5 to 2 membered monocyclic aromatic ring system optionally containing up to 2 heteroatoms selected from N and S,

In the compounds of Formula (I), more preferably R₁ is Cᵢ₋₅ alkyl, mono- or di-(Cᵢ₋₈ alkyl)amino, pyrrolidinyl, or pyridyl optionally substituted with Cᵢ₋₃ alkyl, hydroxy, oxo, a 5 or 6 membered monocyclic aromatic ring wherein said 5 or 6 membered monocyclic aromatic ring contains 1 or 2 heteroatoms selected from N and S, or Cᵢ₋₅ alkyl-C(0)-N(H)-,

In the compounds of Formula (I), most preferably R₁ is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, neopentyl, thiazolylethyl, methylamino, dimethylamino, pyrrolidinyl, pyridyl, or 1-acetylamino-1-methylethyl.

In the compounds of Formula (I), R² is preferably H or Cᵢ₋₄ alkyl, most preferably H.
In the compounds of Formula (I), A is preferably a 5 or 6 membered monocyclic aromatic ring optionally containing up to 2 heteroatoms selected from O, N, and S, wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with up to 2 substituents selected from halo, C_{14} alkyl, halo-substituted C_{14} alkyl, hydroxy, C_{i-4} alkoxy and halo-substituted C_{14} alkoxy, more preferably 5 or 6 membered monocyclic aromatic ring optionally substituted with halo, C_{14} alkyl or C_{i-4} alkoxy, more preferably 5 or 6 membered monocyclic aromatic ring system optionally substituted with halo or C_{14} alkyl, more preferably 5 or 6 membered monocyclic aromatic ring system, most preferably phenyl or pyridyl.

In the compounds of Formula (I), B is preferably C_{3,2} cycloalkylene or C_{i-6} alkylene optionally substituted with an oxo group or C_{i-3} alkyl, more preferably C_{i-3} alkylene optionally substituted with C_{i-3} alkyl, more preferably C_{i-3} alkyrene optionally substituted with methyl, most preferably ethylene or propylene.

In the compounds of Formula (I), W is preferably NH, N-Ci_{i-4} alkyl, O or N-OH, more preferably NH, N-Ci_{i-2} alkyl or O, most preferably NH, N-CH_{3} or O.

In the compounds of Formula (I), Z is preferably a 5 to 12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N, O, and S, wherein said 5 to 12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C_{14} alkyl, halo-substituted C_{14} alkyl, C_{14} alkenyl, hydroxy, C_{iM} alkoxy, nitro, amino, cyano, HO-CM alky, C_{M} alkylsulfonyl, aminosulfonyl, C_{i4} alkylC(=0)-, R^{3}(C(=0))N(R^{4}), HO(=)=C-, C_{14} alkyl-0(=)=C-, C_{14} alkylsulfonylamino, C_{14} alkyl-C(=0)NH-, Q^{-}|S(0)m-, Q^{2}-0-, Q^{2}-N(R^{3})- or Q^{2}-;

m is 0, 1 or 2;

R^{3} and R^{4} are independently selected from H and C_{M} alkyl; and

Q^{2} is a 5 to 12 membered monocyclic or bicyclic aromatic ring, optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5 to 12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C_{M} alkyl, halo-substituted C_{M} alkyl, C_{M} alkenyl, C_{M} alkylnyl, hydroxy, C_{M} alkoxy, halo-substituted C_{i-4} alkoxy, C_{M} alkylthio, mono- or di-(C_{i-4} alkyl)amino, cyano, HO-CM alkyl, C_{M} alkoxy-C_{i4} alkyl, C_{M} alkylsulfonyl, aminosulfonyl, C_{M} alkyl(=0)=C-, R^{3}(R^{4})C(=0)N- HO(=)=C-, C_{i4} alkyl-0(=)=C-, C_{14} alkylsulfonylamino, C_{3,7} cycloalkyl or C_{14} alkyl-C(=0)NH-.

In the compounds of Formula (I), more preferably Z is a 5 to 12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5 to 12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C_{i-4} alkyl, halo-substituted C_{i-4} alkyl, C_{i-4} alkenyl, halo-substituted C_{i-4} alkoxy, nitro, amino, cyano, R^{3} C(=0)N(R^{4}), C_{i4} alkyl-0(=)=C-, Q^{2}-S(0)m-, Q^{2}-0-, Q^{2}-N(R^{3})- or Q^{2}-;
m is 0, 1 or 2;
R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and
Q² is a 5 or 6 membered monocyclic aromatic ring, containing up to 3 heteroatoms selected from N and S, wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with halo,

[0040] In the compounds of Formula (I),
more preferably Z is a 5 to 2 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5 to 2 membered monocyclic aromatic ring is optionally substituted with halo, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkoxy, nitro, amino, cyano, R³ C(=N(R⁴))-, C₁₋₄ alkyl-0(0=)C-,
Q²-S(0)m-, Q²-O-, Q²-N(R³)- or Q²-;
m is 0, 1 or 2;
R³ and R⁴ are independently selected from H and C₆₋₄ alkyl; and
Q² is a 5 or 6 membered monocyclic aromatic ring or, optionally containing 1 sulfur atom wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with halo,

[0041] In the compounds of Formula (I),
more preferably Z is a 5 to 2 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5 to 2 membered monocyclic aromatic ring is optionally substituted with halo, C₁₋₄ alkyl, nitro, R³C(=0)N(R⁴)- or Q²-;
R³ and R⁴ are independently selected from H and C₁₋₄ alkyl; and
Q² is a 5 or 6 membered monocyclic aromatic ring system, more preferably Z is a 5 to 0 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5 to 10 membered monocyclic aromatic ring is optionally substituted with chloro, bromo, methyl, nitro, CH₃C(=0)NH-, tBuC(=0)NH- or phenyl,

[0042] In the compounds of Formula (I),
most preferably Z is phenyl, pyrazolyl, thiazolyl, thiadiazolyl, thienyl, naphthyl or benzothienyl, said phenyl, pyrazolyl, thiazolyl, thiadiazolyl and thienyl being optionally substituted with one to three substituents independently selected from chloro, bromo, methyl, acetylamino, pivaloylamino, nitro and phenyl.

[0043] A preferred group of compounds of Formula (I) includes compounds wherein
Y¹, Y², Y³, and Y⁴ are independently selected from N, CH and C(L);
R¹ is H, C₈₋₁₈ alkyl, C₂₋₈ alkenyl, C₃₋₇ cycloalkyl, C₁₋₈ alkoxy, halo-substituted C₁₋₈ alkoxy, C₁₋₈ alkyl-S(0)m-, Q¹-, pyrrolidinyl, piperidyl, oxypyrrolidinyl, oxopiperidyl, amino, mono- or di-(C₂₋₈ alkyl)amino, C₁₋₄ alkyl-C(=O)-N(R³)- or C₂₋₄ alkyl-S(0)m-N(R³)-, wherein said C₁₋₈ alkyl, C₂₋₄ alkenyl and C₂₋₄ alkynyl are opt-
tionally substituted with halo, C\textsubscript{i-3} alkyl, hydroxy, oxo, C\textsubscript{1,4} alkoxy-, C\textsubscript{1,4} alkyl-S(0)m-, C\textsubscript{3,7} cycloalkyl-, cyano, indanyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, pyrrolidinyl, piperidyl, oxopiperidinyl, oxopiperidyl, Q\textsuperscript{1}, Q\textsuperscript{1}-C(=0)-, Q\textsuperscript{4} O-, Q\textsuperscript{1}-S(0)m-, Q\textsuperscript{1}-C\textsubscript{1,4} alkyl-O-, Q\textsuperscript{1}-C\textsubscript{1,4} alkyl-S(0)m-, Q\textsuperscript{1}-C\textsubscript{1,4} alkyl-C(=0)-N(R \textsuperscript{3})-, or C\textsubscript{1,4} alkyl-C(=0)-N(R \textsuperscript{3})-

Q\textsuperscript{1} is a 5 to 2 membered monocyclic or bicyclic aromatic ring optionally containing up to 4 heteroatoms selected from O, N and S, and is optionally substituted with halo, C\textsubscript{1,4} alkyl, halo-substituted C\textsubscript{1,4} alkyl, hydroxy, C\textsubscript{1,4} alkoxy, halo-substituted C\textsubscript{1,4} alkoxy, C\textsubscript{1,4} alkylthio, nitro, amino, mono- or di-(C\textsubscript{i-4} alkyl)amino, cyano, HO-C\textsubscript{i-4} alkyl, C\textsubscript{i-4} alkoxy-C\textsubscript{i-4} alkyl, C\textsubscript{1,4} alkylsulfonyl, aminosulfonyl, C\textsubscript{1,4} alkylC(=0)-, HO(=)C-, C\textsubscript{1,4} alkyl-0(0)=C-, R\textsuperscript{7}N(R\textsuperscript{4})C(=0)-, C\textsubscript{14} alkylsulfonylamino, C\textsubscript{3,7} cycloalkyl, R\textsuperscript{3}C(=0)N(R \textsuperscript{4}), or NH\textsubscript{2}(HN=)C-;

A is a 5 or 6 membered monocyclic aromatic ring optionally containing up to 2 heteroatoms selected from O, N, and S, wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with up to 2 substituents selected from halo, C\textsubscript{i-4} alkyl, halo-substituted C\textsubscript{i-4} alkyl, hydroxy, C\textsubscript{i-4} alkoxy and halo-substituted C\textsubscript{i-4} alkoxy;

B is C\textsubscript{3,7} cycloalkylene or C\textsubscript{i-6} alkyne optionally substituted with an oxo group or C\textsubscript{i-3} alkyl;

W is NH, N-C\textsubscript{1,4} alkyl, O or N-OH;

R\textsuperscript{2} is H or C\textsubscript{1,4} alkyl;

Z is a 5 to 2 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5 to 2 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C\textsubscript{1,4} alkyl, halo-substituted C\textsubscript{i-4} alkyl, C\textsubscript{1,4} alkenyl, hydroxy, C\textsubscript{1,4} alkoxy, nitro, amino, cyano, HO-C\textsubscript{i-4} alkyl, C\textsubscript{1,4} alkoxy, C\textsubscript{1,4} alkylsulfonyl, aminosulfonyl, C\textsubscript{14} alkylC(=0)-, R\textsuperscript{3}C(=0)N(R \textsuperscript{4}), HO(=)C-, C\textsubscript{1,4} alkyl-0(0)=C-, C\textsubscript{1,4} alkylsulfonylamino, C\textsubscript{14} alkyl-C(=0)NH-, Q\textsuperscript{2}S(0)m-, Q\textsuperscript{2}-O-, Q\textsuperscript{2}-N(R \textsuperscript{3})- or Q\textsuperscript{2}2;-

L is halo, C\textsubscript{i-4} alkyl, halo-substituted C\textsubscript{1,4} alkyl, hydroxy, C\textsubscript{1,4} alkoxy, mono- or di-(C\textsubscript{i-4} alkyl)amino, halo-substituted C\textsubscript{i-4} alkoxy, cyano, HO-C\textsubscript{1,4} alkyl, C\textsubscript{i-4} alkoxy-C\textsubscript{i-4} alkyl, C\textsubscript{1,4} alkoxy, C\textsubscript{1,4} alkylsulfonyl, aminosulfonyl, C\textsubscript{1,4} alkylC(=0)-, HO(=)C-, C\textsubscript{14} alkyl-0(0)=C-, C\textsubscript{3,2} cycloalkyl, R\textsuperscript{3}C(=0)N(R \textsuperscript{4}), R\textsuperscript{3}N(R\textsuperscript{4})C(=0)-, R\textsuperscript{3}N(R \textsuperscript{4})S(0)m-, Q\textsuperscript{2}, Q\textsuperscript{2}-C(=0)-, Q\textsuperscript{2}-O-, Q\textsuperscript{2}-C\textsubscript{1,4} alkyl-0-, or two adjacent L groups are optionally joined together to form an alkyne chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;

m is 0, 1 or 2;

R\textsuperscript{3} and R\textsuperscript{4} are independently selected from H and C\textsubscript{i-4} alkyl; and

Q\textsuperscript{2} is a 5 to 2 membered monocyclic or bicyclic aromatic ring, optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5 to 2 membered
monocyclic or bicyclic aromatic ring is optionally substituted with halo, C\textsubscript{1-4} alkyl, halo-substituted C\textsubscript{1-4} alkyl, C\textsubscript{1-4} alkenyl, d\textsubscript{1-4} alkynyl, hydroxy, d\textsubscript{1-4} alkoxy, halo-substituted C\textsubscript{1-4} alkoxy, C\textsubscript{1-4} alkylthio, mono- or di-(C\textsubscript{1-4} alkyl)amino, cyano, HO-Ci\textsubscript{4} alkyl, Ci\textsubscript{4} alkoxy-Ci\textsubscript{4} alkyl, Ci\textsubscript{4} alkylsulfonyl, aminosulfonyl, C\textsubscript{1-4} alkyl-(0-)(C\textsubscript{1-4} alkyl)-S(0)m-, R\textsuperscript{3}(R\textsuperscript{4})C(0)=N-, HO(0)=C-, C\textsubscript{1-4} alkyl-0(0-)=C-, C\textsubscript{1-4} alkylsulfonlamino, C\textsubscript{3-4} cycloalkyl or C\textsubscript{1-4} alkyl-C(=0)NH-.

\textbf{[0044]} A further preferred group of compounds of Formula (I) includes compounds wherein Y\textsuperscript{1}, Y\textsuperscript{2}, Y\textsuperscript{3}, and Y\textsuperscript{4} are independently selected from N, CH and C(L);

R\textsuperscript{1} is H, Ci\textsubscript{1-8} alkyl, C\textsubscript{2-8} alkenyl, C\textsubscript{2-8} alkynyl, C\textsubscript{3-7} cycloalkyl, Q\textsuperscript{1}, pyrrolidinyl, piperidyl, oxopyrrolidiny, oxopiperidyl, amino, mono- or di-(C\textsubscript{1-8} alkyl)amino, wherein said Ci\textsubscript{1-8} alkyl is optionally substituted with halo, C\textsubscript{1-4} alkyl, hydroxy, oxo, C\textsubscript{1-4} alkoxy-, C\textsubscript{1-4} alkyl-S(0)m-, C\textsubscript{3-2} cycloalkyl-, cyano, indanyli, pyrrolidinyl, piperidyl, oxopyrrolidiny, oxopiperidyl, Q\textsuperscript{1}, Q\textsuperscript{1}-C(0)-, Q\textsuperscript{2}-O-, Q\textsuperscript{2}-S-, Q\textsuperscript{2}-d\textsubscript{4} alkyl-O-, or C\textsubscript{1-4} alkyl-C(0)-N(R\textsuperscript{3})-;

Q\textsuperscript{1} is a 5 to 4 membered monocyclic aromatic ring optionally containing up to 4 heteroatoms selected from N and S, and is optionally substituted with halo, Ci\textsubscript{4} alkyl, Ci\textsubscript{4} alkylosulfonyl and C\textsubscript{1-4} alkyIC(0)=; A is a 5 or 6 membered monocyclic aromatic ring optionally substituted with halo, C\textsubscript{1-4} alkyl or Ci\textsubscript{4} alkoxy;

B is C\textsubscript{3-7} cycloalkylene or C\textsubscript{1-6} alkylene optionally substituted with an oxo group or C\textsubscript{1-3} alkyl;

W is NH, N-Ci\textsubscript{1-4} alkyl, O or N-OH;

R\textsuperscript{2} is H or C\textsubscript{1-4} alkyl;

Z is a 5 to 12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5 to 4 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C\textsubscript{14} alkyl, halo-substituted Ci\textsubscript{4} alkyl, C\textsubscript{1-4} alkenyl, C\textsubscript{1-4} alkoxy, nitro, amino, cyano, R\textsuperscript{1}C(0)=N(R\textsuperscript{4}), C\textsubscript{1-4} alkyl-0(0-)=C-, Q\textsuperscript{2}-S(0)m-, Q\textsuperscript{2}-O-, Q\textsuperscript{2}-N(R\textsuperscript{3})- or Q\textsuperscript{2};

L is halo, C\textsubscript{1-4} alkyl, halo-substituted Ci\textsubscript{1-4} alkyl, hydroxy, C\textsubscript{1-4} alkoxy, halo-substituted Ci\textsubscript{1-4} alkoxy, mono- or di-(Ci\textsubscript{1-4} alkyl)amino, cyano, HO-Ci\textsubscript{4} alkyl, Ci\textsubscript{4} alkylosulfonyl, aminosulfonyl, C\textsubscript{1-4} alkylC(0)=, HO(0)=C-, C\textsubscript{1-4} alkyl-0(0-)=C-, C\textsubscript{1-4} alkylosulfonlamino, C\textsubscript{3-7} cycloalkyl, R\textsuperscript{1}C(0)=N(R\textsuperscript{4}), R\textsuperscript{1}N(R\textsuperscript{4})C(0)=, R\textsuperscript{1}N(R\textsuperscript{4})S(0)m-, Q\textsuperscript{2}, Q\textsuperscript{2}-C(0)=, Q\textsuperscript{2}-O-, Q\textsuperscript{2}-Ci\textsubscript{4} alkyl-O-, or two adjacent L groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;

m is 0, 1 or 2;

R\textsuperscript{3} and R\textsuperscript{4} are independently selected from H and Ci\textsubscript{4} alkyl; and Q\textsuperscript{2} is a 5 or 6 membered monocyclic aromatic ring, containing up to 3 heteroatoms.
selected from N and S, wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with halo.

[0045] A further preferred group of compounds of Formula (I) includes compounds wherein Y1, Y2, Y3 and Y4 are independently selected from N, CH and C(L):

R1 is H, Ci-8 alkyl, C2-4 alkenyl, C2-4 alkynyl or C3-7 cycloalkyl, wherein said Ci-8 alkyl is optionally substituted with halo, Ci-3 alkyl, hydroxy, oxo, d-alkoxy-, Ci-4 alkyl-S(0)m-, C3-7 cycloalkyl-, cyano, indanyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q1-, Q'-C(=0)-, Q'-S-, Q'-C14 alkyl-O-, or C14 alkyl-C(0)-N(R)-;

Q1 is a 5 or 6 membered monocyclic aromatic ring optionally containing up to 4 heteroatoms selected from N and S;

A is a 5 or 6 membered monocyclic aromatic ring system optionally substituted with halo or Ci-4 alkyl;

B is C3-7 cycloalkylene or Ci-6 alkenylene optionally substituted with an oxo group or C1-3 alkyl;

W is NH, N-C1-4 alkyl, O or N-OH;

R2 is H or Ci-4 alkyl;

Z is a 5 to 12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5 to 12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, Ci-4 alkyl, halo-substituted Ci-4 alkyl, Ci-4 alkenyl, Ci-4 alkoxy, nitro, amino, cyano, R'C(=0)N(R4)-, Ci-4 alkyl-0(0)=C-, Q2-S(0)m-, Q2-O-, Q2-N(R3)- or Q2-;

L is halo, Ci-4 alkyl, halo-substituted d-alkoxy, hydroxy, Ci-4 alkoxy, halo-substituted Ci-4 alkoxy, cyano, HO-Ci-4 alkyl, C1-4 alkylsulfonyl, aminosulfonyl, Ci-4 alkylC(=0), HO(0)=C-, C1-4 alkyl-0(0)=C-, Ci-4 alkylsulfonylamino, C3-7 cycloalkyl, R' C(=0)NR4-, R'N(4)C(=0)-, R'N(4)S(0)m-, Q2-, Q2-C(=0)-, Q2-O-, Q2-d-alkyl-0-, or two adjacent L groups are optionally joined together to form an alkyne chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;

m is 0, 1 or 2;

R3 and R4 are independently selected from H and Ci-4 alkyl; and

Q2 is a 5 or 6 membered monocyclic aromatic ring or, optionally containing 1 sulfur atom wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with halo.

[0046] A further preferred group of compounds of Formula (I) includes compounds wherein Y1, Y2, Y3 and Y4 are independently selected from N, CH and C(L):

R1 is Ci-5 alkyl or C3-7 cycloalkyl, wherein said Ci-5 alkyl is optionally substituted with Ci-3 alkyl, hydroxy, oxo, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q1-, or C14 alkyl-C(0)-N(H)-;
Q is a 5 to 12 membered monocyclic aromatic ring system optionally containing up to 2 heteroatoms selected from N and S,
A is a 5 or 6 membered monocyclic aromatic ring system;
B is C-3 alkylene optionally substituted with C-3 alkyl;
W is NH, N-Ci-2 alkyl or O;
R is H;
Z is a 5 to 12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5 to 12 membered monocyclic aromatic ring is optionally substituted with halo, C-1-4 alkyl, nitro, R-3C(=0)N(R)- or Q-
L is halo, d-alkyl, halo-substituted C-1-4 alkyl, hydroxy, C-1-4 alkoxy, halo-substituted C-1-4 alkoxy, cyano, HO-d-alkyl, acetyl, R-3N(R-4)C(=0)-, R-3N(R-4)S(m)-, Q-2-, Q-2-C(m)-, or two adjacent L groups are joined together to form a methylenedioxy group; R-3 and R-4 are independently selected from H and Ci-4 alkyl; and
Q is a 5 or 6 membered monocyclic aromatic ring system.

A further preferred group of compounds of Formula (I) includes compounds wherein
Y is independently selected from N, CH and C(L);
R is C-5 alkyl optionally substituted with C-3 alkyl, hydroxy, oxo, 5 or 6 membered monocyclic aromatic ring, wherein said 5 or 6 membered monocyclic aromatic ring is containing 1 or 2 heteroatoms selected from N and S, or C-4 alkyl-C(0)-N(R)-;
A is phenyl;
B is Ci-2 alkylene optionally substituted with methyl;
W is NH, N-CH-3 or O;
R is H;
R is H or C-1-4 alkyl;
Z is a 5 to 10 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from N and S, wherein said 5 to 10 membered monocyclic aromatic ring is optionally substituted with chloro, bromo, methyl, nitro, CH-5C(=0)NH-, tBuC(=0)NH- or phenyl; and
L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, -C(=0)NH-2, trifluoromethoxy, methanesulfonyl, or 1-hydroxy-1-methyl-ethyl, or two adjacent L groups are joined together to form a methylenedioxy group.

A further preferred group of compounds of Formula (I) includes compounds wherein
Y is independently selected from N, CH and C(L);
R is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, neopentyl, thiazolylethyl, methylamino, dimethylamino, pyrrolidinyl, pyridyl, or 1-acetylamino-1-methylethyl;
A is phenyl;
B is ethylene or propylene;
W is NH, N-CH₃ or O;
R² is H;
Z is phenyl, pyrazolyl, thiazolyl, thia diazolyl, thi enyl, naphthyl or benzo thi enyl, said phenyl, pyrazolyl, thiazolyl, thia diazolyl and thi enyl being optionally substituted with one to three substituents independently selected from chloro, bromo, methyl, acetylamino, pivaloylamino, nitro and phenyl; and
L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, -C(=0)NH₂, trifluoromethoxy, methanesulfonyl, or 1-hydroxy-1-methyl-ethyl, or two adjacent L groups are joined together to form a methylenedioxy group.

A further preferred group of compounds of Formula (I) includes compounds wherein Y¹, Y², Y³ and Y⁴ are selected from the group consisting of a) Y¹ and Y³ are C(L), Y² is CH and Y⁴ is N; b) Y¹ is CH, Y² and Y³ are C(L) and Y⁴ is N; c) Y¹, Y² and Y³ are C(L) and Y⁴ is N; d) Y¹ and Y³ are C(L), Y² is N and Y⁴ is CH; e) Y¹ is C(L) and Y², Y³ and Y⁴ are CH; f) Y¹, Y³ and Y⁴ are CH, and Y² is C(L); g) Y¹, Y² and Y³ are CH, and Y⁴ is C(L); h) Y¹ and Y² are C(L), and Y³ and Y⁴ are CH; i) Y¹ and Y³ are C(L), and Y² and Y⁴ are CH; j) Y¹ and Y⁴ are CH, and Y² and Y³ are C(L); k) Y¹ and Y² are CH, Y³ is C(L) and Y⁴ is N; l) Y¹ and Y³ are CH, Y² is C(L) and Y⁴ is N; m) Y¹, Y², Y³ and Y⁴ are CH; n) Y¹ and Y² are C(L), Y³ is CH and Y⁴ is N; o) Y¹, Y² and Y⁴ are CH, and Y³ is C(L); p) Y¹ and Y² are C(L), Y³ is N and Y⁴ is CH; q) Y¹ and Y³ are C(L), and Y² and Y⁴ are N; r) Y¹ is C(L), Y² and Y³ are CH, and Y⁴ is N; and s) Y² is C(L), Y¹ and Y³ are CH, and Y⁴ is N;
R¹ is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, neopentyl, thiazolylethyl, methylamino, dimethylamino, pyrrolidinyl, pyridyl, or 1-acetylamino-1-methylethyl;
A is phenyl;
B is ethylene or propylene;
W is NH, N-CH₃ or O;
R² is H;
Z is phenyl, pyrazolyl, thiazolyl, thia diazolyl, thi enyl, naphthyl or benzo thi enyl, said phenyl, pyrazolyl, thiazolyl, thia diazolyl and thi enyl being optionally substituted with
one to three substituents independently selected from chloro, bromo, methyl, acetylamino, pivaloylamino, nitro and phenyl; and
L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, -C(=0)NH₂, trifluoromethoxy, methanesulfonyl, or 1-hydroxy-1-methyl-ethyl, or two adjacent L groups are joined together to form a methylenedioxy group.

A further preferred group of compounds of Formula (I) includes compounds wherein Y¹, Y², Y³ and Y⁴ are selected from the group consisting of
a) Y¹ and Y³ are C(L), Y² is CH and Y⁴ is N;
b) Y¹ is CH, Y² and Y³ are C(L) and Y⁴ is N;
c) Y¹, Y² and Y³ are C(L) and Y⁴ is N;
d) Y¹ and Y³ are C(L), Y² is N and Y⁴ is CH;
e) Y¹ is C(L) and Y², Y³ and Y⁴ are CH;
f) Y¹, Y³ and Y⁴ are CH, and Y² is C(L);
g) Y¹, Y² and Y³ are CH, and Y⁴ is C(L);
h) Y¹ and Y² are C(L), and Y³ and Y⁴ are CH;
i) Y¹ and Y³ are C(L), and Y² and Y⁴ are CH; and
j) Y¹ and Y⁴ are CH, and Y² and Y³ are C(L);
R¹ is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, neopentyl, thiazolyylethyl, methylamino, dimethylamino, pyrrolidinyl, pyridyl, or 1-acetylamino-1-methylethyl;
A is phenyl;
B is ethylene or propylene;
W is NH, N-CH₃ or O;
R² is H;
Z is phenyl, pyrazolyl, thiazolyl, thiadiazolyl, thienyl, naphthyl or benzothienyl, said phenyl, pyrazolyl, thiazolyl, thiadiazolyl and thienyl being optionally substituted with one to three substituents independently selected from chloro, bromo, methyl, acetylamino, pivaloylamino, nitro and phenyl; and
L is chloro, methyl, trifluoromethyl, hydroxy, methoxy, cyano, acetyl, -C(=0)NH₂, trifluoromethoxy, methanesulfonyl, or 1-hydroxy-1-methyl-ethyl, or two adjacent L groups are joined together to form a methylenedioxy group.

Preferred individual compounds of Formula (I) are as follows:
3-(4-[2-[[[(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)sulfonyl]amino]carbonyl]amino]ethyl)phenyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine;
3-(4-[2-[[[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]amino]carbonyl]aminoethyl]phenyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine;
6-ethyl-5-
(4-{2-[[[(4-methyl phenyl)sulfonyl]amino]carbonyl]amino}ethyl)phenyl)-5H-[1,3]dioxolo[4,5-f]benzimidazole;
6-chloro-5-cyano-2-ethyl-1-(4-((4-{2-[[[(4-methyl phenyl)sulfonyl]amino]carbonyl]amino}ethyl)phenyl)-IH-benzimidazole;
2-ethyl-5,7-dimethyl-3-(4-[[4-methylphenyl]sulfonyl]amino)carbonyl)amino]ethyl)phenyl)-3H-imidazo[4,5-b]pyridine;
2-ethyl-5,7-dimethyl-3-(4-[[4-methylphenyl]sulfonyl]amino)carbonyl)amino]propyl)phenyl)-3H-imidazo[4,5-b]pyridine;
2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-1-methylethyl(4-methylphenyl)sulfonylcarbamate;
5,7-dimethyl-3-(4-{2-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino}ethyl)phenyl)-2-propyl-3H-imidazo[4,5-b]pyridine;
2-isopropyl-5,7-dimethyl-3-(4-[[4-methylphenyl]sulfonyl]amino)carbonyl)amino]ethyl)phenyl)-3H-imidazo[4,5-b]pyridine;
2-butyl-5,7-dimethyl-3-(4-[[4-methylphenyl]sulfonyl]amino)carbonyl)amino]ethyl)phenyl)-3H-imidazo[4,5-b]pyridine;
2-isobutyl-5,7-dimethyl-3-(4-{2-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino}ethyl)phenyl)-3H-imidazo[4,5-b]pyridine;
2-ethyl-5,6-dimethyl-3-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)-3H-imidazo[4,5-b]pyridine;
5-chloro-2-ethyl-7-methyl-3-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)-3H-imidazo[4,5-b]pyridine;
2-ethyl-4,6-dimethyl-1-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)-1H-imidazo[4,5-c]pyridine;
4-methyl-2-ethyl-3-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)benzimidazole;
7-chloro-2-ethyl-3-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)benzimidazole;
5-methoxy-2-ethyl-3-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)benzimidazole;
5-acetyl-2-ethyl-3-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)benzimidazole;
5-cyano-2-ethyl-1-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)-1H-benzimidazole;
2-ethyl-5-hydroxy-1-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)-1H-benzimidazole;
2-ethyl-4,5-dimethyl-1-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)-1H-benzimidazole;
4,6-dimethyl-2-ethyl-3-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)-1H-benzimidazole;
5,6-dimethyl-1-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)-1H-benzimidazole;
5,6-dichloro-2-ethyl-1-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)-1H-benzimidazole;
2-[4-(5,6-dichloro-2-ethyl-1H-benzimidazol-1-yl)phenyl]ethyl-(4-methylphenyl)sulfonylcarbamate;
6-chloro-5-trifluoromethyl-1-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)-1H-benzimidazole;
4-(6-chloro-2-ethyl-5-trifluoromethyl-1H-benzimidazol-1-yl)phenethyl-(4-methylphenyl)sulfonylcarbamate;
5-chloro-6-methyl-1-(4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino)ethyl)phenyl)-1H-benzimidazole;
2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate;
2-[4-[5,7-dimethyl-2-(methylamino)-3H-imidazo[4,5-b]pyridin-3-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate;
N-[[2-4-[2-ethyl-5-(1-hydroxy-1-methylethyl)-1H-benzimidazol-1-yl]phenyl]ethyl]amino]carbonyl]-4-methylbenzenesulfonamide;
2-ethyl-4,6-dimethyl-l-(4-[2-[[4-methylphenyl)sulfonyl]amino]carbonyl]amino]ethyl]-1H-benzimidazole-5-carboxamide;
2-[4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethyl (2-chlorophenyl)sulfonylcarbamate;
2-[5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-2-pyridinyl]ethyl (4-methylphenyl)sulfonylcarbamate;
2-[4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethyl (5-methyl-2-pyridinyl)sulfonylcarbamate;
2-[4-[6-chloro-2-[1H-pyrazol-3-yl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate;
2-{4-[6-chloro-2-(4-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;
2-{4-[5-(aminocarbonyl)-6-chloro-2-ethyl-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;
N-[(2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl}ethyl)amino]carbonyl]-4-methylbenzenesulfonamide;
2-{4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;
N-[(2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl)amino]carbonyl]-2-thiophenesulfonamide;
2-[4-(4,6-dimethyl-2-phenyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate;
2-[4-(2-butyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl (4-methylphenyl)sulfonylcarbamate; (1S)-2-[4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethyl (5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)sulfonylcarbamate;
2-{4-[4,6-dimethyl-2-[(3-phenylpropyl)-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;
2-[4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;
2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl}ethyl (5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)sulfonylcarbamate;
2-{4-[4,6-dimethyl-2-[(3-phenylpropyl)-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;
2-[4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethyl (5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)sulfonylcarbamate; (1S)-2-[4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethyl 1-methyl ethyl (4-methylphenyl)sulfonylcarbamate;
2-[6-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]-3-pyridinyl]ethyl (4-methylphenyl)sulfonylcarbamate;
N-[(2-4-[6-chloro-2-(1-hydroxy-1-methylethyl)-5-(trifluoromethyl)-1H-benzimidazo-1-yl)phenyl}ethyl)amino]carbonyl]-4-methylbenzenesulfonamide;
N-[(2-[4-[5,7-dimethyl-2-[(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl]phenyl}ethyl)amino]carbonyl]-4-methylbenzenesulfonamide; 2-[(4-1,1-dimethylethyl)-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate;
2-[(4-[2-[1-(acetylamino)-1-methylethyl]-6-chloro-5-(trifluoromethyl)-1H-benzimidazo-1-yl]phenyl}ethyl (4-methylphenyl)sulfonylcarbamate; 6-chloro-2-ethyl-1-(4-[2-[methyl(1[4-(methylphenyl) sulfonyl] amino]carbonyl)amino]ethyl)phenyl]-1H-benzimidazole-5-carboxamide; and salts thereof.

Most preferred individual compounds of Formula (I) are following:
6-ethyl-5-
(4-{2-[4-[5,7-dimethyl-2-[(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl]phenyl]ethyl)amino]carbonyl]-4-methylbenzenesulfonamide.}
6-chloro-5-cyano-2-ethyl-1-(4-{2-([(4-methylphenyl)sulfonyl]amino}carbonyl)amino)ethylphenyl)-IH-benzimidazole;
2-[4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]-l-methylethyl(4-methylphenyl)sulfonylcarbamate;
5,7-dimethyl-3-(4-{2-([(4-methylphenyl)sulfonyl]amino}carbonyl)amino)ethyl-2-[2-(1,3-thiazol-2-yl)ethyl]-3H-imidazo[4,5-b]pyridine;
2-ethyl-5,7-dimethyl-3-(4-{2-([(2-thienyl)sulfonyl]amino}carbonyl)amino)ethylphenyl)-3H-imidazo[4,5-b]pyridine;
3-(4-{2-([(2-chlorophenyl)sulfonyl]amino}carbonyl)amino)ethylphenyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine;
2-ethyl-5,6-dimethyl-3-(4-{2-([(4-methylphenyl)sulfonyl]amino}carbonyl)amino)ethylphenyl)-3H-imidazo[4,5-b]pyridine;
5,6-dichloro-2-ethyl-3-(4-{2-([(4-methylphenyl)sulfonyl]amino}carbonyl)amino)ethylphenyl)-3H-imidazo[4,5-b]pyridine;
2-ethyl-4,6-dimethyl-1-(4-{2-([(4-methylphenyl)sulfonyl]amino}carbonyl)amino)ethylphenyl)-IH-imidazo[4,5-c]pyridine;
5-methoxy-2-ethyl-3-(4-{2-([(4-methylphenyl)sulfonyl]amino}carbonyl)amino)ethylphenyl)benzimidazole;
5-acetyl-2-ethyl-3-(4-{2-([(4-methylphenyl)sulfonyl]amino}carbonyl)amino)ethylphenyl)benzimidazole;
5-cyano-2-ethyl-1-(4-{2-([(4-methylphenyl)sulfonyl]amino}carbonyl)amino)ethylphenyl)-IH-benzimidazole;
2-ethyl-5-hydroxy-1-(4-{2-{[(4-methylphenyl)sulfonyl]amino}carbonyl)amino)ethylphenyl)-IH-benzimidazole;
2-ethyl-4,5-dimethyl-1-(4-{2-{[(4-methylphenyl)sulfonyl]amino}carbonyl)amino)ethylphenyl)-IH-benzimidazole;
4-(6-chloro-2-ethyl-5-trifluoromethyl-IH-benzimidazol-1-yl)phenethyl-(4-methylphenyl)sulfonylcarbamate; and
6-chloro-2-ethyl-1-(4-{2-{[(4-methylphenyl)sulfonyl]amino}carbonyl)amino)ethylphenyl)-IH-benzimidazole-5-carboxamide;
2-[4-(2-ethyl-4,6-dimethyl-IH-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl(4-methylphenyl)sulfonylcarbamate;
2-[4-{5,7-dimethyl-2-(methylamino)-3H-imidazo[4,5-b]pyridin-3-yl}phenyl]ethyl(4-methylphenyl)sulfonylcarbamate;
N-{[2-(4-{5,7-dimethyl-2-(methylamino)-3H-imidazo[4,5-b]pyridin-3-yl}phenyl]ethylamino}carbonyl]-4-methylbenzenesulfonamide;
N-{[2-(4-{2-ethyl-5-(1-hydroxy-l-methylethyl)-IH-benzimidazol-1-yl}phenyl]ethylamino}carbonyl]-4-methylbenzenesulfonamide;
2-ethyl-4,6-dimethyl-1-(4-{{[(4-methylphenyl)sulfonyl]amino}carbonyl}amino)ethyl)phenyl) - 1H-benzimidazole- 5-carboxamide; 
2- [4-[6-chloro-2-ethyl-5-(trifluoromethyl)- 1H-benzimidazol- 1-yl]phenyl]ethyl (2-chlorophenyl)sulfonylcarbamate; 
2- [5-[6-chloro-2-ethyl-5-(trifluoromethyl)- 1H-benzimidazol- 1-yl]-2-pyridinyl]ethyl (4-methylphenyl)sulfonylcarbamate; 
2- [4-[6-chloro-2-ethyl-5-(trifluoromethyl)- 1H-benzimidazol- 1-yl]phenyl]ethyl (5-methyl-2-pyridinyl)sulfonylcarbamate; 
2- [4-[6-chloro-2-(1H-pyrazol-3-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate; 
2- [4-[6-chloro-2-(4-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate; 
2- [4-[5-(aminocarbonyl)-6-chloro-2-ethyl-1H-benzimidazol-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate; 
N-\{[2-[4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl]ethyl]amino\}carbonyl-4-methylbenzenesulfonamide; 
2-[4-[6-chloro-2-ethyl-5-(methylsulfonyl)-1H-benzimidazol-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate; 
N-\{([2-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl]ethyl)amino\}carbonyl-4-methylbenzenesulfonamide; 
2-[4-[4,6-dimethyl-2-phenyl-1H-imidazo[4,5-c]pyridin-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate; 
2-[4-[2-butyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate; 
2- [4-[6-chloro-2-ethyl-5-(trifluoromethyl)- 1H-benzimidazol- 1-yl]phenyl]ethyl (5-chloro- 1,3-dimethyl- 1H-pyrazol-4-yl)sulfonylcarbamate; 
2- [4-[4,6-dimethyl-2-(3-phenylpropyl)-1H-imidazo[4,5-c]pyridin-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate; 
2- [4-[6-chloro-2-(2-pyridinyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]phenyl]ethyl (4-methylphenyl)sulfonylcarbamate; 
(1S)-2- [4-[6-chloro-2-ethyl-5-(trifluoromethyl)- 1H-benzimidazol- 1-yl]phenyl]-1-methyl ethyl(4-methylphenyl)sulfonylcarbamate; 
2- [6- [6-chloro-2-ethyl-5-(trifluoromethyl)- 1H-benzimidazol- 1-yl]-3-pyridinyl]ethyl (4-methylphenyl)sulfonylcarbamate; 
N-\{[(2-[4-[6-chloro-2-(1-hydroxy- 1-methylethyl)-5-(trifluoromethyl)-1H-benzimidazo l-1-yl]phenyl]ethyl)amino]carbonyl\}4-methylbenzenesulfonamide; 
N-[[2-[4-[5,7-dimethyl-2-(1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl]phenyl]ethyl]amino]carbonyl]-4-methylbenzenesulfonamide;
2-{{2-(1,1-dimethylethyl)-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl}phenyl}(4-methylphenyl)sulfonylcarbamate;
2-{{4-[2-[1-acetylamino]-1-methylethyl]-6-chloro-5-(trifluoromethyl)-1H-benzimidazo[1,1-yl]phenyl}ethyl}(4-methylphenyl)sulfonylcarbamate;
6-chloro-2-ethyl-1-(4-[methyl({[(4-methylphenyl)sulfonyl]amino}carbonyl)amino]ethyl)phenyl)-1H-benzimidazole-5-carboxamide; and salts thereof.

[0053] In another preferred aspect, the EP4 receptor ligand (antagonist), which is disclosed in WO 2005/021508, is phenyl or pyridyl amide compounds of the following Formula (II) or pharmaceutically acceptable salts thereof,

[Chem.IO]

\( \text{(II)} \)

wherein A represents a phenyl group or a pyridyl group; B represents an aryl group or a heteroaryl group; 
E represents a 1,4-phenylene group; 
R\(^1\) and R\(^2\) independently represent a hydrogen atom, a halogen atom, an alkyl group having from 1 to 4 carbon atoms, an alkoxyl group having from 1 to 4 carbon atoms, a haloalkyl group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms, a cyano group or an aminocarbonyl group; 
R\(^3\) and R\(^4\) independently represent a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms; or R\(^3\) and R\(^4\) may be joined together to form an alkyne chain having 2 to 6 carbon atoms; 
R\(^5\) represents -C0\(_2\)H, C0\(_2\)W.
R^6 represents an alkyl group having from 1 to 6 carbon atoms, a cycloalkyl group having from 3 to 7 ring atoms, an aryl group or a heteroaryl group;

X represents a methylene group, an oxygen atom or a sulfur atom;
said aryl groups have from 6 to 10 carbon atoms; said heteroaryl groups are 5 to 10-membered aromatic heterocyclic groups containing from 1 to 3 heteroatoms selected from the group consisting of sulfur atom, oxygen atom and nitrogen atom;
said aryl groups and said heteroaryl groups referred to in the definitions of B are unsubstituted or are substituted by at least one substituent selected from the group consisting of substituents alpha; 
said 1,4-phenylene group referred to in the definition of E is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents beta;
said aryl groups and said heteroaryl groups referred to in the definitions of R^6 and alpha are unsubstituted or are substituted by at least one substituent selected from the group consisting of substituents beta;
said substituents alpha are selected from the group consisting of halogen atoms, alkyl groups having from 1 to 4 carbon atoms, alkoxy groups having from 1 to 4 carbon atoms, haloalkyl groups having from 1 to 4 carbon atoms, haloalkoxy groups having from 1 to 4 carbon atoms, cyano groups, alkynyl groups having from 2 to 6 carbon atoms, alkanoyl groups having from 1 to 5 carbon atoms, cycloalkyl groups having from 3 to 7 ring atoms, heteroaryl groups, aryl groups, aralkoxy groups having from 7 to 10 carbon atoms, arylcarbonyl groups, two adjacent alpha groups are optionally joined together to form an alkylene or an alkenylene chain having 3 or 4 carbon atoms, aminocarbonyl groups, alkenyl groups having from 2 to 5 carbon atoms, alkylthio groups having from 1 to 4 carbon atoms, aminosulfinyl groups, aminosulfonfyl groups, hydroxy groups, hydroxyalkyl groups having from 1 to 4 carbon atoms, nitro groups, amino groups, carboxy groups, alkoxy carbonyl groups having from 2 to 5 carbon atoms, alkoxyalkyl groups having from 1 to 4 carbon atoms, alkylsulfonyl groups having from 1 to 4 carbon atoms, alkanoylamino groups having from 1 to 4 carbon atoms, alkanoyl (alkyl) amino groups having from 1 to 6 carbon atoms, alkanoy-
laminoalkyl groups having from 1 to 6 carbon atoms in both the alkanoyl and alkyl part, alkanoyl (alkyl) aminoalkyl groups having from 1 to 6 carbon atoms in both the alkanoyl and each alkyl part, alkylsulfonylamino groups having from 1 to 4 carbon atoms, mono- or di-alkylaminocarbonyl groups having from 1 to 6 carbon atoms, mono- or di-alkylaminosulfanyl groups having from 1 to 6 carbon atoms, mono- or di-alkylaminosulfonyl groups having from 1 to 6 carbon atoms, aminalkyl groups having from 1 to 4 carbon atoms, mono- or di-alkylamino groups having from 1 to 6 carbon atoms, mono- or di-alkylaminoalkyl groups having from 1 to 6 carbon atoms in each alkyl part, aralkyl groups having from 7 to 10 carbon atoms, heteroarylatedalkyl groups having from 1 to 4 carbon atoms in the alkyl part, heteroarylatedkoxy groups having from 1 to 4 carbon atoms in the alkoxy part and alkylsulfonylamino groups having from 1 to 4 carbon atoms;

said substituents beta are selected from the group consisting of halogen atoms, alkyl groups having from 1 to 4 carbon atoms, alkoxy groups having from 1 to 4 carbon atoms, haloalkyl groups having from 1 to 4 carbon atoms, haloalkoxy groups having from 1 to 4 carbon atoms and cyano groups;

W is a pharmaceutically acceptable ester prodrug group; with the proviso R\(^1\) and R\(^2\) do not represent a hydrogen atom simultaneously.

[0054] In the compounds of Formula (II),

B preferably represents an aryl or heteroaryl group such as phenyl, naphthyl, pyridyl, quinolyl or isoquinolyl. B is preferably unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents alpha; said substituents alpha are selected from the group consisting halogen atoms (e. g. fluoro, chloro), alkyl groups having from 1 to 4 carbon atoms (e. g. methyl, ethyl), alkoxy groups having from 1 to 4 carbon atoms (e. g. methoxy), haloalkoxy groups having from 1 to 4 carbon atoms (e. g. trifluoromethoxy), cyano groups, alkynyl groups having from 2 to 6 carbon atoms (e. g. ethynyl), alkanoyl groups having from 1 to 5 carbon atoms (e. g. acetyl), cycloalkyl groups having from 3 to 7 ring atoms (e. g. cyclopentyl), heteroaryl groups (e. g. 2-, 3- or 4-pyridyl, 1-methylimidazol-2-yl, thiazol-2-yl, 2-methylthiazol-4-yl), aryl groups (e. g. phenyl), aralkoxy groups having from 7 to 10 carbon atoms (e. g. benzoxyl), arylcarbonyl groups (e. g. benzyol), two adjacent alpha groups are optionally joined together to form an alkylene chain having 3 carbon atoms, alkylthio groups having from 1 to 4 carbon atoms (e. g. methylthio) and di-alkylaminoalkyl groups having from 1 to 6 carbon atoms in the alkyl part; said heteroaryl groups referred to in the definitions of alpha are unsubstituted or are substituted by alkyl groups having from 1 to 4 carbon atoms (e. g. methyl). In the definition of B, aryl is preferably phenyl or naphthyl and heteroaryl is a 5- to 10-membered aromatic heterocyclic group containing either from 1 to 3 nitrogen het-
eroatoms, or 1 or 2 nitrogen heteroatoms and/or 1 oxygen or 1 sulphur heteroatom.

More preferably B represents a phenyl group optionally substituted by substituent selected from the group consisting of substituents alpha; said substituents alpha are selected from the group consisting of halogen atoms (e.g. fluoro, chloro), alkyl groups having from 1 to 4 carbon atoms (e.g. methyl, ethyl), alkoxy groups having from 1 to 4 carbon atoms (e.g. methoxy), haloalkoxy groups having from 1 to 4 carbon atoms (e.g. trifluoromethoxy), cyano groups, alkynyl groups having from 2 to 6 carbon atoms (e.g. ethynyl), alkanoyl groups having from 1 to 4 carbon atoms (e.g. acetyl), cycloalkyl groups having from 3 to 7 ring atoms (e.g. cyclopentyl), alkylthio groups having from 1 to 4 carbon atoms (e.g. methylthio), di-alkylaminoalkyl groups having from 1 to 6 carbon atoms in the alkyl part, thiazolyl groups, isothiazolyl groups, oxazolyl groups, isoxazolyl groups, imidazolyl groups, pyridyl groups, benzyloxy groups, phenyl groups or benzoyl groups; said thiazolyl groups, isothiazolyl groups, oxazolyl groups, isoxazolyl groups, imidazolyl groups and pyridyl groups referred to in the definitions of alpha are unsubstituted or are substituted by alkyl groups having from 1 to 4 carbon atoms. More preferably B represents a phenyl group optionally substituted by substituent selected from the group consisting of substituents alpha; said substituents alpha are selected from the group consisting of fluorine atoms, chlorine atoms, methyl groups, ethyl groups, methoxy groups, trifluoromethoxy groups, cyano groups, ethynyl groups, acetyl groups, alkylthio groups, dimethylaminoethyl groups, phenyl groups, imidazolyl groups optionally substituted by methyl groups, thiazolyl groups optionally substituted by methyl groups, pyridyl groups or benzyloxy groups. More preferably, B represents a phenyl group substituted by 1 or 2 fluoro or chloro substituents. More preferably, B represents a phenyl group substituted by 1 fluoro or chloro substituent.

Most preferably, B represents 3-fluorophenyl.

In the compounds of Formula (II),

X preferably represents a methylene group or an oxygen atom. More preferably, X represents an oxygen atom.

In the compounds of Formula (II),

preferably, \( R^1 \) and \( R^2 \) independently represent a hydrogen atom, a fluorine atom, a chlorine atom, trifluoromethyl, cyano or aminocarbonyl. More preferably, \( R^1 \) represents a halogen atom (e.g. fluoro, chloro) and \( R^2 \) represents a hydrogen atom.

In the compounds of Formula (II),

preferably, \( R^3 \) and \( R^4 \) independently represent a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms (e.g. methyl, ethyl). More preferably \( R^3 \) represents an alkyl group having from 1 to 4 carbon atoms (e.g. methyl, ethyl) and \( R^4 \) represents a hydrogen atom. Most preferably \( R^3 \) represents a methyl group and \( R^4 \) represents a
hydrogen atom.

In the compounds of Formula (II),
R\textsuperscript{5} preferably represents -C\textsubscript{0}\textsubscript{2}H,
[Chem.12]

; and R\textsuperscript{6} preferably represents an aryl group optionally substituted by halogen atoms or is a heteroaryl group. More preferably, R\textsuperscript{5} represents -C\textsubscript{0}\textsubscript{2}H,
[Chem.13]

and R\textsuperscript{6} represents an aryl group optionally substituted by halogen atoms. More preferably R\textsuperscript{6} represents methyl, cyclohexyl, phenyl group optionally substituted by halogen atoms (such as 2-, 3- or 4-chlorophenyl, 3-fluorophenyl), 3-methylphenyl, 3-methoxyphenyl or 5-methyl-2-pyridyl. Further more preferably R\textsuperscript{5} represents -C\textsubscript{0}\textsubscript{2}H or
[Chem.14]

Most preferably R\textsuperscript{5} represents -C\textsubscript{0}\textsubscript{2}H.

Particularly preferred compounds of the invention include those in which each variable in Formula (II) is selected from the preferred groups for each variable.

Even more preferable compounds of the invention include those where each variable in Formula (II) is selected from the more preferred groups for each variable.
A preferred individual compound of Formula (II) is selected from:

- 4-((lS)-l-{{5-chloro-2-(4-fluorophenoxy)benzoyl]amino} ethyl) benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(4-fluorophenoxy) pyridin-3-yl carbonyl] amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-cyanophenoxy) pyridin-3-yl] carbonyl] amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy) pyridin-3-yl] carbonyl] amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-chlorophenoxy)pyridin-3-yl] carbonyl] amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-chlorophenoxy) benzoyl] amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
- 4-((IS)-l-{{5-chloro-2-(3-fluorophenoxy)benzoyl]amino} ethyl] benzoic acid;
benzoic acid; 4-[(lS)-l-([5-chloro-2-(3-pyridin-2-ylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(4-pyridin-2-ylphenoxy)pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid; 4- [ (lS)-l-([5-chloro-2-(4-pyridin-4-ylphenoxy)pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid; 4- [(lS)-l- ([5-chloro-2-(3-chloro-5-methylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(3-pyridin-2-ylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(4-pyridin-2-ylphenoxy)pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid; 4- [(lS)-l- ([5-chloro-2-(3-chloro-5-methylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(3-pyridin-2-ylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(4-pyridin-2-ylphenoxy)pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid; 4- [(lS)-l- ([5-chloro-2-(3-chloro-5-methylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(3-pyridin-2-ylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(4-pyridin-2-ylphenoxy)pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid; 4- [(lS)-l- ([5-chloro-2-(3-chloro-5-methylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(3-pyridin-2-ylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(4-pyridin-2-ylphenoxy)pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid; 4- [(lS)-l- ([5-chloro-2-(3-chloro-5-methylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(3-pyridin-2-ylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(4-pyridin-2-ylphenoxy)pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid; 4- [(lS)-l- ([5-chloro-2-(3-chloro-5-methylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(3-pyridin-2-ylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(4-pyridin-2-ylphenoxy)pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid; 4- [(lS)-l- ([5-chloro-2-(3-chloro-5-methylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(3-pyridin-2-ylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(4-pyridin-2-ylphenoxy)pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid; 4- [(lS)-l- ([5-chloro-2-(3-chloro-5-methylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-[(lS)-l-([5-chloro-2-(3-pyridin-2-ylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
A further preferred individual compound of Formula (II) is selected from
4-((lS)-l-([5-chloro-2-(4-fluorophenoxy)pyridin-3-yl] carbonyl) amino) ethyl) benzoic acid;
4-((lS)-l-([5-chloro-2-(4-fluorophenoxy)pyridin-3-yl] carbonyl) amino) ethyl) benzoic acid; 4- [(lS)-l- ([5-chloro-2-(3-chloro-5-methylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-((lS)-l-([5-chloro-2-(4-fluorophenoxy)pyridin-3-yl] carbonyl) amino) ethyl) benzoic acid; 4- [(lS)-l- ([5-chloro-2-(3-chloro-5-methylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-((lS)-l-([5-chloro-2-(4-fluorophenoxy)pyridin-3-yl] carbonyl) amino) ethyl) benzoic acid; 4- [(lS)-l- ([5-chloro-2-(3-chloro-5-methylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-((lS)-l-([5-chloro-2-(4-fluorophenoxy)pyridin-3-yl] carbonyl) amino) ethyl) benzoic acid; 4- [(lS)-l- ([5-chloro-2-(3-chloro-5-methylphenoxy) pyridin-3-yl] carbonyl) amino) ethyl] benzoic acid;
4-

In another preferred aspect, the EP4 receptor ligand (antagonist), which is disclosed in WO 05/105732, is substituted methyl aryl or heteroaryl amide compounds of the following Formula (III)

\[
\text{[Chem.15]}
\]

wherein X represents -CH- or a nitrogen atom;
Y represents -NR^4, an oxygen atom or a sulfur atom;
R^4 represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms;
Z represents a hydrogen atom or a halogen atom;
R^1 represents an alkyl group having from 1 to 6 carbon atoms optionally substituted with an alkoxy group having from 1 to 6 carbon atoms or a cycloalkyl group having from 3 to 7 carbon atoms; a cycloalkyl group having from 3 to 7 carbon atoms optionally substituted with an alkyl group having from 1 to 3 carbon atoms; a phenyl
group optionally substituted with one or more substituents alpha; or a group Het\(^1\) optionally substituted with one or more substituents alpha;
Het\(^1\) represents a heterocyclic group having from 4 to 7 ring atoms which contains either from 1 to 4 nitrogen ring heteroatoms or from 0 to 2 nitrogen ring heteroatoms and 1 oxygen or 1 sulfur ring heteroatom;
R\(^2\) and R\(^3\) independently represent a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms; or R\(^2\) and R\(^3\) together form an alkylene chain having from 3 to 6 carbon atoms; and
said substituent alpha is selected from the group consisting of halogen atoms, alkyl groups having from 1 to 4 carbon atoms, haloalkyl groups having from 1 to 4 carbon atoms, hydroxy groups, alkoxy groups having from 1 to 4 carbon atoms, haloalkoxy groups having from 1 to 4 carbon atoms, cyano groups, hydroxy alkyl groups having from 1 to 4 carbon atoms, alkoxyalkyl groups having from 1 to 4 carbon atoms in alkoxy and alkyl groups, alkylsulfonyl groups having from 1 to 4 carbon atoms, alkanoyl groups having from 2 to 5 carbon atoms, alkenyl groups having from 2 to 4 carbon atoms, alkynyl groups having from 2 to 4 carbon atoms, alkylthio groups having from 1 to 4 carbon atoms, nitro groups, amino groups, mono- or di-alkylamino groups having from 1 to 4 carbon atoms, aminosulfonyl groups, alkoxy carbonyl groups having from 1 to 4 carbon atoms, alkylsulfonylamino groups having from 1 to 4 carbon atoms, cycloalkyl groups having from 3 to 7 carbon atoms and a mono- or di-alkylaminocarbonyl groups having from 1 to 6 carbon atoms;
or a pharmaceutically acceptable ester of such compound;
or a pharmaceutically acceptable salt thereof.

[0065] In the compounds of Formula (III),
Y preferably represents NR\(^4\) or an oxygen atom; and R\(^4\) represents an alkyl group having from 1 to 3 carbon atoms. More preferably, Y represents NCH\(_3\) or an oxygen atom. Most preferably, Y represents an oxygen atom.

[0066] In the compounds of Formula (III),
Z preferably represents a halogen atom. More preferably, Z represents a chlorine atom or a fluorine atom.

[0067] In the compounds of Formula (III),
R\(^1\) preferably represents an alkyl group having from 1 to 6 carbon atoms; a cycloalkyl group having from 3 to 7 carbon atoms, a phenyl group optionally substituted with one or more substituents alpha; or a group Het\(^1\) optionally substituted with one or more substituents alpha;
Het\(^1\) represents a heterocyclic group having from 5 to 6 ring atoms which contains either from 1 to 2 nitrogen ring heteroatoms or from 0 to 2 nitrogen ring heteroatoms and 1 oxygen or 1 sulfur ring heteroatom; said substituents alpha are selected from the
group consisting of halogen atoms, alkyl groups having from 1 to 4 carbon atoms, haloalkyl groups having from 1 to 4 carbon atoms, haloalkoxy groups having from 1 to 4 carbon atoms, cyano groups, hydroxy alkyl groups having from 1 to 4 carbon atoms, alkoxyalkyl groups having from 1 to 4 carbon atoms in alkoxy and alky groups, alkylsulfonyl groups having from 1 to 4 carbon atoms and alkanoyl groups having from 2 to 5 carbon atoms.

More preferably, $R^1$ represents an alkyl group having from 1 to 6 carbon atoms, a cycloalkyl group having from 4 to 6 carbon atoms, a phenyl group, a pyridyl group, an oxazolyl group, a pyrazolyl group, a thiazolyl group, a tetrahydrofuranyl group or a tetrahydropyranyl group; said phenyl group, pyridyl group, oxazolyl group, pyrazolyl group, thiazolyl group, tetrahydrofuranyl group and tetrahydropyranyl group referred to in the definitions of $R^1$ are un-substituted or are substituted by at least one substituent selected from the group consisting of substituents alpha; said substituents alpha are selected from the group consisting of halogen atoms, alkyl groups having from 1 to 2 carbon atoms and cyano groups.

More preferably, $R^1$ represents a butyl group, a pyridyl group, a phenyl group, an oxazolyl group, a pyrazolyl group or a thiazolyl group; said phenyl group, pyridyl group, oxazolyl group, pyrazolyl group, thiazolyl group referred to in the definitions of $R^1$ are un-substituted or are substituted by 1 to 2 substituent selected from the group consisting of substituents alpha; said substituents alpha are selected from the group consisting of halogen atoms and alkyl groups having from 1 to 2 carbon atoms.

Most preferably, $R^1$ represents a phenyl group, optionally substituted by 1 to 2 groups independently selected from a fluorine atom, a chlorine atom and a methyl group.

[0068] In the compounds of Formula (III),

preferably, $R^2$ and $R^3$ independently represent a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms. More preferably, $R^2$ represents a hydrogen atom; and $R^3$ represents a methyl group.

[0069] Particularly preferred compounds of the invention include those in which each variable in Formula (III) is selected from the preferred groups for each variable. Even more preferable compounds of the invention include those where each variable in Formula (III) is selected from the more preferred groups for each variable.

[0070] A preferred individual compound of Formula (III) is selected from

4-[(1S)-1-{(5-Chloro-2-[(4-chlorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[(1S)-1-{(5-Chloro-2-[(4-methylphenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[(1S)-1-{(5-Chloro-2-[(3-chlorophenoxy)methyl]benzoyl}amino)ethyl]benzoic
acid;
4-[(IS)-1-([(5-Chloro-2-[(4-fluorophenoxy)methyl]benzoyl]amino)ethyl]benzoic acid;
4-[(IS)-1-([(5-Chloro-2-[(2,3-difluorophenoxy)methyl]benzoyl]amino)ethyl]benzoic acid;
4-[(IS)-1-([(5-Chloro-2-[(3,4-difluorophenoxy)methyl]benzoyl]amino)ethyl]benzoic acid;
4-[(IS)-1-([(5-Chloro-2-[(2,4-difluorophenoxy)methyl]benzoyl]amino)ethyl]benzoic acid;
4-[(IS)-1-([(5-Chloro-2-[(3-chlorophenoxy)methyl]pyridin-3-yl]carbonyl)amino]ethyl]benzoic acid;
4-[(IS)-1-([(5-Chloro-2-[(2-chlorophenoxy)methyl]benzoyl]amino)ethyl]benzoic acid;
4-[(IS)-1-([(5-Chloro-2-[(3,5-difluorophenoxy)methyl]benzoyl]amino)ethyl]benzoic acid;
4-[(IS)-1-([(5-Chloro-2-[(4-chlorophenoxy)methyl]pyridin-3-yl]carbonyl)amino]ethyl]benzoic acid;
4-[(IS)-1-([(5-Chloro-2-[(3-fluorophenoxy)methyl]benzoyl]amino)ethyl]benzoic acid;
4-[(IS)-1-([(5-Chloro-2-[(2,6-difluorophenoxy)methyl]benzoyl]amino)ethyl]benzoic acid;
4-[(IS)-1-([(5-Chloro-2-[(2-fluorophenoxy)methyl]benzoyl]amino)ethyl]benzoic acid;
4-[(IS)-1-([(5-Chloro-2-[(2,5-difluorophenoxy)methyl]benzoyl]amino)ethyl]benzoic acid; and
4-[(IS)-1-([(2-[(4-Chlorophenoxy)methyl]-5-fluoropyridin-3-yl]carbonyl)amino]ethyl]benzoic acid;

or a pharmaceutically acceptable ester of such compound;
or a pharmaceutically acceptable salt thereof.

[0071] In another preferred aspect, the EP4 receptor ligand (antagonist), which is disclosed in WO 2004/067524, is a compound of the following Formula (IV) or a pharmaceutically acceptable salt thereof.

[Chem.16]

![Formula IV](image)

[0072] A more preferred compound of Formula (IV) is sodium
In another preferred aspect, the EP4 receptor ligand (antagonist), which is disclosed in Marc Blouin et al., J. Med. Chem. (DOI 10.1021/jm901771h) and WO2008/017164, is a compound of the following Formula (Va) or (Vb), or a pharmaceutically acceptable salt thereof:

(4-((4-(5-methoxypyridin-2-yl)phenoxy)methyl)-5-methylfuran-2-carbonyl)(o-tolylsulfonyl)amide.

[0073]

[Chem. 17]

(Va)

or

[Chem. 18]

(Vb)

wherein X and Y are independently selected from the group consisting of: N and C(R¹)
¹), wherein each R¹ is independently selected from the group consisting of: hydrogen, halo and C₁₋₅ alkyl;

B is selected from the group consisting of: -C(R³)(R⁶)-, -0-, -S-, -S(O)-, -SO₂-, -C(R⁵)
⁵)(R⁶)-C(R⁷)(R⁸)-, -0-C(R ⁵)(R⁶)-, -S-C(R ⁵)(R⁶)-, -S(0)-C(R ⁵)(R⁶)- and -SO₂-C(R ³)(R⁶)-;
C is selected from the group consisting of aryl and heteroaryl, or a fused analog of aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from R^10;
E is selected from the group consisting of: -C(0)OH, -C(0)OCi_alkyl, tetrazolyl and

\[
\begin{align*}
\text{[Chem.19]} \\
\end{align*}
\]

wherein R is selected from the group consisting of: Ci_alkyl, aryl and heteroaryl, or a fused analog of aryl or heteroaryl, wherein aryl and heteroaryl or the fused analogs thereof are optionally substituted with one to three substituents independently selected from R^10;
R^1 to R^8 are independently selected from the group consisting of: H, halo, -O-R^12, Ci_6 alkyl and C_3-C_6 cycloalkyl, and one or more pairs of R^1 and R^2, R^5 and R^6, and R^7 and R^8 may be joined together with the carbon atom to which they are attached to form a 3- to 5-membered monocyclic cycloalkyl ring, and R^5 and R^6 or R^7 and R^8 may be joined together to form carbonyl;
R^8 is independently selected from the group consisting of: halo, hydroxyl and Ci_alkyl;
R^10 is selected from the group consisting of: halo, cyano, Ci_alkyl, CI_4 fluoroalkyl, CI_alkoxy, CI_thioalkoxy and CI_fluoroalkoxy; and
each R^12 is selected from the group consisting of: H, CI_alkyl, C_3-C_6 cycloalkyl and heterocyclyl.

[0074] A preferred individual compound of Formula (Va) or (Vb), is selected from
5-chloro-3-[(3-chlorophenyl)methyl]-N- [1- [4-(2H-tetrazol-5-yl)phenyl]ethyl]-2-thiophenecarboxamide,
2,5-dimethyl-N- [[(IS)-1- [4- [((methylsulfonyl)amino] carbonyl] phenyl] ethyl]-4- [[4-(tri fluoromethyl)phenyl] methyl]-3-thiophenecarboxamide,
2,5-dimethyl-N- [[(IS)-1- [4- [((phenylsulfonyl)amino] carbonyl] phenyl] ethyl]-4- [[4-(tri fluoromethyl)phenyl] methyl]-3-thiophenecarboxamide,
2,5-dimethyl-N- [1- [4- (2H-tetrazol-5-yl) phenyl] cyclopropyl]-4- [[3-(trifluoromethyl) phenyl] methyl]-3-thiophenecarboxamide,
2,5-dimethyl-N- [1- [4- (2H-tetrazol-5-yl) phenyl] cyclopropyl]-4- [[4-(trifluoromethyl) phenyl] methyl]-3-thiophenecarboxamide,
2-chloro-4- [[[(3-chlorophenyl) methyl]-2,5-dimethyl-3-thienyl] carbonyl] amino] methyl]-benzoic acid,
4-[(IR)-1-[[2,5-dichloro-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dibromo-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dichloro-4-(3-chlorobenzoyl)-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dichloro-4-[(3-chlorophenyl)((tetrahydro-2H-pyran-2-yl)oxy)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dichloro-4-[(3-chlorophenyl)hydroxymethyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dichloro-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dichloro-4-[[3-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dimethyl-4-[[3-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dimethyl-4-[[4-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dimethyl-4-[[4-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[4-[(3-chlorophenyl)methyl]-2,5-dimethyl-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[5-bromo-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[[[2,5-dichloro-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]methyl]-benzoic acid,
4-[[2,5-dimethyl-4-[[3-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]cyclopropyl]-benzoic acid,
4-[[[5-chloro-3-[(3-chlorophenyl)methyl]-2-thienyl]carbonyl]amino]ethyl]-benzoic acid,
and
4-[(2,5-dimethyl-4-[(4-trifluoromethyl)benzyl]-3-thienyl]carbonyl]amino]cyclopropyl]-benzoic acid.

A preferred compound of this invention is selected from:
3-[2-(4-{2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl}phenyl]ethyl]-l-[(4-methylbenzene)sulfonyl]urea;
3- [2- (4- {2-ethyl-4,6-dimethyl-lH-imidazo[4,5-c]pyridin-1-yl}phenyl)ethyl] - 1- [(4-methylbenzene)sulfonyl]urea;  
1 - [2 - {4- (5-acetyl-2-ethyl-1H-1,3-benzodiazol-1-yl)phenyl}ethyl ]; 3- [4-methylbenzene]sulfonylurea;  
3- [2- (4- (2-ethyl-5-methoxy-1H-1,3-benzodiazol-1-yl)phenyl)ethyl ] - 1- [(4-methylbenzene)sulfonyl]urea;  
2- [4- {6-chloro-2-ethyl-5- (trifluoromethyl)- lH-1,3-benzodiazol-1-yl}phenyl]ethyl N- [(4-methylbenzene)sulfonyl]carbamate;  
3- [2- [4- (6-chloro-5-cyano-2-ethyl-1H-1,3-benzodiazol-1-yl)phenyl]ethyl ] - 1- [(4-methylbenzene) sulfonyl]urea;  
2- (2- {4- (2-ethyl-4,6-dimethyl-IH-imidazo[4,5-c]pyridin-1-yl)phenyl}ethyl N- [(4-methylbenzene)sulfonyl] carbamate;  
2- (2- {4- (2-tert-butyl-4,6-dimethyl-IH-imidazo[4,5-c]pyridin-1-yl)phenyl}ethyl N- [(4-methylbenzene)sulfonyl] carbamate;  
2- [4- (5-carbamoyl-6-chloro-2-ethyl- lH-1,3-benzodiazol-1-yl)phenyl]ethyl N- [(4-methylbenzene) sulfonyl]carbamate;  
1- (2- {4- [2-ethyl-5-(1-hydroxyethyl)-1H-1,3-benzodiazol-1-yl]phenyl }ethyl)-3- [(4-methylbenzene) sulfonyl]urea;  
1- (2- {4- [6-chloro-2-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)- lH-1,3-benzodiazol-1-yl]phenyl}ethyl)-3- [(4-methylbenzene)sulfonyl]urea;  
2- [4- {6-chloro-2-(pyridin-2-yl)-5- (trifluoromethyl)- lH-1,3-benzodiazol-1-yl}phenyl]ethyl N- [(4-methylbenzene)sulfonyl]carbamate;  
3- [2- [5- {6-chloro-2-ethyl-5-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]pyridin-2-yl]ethyl]- 1- [(4-methylbenzene)sulfonyl]urea;  
2- [4- {6-chloro-2-ethyl-5-(trifluoromethyl)- lH-1,3-benzodiazol-1-yl]phenyl}ethyl N- [(2-chlorobenzene)sulfonyl]carbamate;  
3- [2- [4- [5,7-dimethyl-2-(methylamino)-3H-imidazo[4,5-b]pyridin-3-yl]phenyl]ethyl]- 1- [(4-methylbenzene)sulfonyl]urea;  
4- ([IS]-1- {{5-chloro-2-(4-fluorophenoxy)benzoyl}amino}ethyl)benzoic acid;  
4- ([IS]-1- {{5-chloro-2-(4-fluorophenoxy)pyridin-3-yl}carbonyl}amino)ethyl]benzoic acid;  
4- ([IS]-1- {{5-chloro-2-(3-cyanophenoxy)pyridin-3-yl}carbonyl}amino)ethyl]benzoic acid;  
4- ([IS]-1- {{5-chloro-2-(3-fluorophenoxy)pyridin-3-yl}carbonyl}amino)ethyl]benzoic acid;  
4- ([IS]-1- {{5-chloro-2-(3-chlorophenoxy)pyridin-3-yl}carbonyl}arnino)ethyl]benzoic acid;  
4- ([IS]-1- {{5-chloro-2-(3-fluorophenoxy)benzoyl}amino}ethyl)benzoic acid;
4-((lS)-l-{(5-chloro-2-(3-chlorophenoxy)benzoyl)amino}ethyl)benzoic acid;
4-((lS)-l-{{5-chloro-2-(2-chloro-4-fluorophenoxy)pyridin-3-yl}carbonyl}amino)ethyl]
benzoic acid;
4-((lS)-l-{{5-chloro-2-(3,4-difluorophenoxy)pyridin-3-yl}carbonyl}amino)ethyl]benzoic
acid;
4-((lS)-l-{{5-chloro-2-(2,3-difluorophenoxy)pyridin-3-yl}carbonyl}amino)ethyl]benzoic
acid;
4-((lS)-l-{{5-chloro-2-(2,3-difluorophenoxy)benzoyl}amino}ethyl)benzoic acid;
4-((lS)-l-{{5-chloro-2-(3,4-difluorophenoxy)benzoyl}amino}ethyl)benzoic acid;
4-((lS)-l-{{5-chloro-2-(3-chloro-5-fluorophenoxy)pyridin-3-yl}carbonyl}amino)ethyl]benzoic
acid;
4-((lS)-l-{{5-chloro-2-[(4-chlorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-l-{{5-chloro-2-[(3-chlorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[(4-fluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[(3,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[(2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;
4-((lS)-1-{{5-chloro-2-[2,4-difluorophenoxy)methyl]benzoyl}amino}ethyl)benzoic acid;

[0076] Those skilled in the art will fully understand the terms used herein in the description and the appendant claims to describe the present invention. Nonetheless, unless otherwise provided herein, the following terms are as described immediately below.

[0077] The term "cartilage disease", as used herein, means diseases associated with destruction, damage or injury of articular cartilage. Examples of such cartilage disease include osteoarthritis, rheumatoid arthritis and arthritis/inflammation associated with
cartilage degradation and the like.

[0078] By "EP4 receptor antagonist" is meant a chemical substance that reduces or attenuates the biological activity of an EP4 receptor. Such antagonists may include proteins such as anti-EP4 antibodies, nucleic acids, amino acids, peptides, carbohydrates, small molecules (organic or inorganic), or any other compound or composition which decreases the activity of an EP4 receptor either by reducing the amount of EP4 receptor present in a cell, or by decreasing the binding or signaling activity of the EP4 receptor.

[0079] The term "alkyl", as used herein, means a straight or branched saturated monovalent hydrocarbon radical including, but not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, neopentyl and the like.

[0080] The term "alkenyl", as used herein, means a hydrocarbon radical having at least one double bond including, but not limited to, ethenyl, propenyl, 1-butenyl, 2-butenyl and the like.

[0081] The term "alkynyl", as used herein, means a hydrocarbon radical having at least one triple bond including, but not limited to, ethynyl, propynyl, 1-butylnyl, 2-butylnyl and the like.

[0082] The term "halo", as used herein, refers to F, Cl, Br or I, preferably F or Cl.

[0083] The term "cycloalkyl", as used herein, means a saturated carbocyclic radical including, but not limited to, cyclopropyl, cyclobutyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like.

[0084] The term "alkoxy", as used herein, means an O-alkyl group wherein "alkyl" is defined above.

[0085] The term "monocyclic aromatic ring", as used herein, means a monocyclic aromatic carbocyclic or heterocyclic ring (and containing 0-4 heteroatoms selected from O, N and S) including, but not limited to, phenyl, pyrazolyl, furyl, thiophenyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyrrolyl, thiophenyl, pyrazinyl, pyridazinyl, isooxazolyl, isothiazolyl, triazolyl, furazanyl and the like.

[0086] The term "bicyclic aromatic ring", as used herein, means a monocyclic or bicyclic aromatic carbocyclic or heterocyclic ring (and containing 0-4 heteroatoms selected from O, N and S) including, but not limited to, naphthyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, indolyl, isoindolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl and the like.

[0087] The term "alkylene", as used herein, means a saturated hydrocarbon (straight chain or branched) wherein a hydrogen atom is removed from each of the terminal carbons such as methylene, ethylene, propylene, butylene, pentylene, hexylene and the like.
The term "cycloalkylene", as used herein, means divalent cycloalkyl groups including, but not limited to, cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene and cycloheptylene and the like.

The term "alkenylene", as used herein, means a straight or branched hydrocarbon chain spacer radical having at least one double bond including, but not limited to, -CH=CH-, -CH=CHCH₂-, -CH=CH(CH₃)₂- and the like.

The term "alkynylene", as used herein, means a straight or branched hydrocarbon chain spacer radical having at least one triple bond including, but not limited to,

\[-\text{CH}=-\text{CH}=-\text{CH}-\]

and the like.

The term "two adjacent L groups are optionally joined together to form an alkylene chain having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms", as used herein, means, but not limited to, -0-CH₂-0-, -CH₂=0-CH₂-, -CH₂=0-CH₂-, -CH₂=0-CH₂-, -CH₂=0-CH₂-, -0-CH₂=0-CH₂-, -CH₂=0-CH₂-, -CH₂=0-CH₂-, and the like.

The term "aryl", as used herein, means aromatic radicals including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl and the like.

The term "protecting group", as used herein, means a hydroxy or amino protecting group which is selected from typical hydroxy or amino protecting groups described in Protective Groups in Organic Synthesis edited by T. W. Greene et al. (John Wiley & Sons, 1991).

The term "ester prodrug group" means a protecting group which can be cleaved in vivo by a biological method such as hydrolysis and forms a free acid or salt thereof. Whether a compound is such a derivative or not can be determined by administering it by intravenous injection to an experimental animal, such as a rat or mouse, and then studying the body fluids of the animal to determine whether or not the compound or a pharmaceutically acceptable salt thereof can be detected.

Preferred examples of groups for an ester of a carboxyl group or a hydroxy group include: (1) aliphatic alkanoyl groups, for example: alkanoyl groups such as the formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, nonanoyl, decanoyl, 3-methylnonanoyl, 8-methylnonanoyl, 3-ethyloctanoyl, 3,7-dimethyloctanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, 1-methylpentadecanoyl, 14-methylpentadecanoyl, 13,13-dimethyltetradecanoyl, heptadecanoyl, 15-methylhexadecanoyl, octadecanoyl, 1-methylheptadecanoyl, nonadecanoyl, icosanoyl and henticosanoyl groups; halogenated alkylcarbonyl groups such as the chloroacetyl, dichloroacetyl,
trichloroacetyl, and trifluoroacetyl groups; alkoxyalkanoyl groups such as the methoxyacetyl group; and unsaturated alkanoyl groups such as the acryloyl, propioloyl, methacryloyl, crotonoyl, isocrotonoyl and (E)-2-methyl-2-butenoyl groups; (2) aromatic alkanoyl groups, for example: arylcarbonyl groups such as the benzoyl, alpha-naphthoyl and beta-naphthoyl groups; halogenated arylcarbonyl groups such as the 2-bromobenzoyle and 4-chlorobenzoyle groups; alkylated arylcarbonyl groups such as the 2,4,6-trimethylbenzoyl and 4-toluoyl groups; alkoxylated aryl-carbonyl groups such as the 4-anisoyl group; nitrated arylcarbonyl groups such as the 4-nitrobenzoyl and 2-nitrobenzoyl groups; alkoxy carbonylated arylcarbonyl groups such as the 2-(methoxycarbonyl)benzoyl group; and arylated arylcarbonyl groups such as the 4-phenylbenzoyl group; (3) alkoxy carbonyl groups, for example: alkoxy- carbonyl groups such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butyoxycarbonyl, sec-butoxycarbonyl, t-butoxycarbonyl and isobutoxycarbonyl groups; and halogen- or tri(alkyl)silyl-substituted alkoxy carbonyl groups such as the 2,2,2-trichloroethoxycarbonyl and 2-trimethylsilyl ethoxycarbonyl groups; (4) tetrahydropyryl or tetrahydrothiopyryl groups such as: tetrahydropyran-2-yl, 3-bromotetrahydropyran-2-yl, 4-methoxytetrahydropyran-4-yl, tetrahydrothiopyran-2-yl, and 4-methoxytetrahydrothiopyran-4-yl groups; tetrahydrofuran-2-yl and tetrahydrofuran-2-yl groups; (5) silyl groups, for example: tri(alkyl)silyl groups such as the trimethylsilyl, triethylsilyl, isopropyldimethylsilyl, t-butyldimethylsilyl, methylidisopropylsilyl, methyldi-t-butylsilyl and triisopropylsilyl groups; and silyl groups substituted by one or more aryl and alkyl groups such as the diphenylmethylsilyl, diphenylbutyisilyl, diphenylisopropylsilyl and phenylidiisopropylsilyl groups; (6) alkoxy methyl groups, for example: alkoxy methyl groups such as the methoxymethyl, 1,1-dimethyl-1-methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butyoxymethyl and t-butoxymethyl groups; alkoxylated alkoxy methygly groups such as the 2-methoxyethoxymethyl group; and halo(alkoxy)methyl groups such as the 2,2,2-trichloroethoxymethyl and bis(2-chloroethoxy)methyl groups; (7) substituted ethyl groups, for example: alkoxylated ethyl groups such as the 1-ethoxyethyl and 1-(isopropoxy)ethyl groups; and halogenated ethyl groups such as the 2,2,2-trichloroethyl group; (8) aralkyl groups, for example: alkyl groups substituted by from 1 to 3 aryl groups such as the benzyl, alpha-naphthylmethyl, beta-naphthylmethyl, diphenylmethyl, triphenylmethyl, alpha-naphthyl diphenylmethyl and 9-anthrylmethyl groups; alkyl groups substituted by from 1 to 3 substituted aryl groups, where one or more of the aryl groups are substituted by one or more alkyl, alkoxy, nitro, halogen or cyano substituents such as the 4-methylbenzyl, 2,4,6-trimethylbenzyl, 3,4,5-trimethylbenzyl, 4-methoxybenzyl,
4-methoxyphenyldiphenylmethyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl and 4-cyanobenzyl groups; alkenyloxy carbonyl groups such as the vinylloxy carbonyl; aryloxy carbonyl groups such as phenoxy carbonyl; and aralkyloxy carbonyl groups in which the aryl ring may be substituted by 1 or 2 alkoxy or nitro groups, such as benzyloxy carbonyl, 4-methoxybenzyl oxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl groups.

[0096] The term "treating", as used herein, refers to reversing, recovering, alleviating, inhibiting, or preventing the onset or the progression of the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment" as used herein refers to the act of treating, as "treating" is defined immediately above.

[0097] It has been known that a compound of formula (I), (II), (III), (IV), (Va) or (Vb) exhibits an excellent EP4 antagonistic activities, and that it shows various effects based on the activities. However, it has never been known that a compound of formula (I), (II), (III), (IV), (Va) or (Vb) normalizes the condition of the cartilage lesion by excellent chondroprotective effect, cartilage destruction suppressing effect and anti-catabolic effect on cartilage.

[0098] In this point the present invention is quite different from the above mentioned prior art. Therefore the pharmaceutical composition comprising a compound of formula (I), (II), (III), (IV), (Va) or (Vb) of the present invention is useful for preventing or treating the cartilage disease, that it is especially effective for preventing or treating such disease before sickness reaches bone itself. Therefore the composition can be used not only for treating early stage of a cartilage defect, chronic rheumatoid arthritis and osteoarthritis, but also for preventing these diseases.

[0099] Since a compound of formula (I), (II), (III), (IV), (Va) or (Vb) has potent cartilage destruction suppressing effect, chondroprotective effect, anti-catabolic effect on cartilage, inhibition of matrix metalloprotease(MMP)-mediated type I collagen degradation and MMP-mediated aggrecan degradation, and is more excellent in terms of clinically useful characteristics such as stability, absorption, bioavailability, it can be used for prevention and treatment of a cartilage destruction in a joint in any of various cartilage diseases such as cartilage defect, chronic rheumatoid arthritis involving a cartilage, osteoarthritis involving a cartilage as well as disorders related thereto, in animals (e.g., human, rat, mouse, cat, dog, rabbit, cattle, pig, horse etc.).

[0100] Other features and advantages of the invention will be apparent from the following detailed description and from the claims. While the invention is described in connection with specific embodiments, it will be understood that other changes and modifications that may be practiced are also part of this invention and are also within
the scope of the appendant claims. This application is intended to cover any equivalents, variations, uses, or adaptations of the invention that follow, in general, the principles of the invention, including departures from the present disclosure that come within known or customary practice within the art. All publications mentioned herein are incorporated by reference in their entireties.

[0101] The present invention is directed to the use of an EP4 receptor antagonist in the manufacture of a medicament for the treatment of cartilage diseases.

[0102] Therapeutic Methods

Agents identified as EP4 receptor antagonist are administered in a dose effective to treat cartilage diseases. Such therapeutically effective amounts will be determined using routine optimization techniques that are dependent on the particular condition to be treated, the condition of the patient, the route of administration, the formulation, the judgment of the practitioner, and other factors evident to those skilled in the art in light of this disclosure.

[0103] An agent that inhibits EP4 activity can be incorporated into a therapeutic composition. Such EP4 receptor antagonists can include small molecules, nucleic acids, e.g., EP4 antisense nucleic acids, amino acids, peptides, carbohydrates, and anti-EP4 antibodies. Preferably, such agents are combined with a pharmaceutically acceptable delivery vehicle or carrier. Examples of EP4 antibodies include, for example, polyclonal, monoclonal, humanized, anti-idiotypic, chimeric or single chain antibodies, Fab, F(ab‘)2, and Fab expression library fragments, scFV molecules, and epitope-binding fragments thereof. An antisense oligonucleotide directed to the EP4 gene or mRNA to inhibit its expression is made according to standard techniques (see, e.g., Agrawal et al., Methods in Molecular Biology: Protocols for Oligonucleotides and Analogs, Vol. 20 (1993)).

[0104] As used herein, a pharmaceutically acceptable delivery vehicle includes solvents, dispersion media, coatings, antibacterial and antifungal agents, and isotonic and absorption delaying agents that are compatible with pharmaceutical administration. The vehicle may also include other active or inert components, and/or may be targeted to joint tissue by virtue of its composition.

[0105] A therapeutic composition is formulated to be compatible with its intended route of administration. Non-limiting examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., by ingestion or inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions can be made as described in Remington's Pharmaceutical Sciences, (18th ed., Gennaro, ed., Mack Publishing Co., Easton, PA, (1990)).

[0106] Therapeutic efficacy of such EP4 antagonists can be determined in light of this disclosure by standard therapeutic procedures in cell cultures or experimental animals,
e.g., for determining the ED\textsubscript{50} (the dose therapeutically effective in 50% of the population).

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage may vary depending upon the formulation and the route of administration. For any EP4 antagonist used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC\textsubscript{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

The compound with EP4 antagonistic activity, or a pharmaceutically acceptable salt thereof can be used in combination with one or more additional compounds known to be useful in the treatment or prevention of cartilage disease or the symptoms thereof. Such example includes, but not limited to, NSAIDs, COX-2 inhibitors, steroids, matrix metalloproteinase inhibitors and hyaluronic acid.

The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a mammal including, but not limited to, the severity of the disease or disorder, previous treatments, the general health and/or age of the mammal, and other diseases present. Moreover, treatment of a mammal with a therapeutically effective amount of an EP4 antagonist can include a single treatment or, preferably, can include a series of treatments.

Examples

Comounds list:

3-[2-(4-[2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl]phenyl)ethyl]-l-[(4-methylbenzene)sulfonyl]urea;

3-[2-(4-[2-ethyl-4,6-dimethyl-IH-imidazo[4,5-c]pyridin-1-yl]phenyl)ethyl]-l-[(4-methylbenzene)sulfonyl]urea (Compound A);

1-[2-[4-(5-acetyl-2-ethyl-1H-1,3-benzodiazol-1-yl)phenyl]ethyl]-3-[(4-methylbenzene)sulfonyl]urea;

3-[2-[4-(2-ethyl-5-methoxy-1H-1,3-benzodiazol-1-yl)phenyl]ethyl]-1-[(4-methylbenzene)sulfonyl]urea;

2-[4-[6-chloro-2-ethyl-5-(trifluoromethyl)-IH-1,3-benzodiazol-1-yl]phenyl]ethyl N-[(4-methylbenzene)sulfonyl]carbamate;

3-[2-[4-(6-chloro-5-cyano-2-ethyl-1H-1,3-benzodiazol-1-yl)phenyl]ethyl]-1-[(4-methylbenzene)sulfonyl]urea;

2-(4-[2-ethyl-4,6-dimethyl-IH-imidazo[4,5-c]pyridin-1-yl]phenyl)ethyl N-
[(4-methylbenzene)sulfonyl]carbamate;
2-[(2-tert-butyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl N-
[(4-methylbenzene)sulfonyl]carbamate;
2-[(4-(carbamoyl)-2-chloro-6-ethyl-1H-1,3-benzodiazol-1-yl)phenyl]ethyl N-
[(4-methylbenzene)sulfonyl]carbamate;
1-[(2-[(2-ethyl-5-(1-hydroxyethyl)-1H-1,3-benzodiazol-1-yl]phenyl)ethyl]-3-[(4-methylbenzene)sulfonyl]urea;
1-[(2-[(2-ethyl-5-[6-chloro-2-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]phenyl)ethyl]-3-[(4-methylbenzene)sulfonyl]urea;
2-[(4-[(6-chloro-2-(pyridin-2-yl)-5-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]phenyl)ethyl] N-
[(4-methylbenzene)sulfonyl]carbamate;
3-[(2-[(5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1,3-benzodiazol-1-yl]pyridin-2-yl]ethyl)-1-[(4-methylbenzene)sulfonyl]urea;
2-[(4-[(6-chloro-2-ethyl-5-(trifluoromethyl)-1H,1,3-benzodiazol-1-yl]phenyl)ethyl N-
[(2-chlorobenzene)sulfonyl]carbamate;
3-[(2-[(5,7-dimethyl-2-(methylamino)-3H-imidazo[4,5-b]pyridin-3-yl]phenyl)ethyl]-1-[(4-methylbenzene)sulfonyl]urea;
4-((lS)-1-[[5-chloro-2-(4-fluorophenoxy)benzoyl]amino]ethyl)benzoic acid;
4-((lS)-1-[[5-chloro-2-(4-fluorophenoxy)pyridin-3-yl]carbonyl]amino)ethylbenzoic acid;
4-((lS)-1-[[5-chloro-2-(3-cyanophenoxy)pyridin-3-yl]carbonyl]amino)ethylbenzoic acid;
4-((lS)-1-[[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl]amino)ethylbenzoic acid;
4-((lS)-1-[[5-chloro-2-(3-chlorophenoxy)pyridin-3-yl]carbonyl]amino)ethylbenzoic acid;
4-((lS)-1-[[5-chloro-2-(2-chloro-4-fluorophenoxy)pyridin-3-yl]carbonyl]amino)ethylbenzoic acid;
4-((lS)-1-[[5-chloro-2-(3,4-difluorophenoxy)pyridin-3-yl]carbonyl]amino)ethylbenzoic acid;
4-((lS)-1-[[5-chloro-2-(2,3-difluorophenoxy)pyridin-3-yl]carbonyl]amino)ethylbenzoic acid;
4-((lS)-1-[[5-chloro-2-(3,4-difluorophenoxy)benzoyl]amino]ethyl)benzoic acid;
4-((lS)-1-[[5-chloro-2-(2,3-difluorophenoxy)pyridin-3-yl]carbonyl]amino)ethylbenzoic acid;
4-[(1S)-1-{([5-chloro-2-[(4-chlorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[(1S)-1-{([5-chloro-2-[(3-chlorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[(1S)-1-{([5-chloro-2-[(4-fluorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[(1S)-1-{([5-chloro-2-[(3,4-difluorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[(1S)-1-{([5-chloro-2-[(4-fluorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[(1S)-1-({5-chloro-2-[(3-chlorophenoxy)methyl]pyridin-3-yl}carbonyl)amino]ethyl benzoic acid (Compound C);
4-[(1S)-1-{([5-chloro-2-[(3,5-difluorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[(1S)-1-{([5-chloro-2-[(3-fluorophenoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-[(1S)-1-({5-chloro-2-[(cyclohexylmethoxy)methyl]benzoyl}amino)ethyl]benzoic acid;
4-((4-(5-methoxypyridin-2-yl)phenoxy)methyl)-5-methyl-N-(o-tolylsulfonyl)furan-2-carboxamide (Compound D),
4-1-[(2,5-dimethyl-4-[4-(trifluoromethyl)benzyl]-3-thienyl]carbonyl]amino)cyclopropyl]benzoic acid (Compound E),
5-chloro-3-[(3-chlorophenyl)methyl]-N-[1-[4-(2H-tetrazol-5-yl)phenyl]ethyl]-2-thiophene carboxamide,
2,5-dimethyl-N-[(1S)-1-{4-[(methylsulfonyl)amino]carbonyl]phenyl}ethyl]-4-[(3-(trifluoromethyl)phenyl]methyl]-3-thiophene carboxamide,
2,5-dimethyl-N-[(1S)-1-{4-[(methylsulfonyl)amino]carbonyl]phenyl}ethyl]-4-[(3-(trifluoromethyl)phenyl]methyl]-3-thiophene carboxamide,
2,5-dimethyl-N-[(1S)-1-{4-[(2H-tetrazol-5-yl)phenyl]cyclopropyl}4-[(3-(trifluoromethyl)phenyl]methyl]-3-thiophene carboxamide,
2-chloro-4-[[4-[(3-chlorophenyl)methyl]-2,5-dimethyl-3-thienyl]carbonyl]amino]met hyl]-benzoic acid,
4-[(IR)-1-{{2,5-dichloro-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino}ethyl] -benzoic acid,
4-[(1S)-1-{{2,5-dibromo-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl}amino}ethyl] -benzoic acid,
4-[(1S)-1-{{2,5-dichloro-4-(3-chlorobenzoyl)-3-thienyl]carbonyl}amino}ethyl] -benzoic acid,
4-[(lS)-l-[[2,5-dichloro-4-[(3-chlorophenyl)hydroxymethyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(lS)-l-[[2,5-dichloro-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(lS)-l-[[2,5-dichloro-4-[[3-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(lS)-l-[[2,5-dimethyl-4-[[3-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(lS)-l-[[2,5-dimethyl-4-[[4-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(lS)-l-[[2,5-dimethyl-4-[[4-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(lS)-l-[[2,5-dimethyl-4-[[4-[(3-chlorophenyl)methyl]-2,5-dimethyl-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(lS)-l-[[4-[(3-chlorophenyl)methyl]-2,5-dimethyl-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(lS)-l-[[4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(lS)-l-[[5-bromo-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[[[2,5-dichloro-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]methyl]-benzoic acid,
4-[[[2,5-dimethyl-4-[[3-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]methyl]-benzoic acid,
4-[[[2,5-dimethyl-4-[[4-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]methyl]-benzoic acid,
4-[[5-bromo-4-[(3-chlorophenyl)methyl]-2-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[[5-chloro-3-[(3-chlorophenyl)methyl]-2-thienyl]carbonyl]amino]ethyl]-benzoic acid,

Compound A, Compound B, Compound C, Compound D or Compound E is a representative compound in Formula (I), Formula (II), Formula (III), Formula (IV) and Formula (Va, Vb), respectively.

A compound which has EP4 receptor antagonistic activity can be confirmed by known method (For example, Eur J Pharmacol. 1997: 340: 227-241).

The in vitro assays for assessing EP4 receptor antagonistic activity are typically membrane binding assay and cell-based functional assay. The binding activity of compounds for EP4 receptor was determined with using membrane prepared from HEK293 cells expressing EP4 receptor and radiolabeled ligands PGE2. The antagonistic activity of compounds on the EP4 receptor was determined by using HEK293 cells expressing EP4 receptor and PGE2. The inhibition of the PGE2-evoked
cAMP level by compounds was analyzed.

[0112] Example 1: ex vivo bovine cartilage explant model

The method of this assay is described in the following literature (Rheumatol Int. 2013 Feb;33(2):401-II).

Full-depth cartilage explants were harvested from the knee of either back legs of a cow less than 24 month old. All the FDC explants are divided into different treatment group according to the explants weight and metabolic activity (viability) measured by Alamar Blue. Compounds were freshly added to the explants at each media change. The explants were cultured in serum-free conditions. Supernatants retrieved from the culture were analyzed by biomarkers (P2NP, C2M, AGNx1, AGNx2) at day 7, 14 and 21.

[0113] These results are shown in Fig. 1 and Fig. 2.

[0114] From results of Fig. 1, Compound A and Compound B shows dose-dependent inhibition of cartilage destruction in ex vivo bovine cartilage explant model

[0115] The similar inhibition of cartilage destruction in ex vivo bovine cartilage explant model is shown in Compound C (4-\{1S\}-1-\{5-chloro-2-\{(3-chlorophenoxo)methyl\}pyridin-3-yl\}carbonyl)amino\{\text{ethy} 1\}benzoic acid), Compound D (4-\{(4-\{\text{methoxypyridin-2-yl\}}\text{phenoxy}\}methyl\})-5-methyl-N-(o-tolylsulfonyl)furan-2-carboxamide) and Compound E (4-\{1-\{(2,5-dimethyl-4-\{\text{4-( trifluoromethyl\}}benzyl\}-3-thienyl\}carbonyl)amino\}cyclopropylyl\}benzoic acid).

[0116] The compounds describe in the compounds list are similarly conducted in this cartilage destruction assay. The dose-dependent inhibition of cartilage destruction in ex vivo bovine cartilage explant model is observed in all cases.

^p-cO.0001 versus disease control by ANOVA test.

[0117] Example 2: rat mono-iodoacetate and/or meniscal transection model

The compounds described in the compounds list are conducted in the rat mono-iodoacetate and/or meniscal transection induced osteoarthritis model. These compounds exhibit potent inhibitory activities on cartilage destruction and serum biochemical markers associated with cartilage degradation and tissue inflammation in the rat mono-iodoacetate and/or meniscal transection model.

[0118] The study was performed in female Sprague-Dawley rats, age 6 months at MNX surgery.

7 days after MNX surgery monoiodoacetate 2 mg/0.2ml was injected intra-articularly in the right knee joint. The test compounds or vehicle is injected to the animals after the MNX. In the MNX or sham group, the test compounds or vehicle was administered until termination.
Weekly fasting blood sampling are taken for the analysis of biomarker (P2NP, C2M, AGNxl, AGNx2). Knee joints is isolated at termination. Cartilage damage is scored by experienced histo-pathologist according to Colombo score.

The compounds described in the compounds list are similarly conducted in rat mono-iodoacetate and/or meniscal transection model. The potent activities are observed in all cases.

Example 3: rat meniscal transection and/or ovariectomised model

The compounds describe in the compounds list are conducted in the rat meniscal (MNX) transection and/or ovariectomised (OVA) induced osteoarthritis model. These compounds exhibit excellent inhibitory activities on cartilage destruction and serum biochemical markers associated with cartilage degradation and tissue inflammation in the rat meniscal transection and/or ovariectomised model.

The study is performed in female Sprague-Dawley rats with MNX and OVX surgery. The test compounds or vehicle is injected to the animals after the surgery. In the MNX/OVX or sham group, the test compounds or vehicle was administered until termination.

Weekly fasting blood sampling are taken for the analysis of biomarker (P2NP, C2M, AGNxl, AGNx2). Knee joints is isolated at termination. Cartilage damage is scored by experienced histo-pathologist according to Colombo score.

The compounds describe in the compounds list are similarly conducted in rat mono-iodoacetate and/or meniscal transection model. The potent activities are observed in all cases.

**Industrial Applicability**

According to the present invention, a compound of formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof is useful for the treatment and/or prevention of cartilage disease.

All publications, including but not limited to, issued patents, patent applications, and journal articles, cited in this application are each herein incorporated by reference in their entirety. Although the invention has been described above with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention. It should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.
Claims

[Claim 1] Use of a compound with EP4 antagonistic activity, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cartilage diseases in an animal subject including a mammalian subject.

[Claim 2] Use of a compound of the formula (I), (II), (III), (IV), (Va) or (Vb), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cartilage diseases in an animal subject including a mammalian subject:

[Chem.1]![Chemical Structure Image]

wherein Y1, Y2, Y3, and Y4 are independently selected from N, CH and C(L);

R1 is H, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C3-7 cycloalkyl, Ci-8 alkoxy, halo-substituted Ci-8 alkoxy, Ci-8 alkyl-S(0)m-, Q1-, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, amino, mono- or di-(d_8 alkyl)amino, C14 alkyl-C(=0)-N(R 3)- or C14alkyl-S(0)m-N(R 3)-, wherein said Ci-8 alkyl, C2-8 alkenyl and C2-8 alkynyl are optionally substituted with halo, Ci-3 alkyl, hydroxy, oxo, Ci-4 alkoxy-, Ci-4 alkyl-S(0)m-, C3-7 cycloalkyl-, cyano, indanyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q1-, Q1-C(=0)-, Q1-O-, Q1-S(0)m-, Q'1,-C14 alkyl-O-, Q'-C14 alkyl-S(0)m-, Q'1-C^N alkyl-C(0)-N(R 3)-, Q'1-C14 alkyl-N(R 3)- or C14 alkyl-C(0)-N(R 3)-;

Q1 is a 5 to 12 membered monocyclic or bicyclic aromatic ring optionally containing up to 4 heteroatoms selected from O, N and S, and
is optionally substituted with halo, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, hydroxy, d<sub>-4</sub> alkoxy, halo-substituted C<sub>1-4</sub> alkoxy, C<sub>1,4</sub> alkylthio, nitro, amino, mono- or di-(C<sub>1-4</sub> alkyl)amino, cyano, H-O-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy-C<sub>1-4</sub> alkyl, C<sub>1,4</sub> alkylsulfonyl, aminosulfonyl, C<sub>1,4</sub> alkylC(=0)-, H-O(0=)C-, C<sub>1,4</sub> alkyl-0(0=)C-, R<sup>3</sup>N(R<sup>4</sup>)C(=0)-, d<sub>-4</sub> alkylsulfonylamino, C<sub>3,7</sub> cycloalkyl, R<sup>3</sup>C(=0)N(R<sup>4</sup>)- or NH<sub>2</sub>(HN=)=C-.

A is a 5 or 6 membered monocyclic aromatic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5 or 6 membered monocyclic aromatic ring is optionally substituted with up to 3 substituents selected from halo, C<sub>1,4</sub> alkyl, halo-substituted C<sub>1,4</sub> alkyl, hydroxy, C<sub>1,4</sub> alkoxy, halo-substituted C<sub>1,4</sub> alkoxy, C<sub>1,4</sub> alkylthio, nitro, amino, mono- or di-(C<sub>1-4</sub> alkyl)amino, cyano, H-O-C<sub>1,4</sub> alkyl, C<sub>1,4</sub> alkoxy-C<sub>1,4</sub> alkyl, C<sub>1,4</sub> alkylsulfonyl, aminosulfonyl, acetyl, R<sup>3</sup>N(R<sup>4</sup>)C(=0)-, H-O(0=)C-, C<sub>1,4</sub> alkyl-0(0=)C-, C<sub>1,4</sub> alkylsulfonylamino, C<sub>3,7</sub> cycloalkyl, R<sup>3</sup>C(=0)N(R<sup>4</sup>)- and NH<sub>2</sub>(HN=)=C-.

B is halo-substituted C<sub>1,6</sub> alkylene, C<sub>3,7</sub> cycloalkylene, C<sub>2,6</sub> alkenylene, C<sub>2,6</sub> alkylenyl, -O-C<sub>1,5</sub> alkenyl, C<sub>1,2</sub> alkenylene-0-Ci<sub>-2</sub> 2 alkenylene or C<sub>1,6</sub> alkenylene optionally substituted with an oxo group or C<sub>1,3</sub> alkyl.

W is NH, N-Ci<sub>-4</sub> alkyl, O, S, N-OR<sup>5</sup> or a covalent bond.

R<sup>2</sup> is H, C<sub>1,4</sub> alkyl, OH or C<sub>1,4</sub> alkoxy.

Z is a 5 to 12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5 to 12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C<sub>1,4</sub> alkyl, halo-substituted C<sub>1,4</sub> alkyl, C<sub>1,4</sub> alkenyl, C<sub>-4</sub> alkenyl, hydroxy, C<sub>-4</sub> alkoxy, halo-substituted C<sub>-4</sub> alkoxy, C<sub>-4</sub> alkylthio, nitro, amino, mono- or di-(C<sub>-4</sub> alkyl)amino, cyano, H-O-C<sub>-4</sub> alkyl, C<sub>-4</sub> alkoxy-C<sub>-4</sub> alkyl, C<sub>-4</sub> alkylsulfonyl, aminosulfonyl, C<sub>-4</sub> alkylC(=0)-, H-O(0=)C-, C<sub>-4</sub> alkyl-0(0=)C-, C<sub>-4</sub> alkylsulfonylamino, C<sub>3,7</sub> cycloalkyl, NH<sub>2</sub>(HN=)=C-, Q<sup>2</sup>-S(0)m-, Q<sup>2</sup>-O-, Q<sup>2</sup>-N (R<sup>3</sup>)- or Q<sup>2</sup>.

L is halo, C<sub>1,4</sub> alkyl, halo-substituted C<sub>-4</sub> alkyl, hydroxy, C<sub>1,4</sub> alkoxy, C<sub>-4</sub> alkenyl, nitro, amino, mono- or di-(C<sub>-4</sub> alkyl)amino, halo-substituted C<sub>-4</sub> alkoxy, cyano, H-O-C<sub>-4</sub> alkyl, C<sub>-4</sub> alkoxy-Ci<sub>-4</sub> alkyl, C<sub>-4</sub> alkylsulfonyl, aminosulfonyl, C<sub>-4</sub> alkylC(=0)-, H-O(0=)C-, C<sub>-4</sub> alkyl-0(0=)C-, C<sub>-4</sub> alkylsulfonylamino, C<sub>3,7</sub> cycloalkyl, R<sup>3</sup>C(=0)N(R<sup>4</sup>)-, NH<sub>2</sub>(HN=)=C-, R<sup>3</sup>N(R<sup>4</sup>)C(=0)-, R<sup>3</sup>N(R<sup>4</sup>)S(0)m-, Q<sup>2</sup>-C(=0)-, Q<sup>2</sup>-O-, Q<sup>2</sup>-Ci<sub>-4</sub> alkyl-0-, or two adjacent L groups are optionally joined together to form an alkenylene chain having 3 or 4 members in which one or two
(non-adjacent) carbon atoms are optionally replaced by oxygen atoms; m is 0, 1 or 2; R³ and R⁴ are independently selected from H and C₁₄ alkyl; R⁵ is H, C₁₄ alkyl, C₁₄ alkyl-(0=)C- or C₁₄ alkyl-0-(0=)-C--; and Q² is a 5 to 12 membered monocyclic or bicyclic aromatic ring, optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5 to 12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C₁₄ alkyl, halo-substituted C₁₄ alkyl, C₁₄ alkenyl, C₁₄ alkynyl, hydroxy, C₁₄ alkoxy, halo-substituted C₁₄ alkoxy, d₄ alkylthio, nitro, amino, mono- or di-(C₁₄ alkyl)amino, cyano, HO-C₁₄ alkyl, C₁₄ alkoxy-C₁₄ alkyl, C₁₄ alkylsulfonyl, aminosulfonyl, C₁₄ alkyl-(0=)C-, R³(R⁴)C(=0)N-, HO(0=)C-, C₁₄ alkyl-0(0=)-C-, C₁₄ alkylsulfonylamino, C₃₋₇ cycloalkyl, C₁₋₄ alkyl-C(=0)NH- or NH₂ (HN)=)C--; [Chem.2]

wherein A represents a phenyl group or a pyridyl group; B represents an aryl group or a heteroaryl group; E represents a 1,4-phenylene group; R¹ and R² independently represent a hydrogen atom, a halogen atom, an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms, a haloalkyl group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms, a cyano group or an aminocarbonyl group; R³ and R⁴ independently represent a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms; or R³ and R⁴ may be joined together to form an alkylene chain having 2 to 6 carbon atoms; R⁵ represents -C0₂H, C0₂W,
R\textsuperscript{6} represents an alkyl group having from 1 to 6 carbon atoms, a cycloalkyl group having from 3 to 7 ring atoms, an aryl group or a heteroaryl group;

X represents a methylene group, an oxygen atom or a sulfur atom; said aryl groups have from 6 to 10 carbon atoms;
said heteroaryl groups are 5 to 10-membered aromatic heterocyclic groups containing from 1 to 3 heteroatoms selected from the group consisting of sulfur atom, oxygen atom and nitrogen atom;
said aryl groups and said heteroaryl groups referred to in the definitions of B are unsubstituted or are substituted by at least one substituent selected from the group consisting of substituents alpha;
said 1,4-phenylene group referred to in the definition of E is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents beta;
said aryl groups and said heteroaryl groups referred to in the definitions of R\textsuperscript{6} and alpha are unsubstituted or are substituted by at least one substituent selected from the group consisting of substituents beta;
said substituents alpha are selected from the group consisting of halogen atoms, alkyl groups having from 1 to 4 carbon atoms, alkoxy groups having from 1 to 4 carbon atoms, haloalkyl groups having from 1 to 4 carbon atoms, haloalkoxy groups having from 1 to 4 carbon atoms, cyano groups, alkynyl groups having from 2 to 6 carbon atoms, alkanoyl groups having from 1 to 5 carbon atoms, cycloalkyl groups having from 3 to 7 ring atoms, heteroaryl groups, aryl groups, aralkoxy groups having from 7 to 10 carbon atoms, arylcarbonyl groups, two adjacent alpha groups are optionally joined together to form an alkylene or an alkenylene chain having 3 or 4 carbon atoms, aminocarbonyl groups, alkenyl groups having from 2 to 5 carbon atoms, alkylthio groups having from 1 to 4 carbon atoms, aminosulfanyl groups, aminosulfonyl groups, hydroxy groups, hydroxyalkyl groups having from 1 to 4 carbon atoms, nitro groups, amino groups, carboxy groups, alkoxy carbonyl groups having from 2 to 5 carbon atoms,
alkoxyalkyl groups having from 1 to 4 carbon atoms, alkylsulfonyl groups having from 1 to 4 carbon atoms, alkanoylamino groups having from 1 to 4 carbon atoms, alkanoyl (alkyl) amino groups having from 1 to 6 carbon atoms, alkanoylaminoalkyl groups having from 1 to 6 carbon atoms in both the alkanoyl and alkyl part, alkanoyl (alkyl) aminoalkyl groups having from 1 to 6 carbon atoms in both the alkanoyl and each alkyl part, alkylsulfonylamino groups having from 1 to 4 carbon atoms, mono- or di-alkylaminocarbonyl groups having from 1 to 6 carbon atoms, mono- or di-alkylaminosulfinyl groups having from 1 to 6 carbon atoms, mono- or di-alkylaminosulfonyl groups having from 1 to 6 carbon atoms, aminoalkyl groups having from 1 to 4 carbon atoms, mono- or di-alkylamino groups having from 1 to 6 carbon atoms, aralkyl groups having from 7 to 10 carbon atoms, heteroarylalkyl groups having from 1 to 4 carbon atoms in the alkyl part, heteroarylalkoxy groups having from 1 to 4 carbon atoms in the alkoxy part and alkylsulfonylamino groups having from 1 to 4 carbon atoms;

said substituents beta are selected from the group consisting of halogen atoms, alkyl groups having from 1 to 4 carbon atoms, alkoxy groups having from 1 to 4 carbon atoms, haloalkyl groups having from 1 to 4 carbon atoms, haloalkoxy groups having from 1 to 4 carbon atoms and cyano groups;

W is a pharmaceutically acceptable ester prodrug group; with the proviso R\(^1\) and R\(^2\) do not represent a hydrogen atom simultaneously;

[Chem.4]
Z represents a hydrogen atom or a halogen atom;
R represents an alkyl group having from 1 to 6 carbon atoms optionally substituted with an alkoxy group having from 1 to 6 carbon atoms or a cycloalkyl group having from 3 to 7 carbon atoms; a cycloalkyl group having from 3 to 7 carbon atoms optionally substituted with an alkyl group having from 1 to 3 carbon atoms; a phenyl group optionally substituted with one or more substituents alpha; or a group Het optionally substituted with one or more substituents alpha; Het represents a heterocyclic group having from 4 to 7 ring atoms which contains either from 1 to 4 nitrogen ring heteroatoms or from 0 to 2 nitrogen ring heteroatoms and 1 oxygen or 1 sulfur ring heteroatom;
R and R independently represent a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms; or R and R together form an alkylenec having from 3 to 6 carbon atoms; and said substituent alpha is selected from the group consisting of halogen atoms, alkyl groups having from 1 to 4 carbon atoms, haloalkyl groups having from 1 to 4 carbon atoms, hydroxy groups, alkoxy groups having from 1 to 4 carbon atoms, haloalkoxy groups having from 1 to 4 carbon atoms, cyano groups, hydroxy alkyl groups having from 1 to 4 carbon atoms, alkoxyalkyl groups having from 1 to 4 carbon atoms in alkoxy and alky groups, alkylsulfonyl groups having from 1 to 4 carbon atoms, alkanoyl groups having from 2 to 5 carbon atoms, alkenyl groups having from 2 to 4 carbon atoms, alkynyl groups having from 2 to 4 carbon atoms, alkylthio groups having from 1 to 4 carbon atoms, nitro groups, amino groups, mono- or di-alkylamino groups having from 1 to 4 carbon atoms, aminosulfonyl groups, alkoxycarbonyl groups having from 1 to 4 carbon atoms, alkylsulfonylamino groups having from 1 to 4 carbon atoms, cycloalkyl groups having from 3 to 7 carbon atoms and a mono- or di-alkylaminocarbonyl groups having from 1 to 6 carbon atoms;
or a pharmaceutically acceptable ester of such compound;
wherein X and Y are independently selected from the group consisting of: N and C(R^11), wherein each R^11 is independently selected from the group consisting of: hydrogen, halo and C_i_4_alkyl;
B is selected from the group consisting of: -C(R^5)(R^6)-, -0-, -S-, -S(O)-, -S0_2, -C(R^3)(R^6)-C(R^5)(R^6)-, -0-C(R^5)(R^6)-, -S-C(R^5)(R^6)-, -S(0)-C(R^5)(R^6)-, and -S0_2-C(R^5)(R^6)-;
C is selected from the group consisting of aryl and heteroaryl, or a
fused analog of aryl or heteroaryl, each optionally substituted with one
to three substituents independently selected from R^10;
E is selected from the group consisting of: -C(0)OH, -C(0)OCi_alkyl, tetrazolyl and
[Chem.8]

wherein R is selected from the group consisting of: Ci_alkyl, aryl and heteroaryl, or a fused analog of aryl or heteroaryl, wherein aryl and heteroaryl or the fused analogs thereof are optionally substituted with one to three substituents independently selected from R^10;
R^1 to R^8 are independently selected from the group consisting of: H, halo, -O-R^12, Ci_alkyl and C_36cycloalkyl, and one or more pairs of R^1 and R^2, R^5 and R^6, and R^7 and R^8 may be joined together with the carbon atom to which they are attached to form a 3- to 5-membered monocyclic cycloalkyl ring, and R^5 and R^6 or R^7 and R^8 may be joined together to form carbonyl;
R^9 is independently selected from the group consisting of: halo, hydroxy l and Ci_alkyl;
R^{10} is selected from the group consisting of: halo, cyano, Ci_alkyl, C_14 fluoroalkyl, Ci_alkoxy, Ci_thioalkoxy and Ci_fluoroalkoxy; and
each R^{12} is selected from the group consisting of: H, Ci_alkyl, C_36cycloalkyl and heterocyclyl.

[Claim 3]
The use of Claim 2, wherein the compound of (I), (II), (III), (IV), (Va) or (Vb) is selected from:
3-[2-(4-{2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl}phenyl)ethyl]-1-[(4-methylbenzene)sulfonyl]urea;
3-[2-(4-{2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl}phenyl)ethyl]-1-[(4-methylbenzene)sulfonyl]urea;
1-{2-[4-(5-acetyl-2-ethyl-1H-1,3-benzodiazol-1-yl)phenyl]ethyl}]-3-[(4-methylbenzene)sulfonyl]urea;
3-{2-[4-(2-ethyl-5-methoxy-1H-1,3-benzodiazol-1-yl)phenyl]ethyl}]-1-[(4-methylbenzene)sulfonyl]urea;
2-{4-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]phenyll]ethyl N-[(4-methylbenzene)sulfonyl]carbamate;
3-{2-[4-(6-chloro-5-cyano-2-ethyl-1H-1,3-benzodiazol-1-yl)phenyl]ethyl}-1-[(4-methylbenzene)sulfonyl]urea;
2-(4-{2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl}phenyl)ethylN-[(4-methylbenzene)sulfonyl]carbamate;
2-(4-{2-tert-butyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl}phenyl)ethylN-[(4-methylbenzene)sulfonyl]carbamate;
2-[4-(5-carbamoyl-6-chloro-2-ethyl-1H-1,3-benzodiazol-1-yl)phenyl]ethylN-[(4-methylbenzene)sulfonyl]carbamate;
1-(2-{4-[2-ethyl-5-([1-hydroxyethyl]-1H,1,3-benzodiazol-1-yl)phenyl]ethyl}-3-[(4-methylbenzene)sulfonyl]urea;
1-(2-{4-[6-chloro-2-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]phenyl}ethyl)-3-[(4-methylbenzene)sulfonyl]urea;
2-{4-[6-chloro-2-(pyridin-2-yl)-5-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]phenyl}ethylN-[(4-methylbenzene)sulfonyl]carbamate;
3-{2-{5-[6-chloro-2-ethyl-5-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]pyridin-2-yl}ethyl]N-[(2-chlorobenzene)sulfonylethyl]carbamate;
3-{2-{4-[5,7-dimethyl-2-(methylamino)-3H-imidazo[4,5-b]pyridin-3-yl]phenyl}ethyl)-1-[(4-methylbenzene)sulfonyl]urea;
4-((1S)-1-[[5-chloro-2-(4-fluorophenoxy)benzoyl]amino]ethyl)benzoic acid;
4-{(1S)-1-[[5-chloro-2-(3-cyanophenoxy)pyridin-3-yl]carbonyl]amino}ethylbenzoic acid;
4-{(1S)-1-[[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl]amino}ethylbenzoic acid;
4-{(1S)-1-[[5-chloro-2-(3-chlorophenoxy)pyridin-3-yl]carbonyl]amino}ethylbenzoic acid;
4-{(1S)-1-[[5-chloro-2-(2-chloro-4-fluorophenoxy)pyridin-3-yl]carbonyl]amino}ethylbenzoic acid;
4-{(1S)-1-[[5-chloro-2-(3,4-difluorophenoxy)pyridin-3-yl]carbonyl]amino}ethylbenzoic acid;
4-[(lS)-l-({[5-chloro-2-(2,3-difluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
4-((lS)-l- {[5-chloro-2-(2,3-difluorophenoxy)benzoyl]amino}ethyl)benzoic acid;
4-((lS)-l- {[5-chloro-2-(3,4-difluorophenoxy)benzoyl]amino}ethyl)benzoic acid;
4-[(lS)-l- {[5-chloro-2-(3-chloro-5-fluorophenoxy)pyridin-3-yl]carbonyl}amino]ethyl]benzoic acid;
4-[(1S)-1-l- {[5-chloro-2- [(4-fluorophenoxy)methyl]benzoyl] amino}ethyl]benzoic acid;
4-[(1S)-1-l- {[5-chloro-2- [(3-chlorophenoxy)methyl]benzoyl] amino}ethyl]benzoic acid;
4-[(1S)-1-l- {[5-chloro-2- [(4-fluorophenoxy)methyl]benzoyl] amino}ethyl]benzoic acid;
4-[(1S)-1-l- {[5-chloro-2- [(3,4-difluorophenoxy)methyl]benzoyl] amino}ethyl]benzoic acid;
4-[(1S)-1-l- {[5-chloro-2- [(2,4-difluorophenoxy)methyl]benzoyl] amino}ethyl]benzoic acid;
4-[(lS)-l- {[5-chloro-2- [(3-chlorophenoxy)methyl]benzoyl] amino}ethyl]benzoic acid;
4-[(lS)-l- {[5-chloro-2- [(3,5-difluorophenoxy)methyl]benzoyl] amino}ethyl]benzoic acid;
4-[(lS)-l- {[5-chloro-2- [(3-fluorophenoxy)methyl]benzoyl] amino}ethyl]benzoic acid;
4-{{(1S)-l- {[2-(4-chlorophenoxy)methyl]-5-fluoropyridin-3-yl} carbonyl}amino}ethyl]benzoic acid;
4-[(1S)-l- {[5-chloro-2- [(3,5-difluorophenoxy)methyl]benzoyl] amino}ethyl]benzoic acid;
4-[(1S)-l- {[5-chloro-2- [(3-fluorophenoxy)methyl]benzoyl] amino}ethyl]benzoic acid;
4-{{(2-[(4-chlorophenoxy)methyl]-5-fluoropyridin-3-yl)carbonyl}amino}ethyl]benzoic acid;
4-{{(1S)-l- {[5-chloro-2- [(cyclohexylmethoxy)methyl]benzoyl] amino}ethyl]benzoic acid;
4-{{(4-(5-methoxypyridin-2-yl)phenoxy)methyl}-5-methyl-N-(o-tolylsulfonyl)furan-2-carboxamide.
5-chloro-3-[[3-chlorophenyl]methyl]-N-[1-[(methylsulfonyl)amino]carbonyl]phenyl]ethyl]-2-thiophenecarboxamide,
2,5-dimethyl-N- [[1S]-1-[[methylsulfonyl]amino]carbonyl]phenyl]ethyl]-2-thiophenecarboxamide,
2,5-dimethyl-N-[1-[4-(2H-tetrazol-5-yl)phenyl]cyclopropyl]-4-[[4-(trifluoromethyl)phenyl]methyl]-3-thiophenecarboxamide,
2-chloro-4-[[[4-[(3-chlorophenyl)methyl]-2,5-dimethyl-3-thienyl]carbonyl]amino]methyl]-benzoic acid,
4-[(IR)-1-[[2,5-dichloro-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dibromo-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dichloro-4-(3-chlorobenzoyl)-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
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4-[(IS)-1-[[2,5-dibromo-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
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4-[(IS)-1-[[2,5-dichloro-4-[3-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dimethyl-4-[3-(trifluoromethyl)phenyl]methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-[(IS)-1-[[2,5-dimethyl-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
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4-[(IS)-1-[[2,5-dimethyl-4-[(3-chlorophenyl)methyl]-3-thienyl]carbonyl]amino]ethyl]-benzoic acid,
4-{1-[(2,5-dimethyl-4-[4-(trifluoromethyl)benzyl]-3-thienyl)carbonyl]amino)cyclopropyl} benzoic acid, or a pharmaceutically acceptable salt thereof.

[Claim 4] The use of Claim 2 or Claim 3, wherein the compound of (I), (II), (III), (IV), (Va) or (Vb) is selected from:
3-[2-(4-[2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl]phenylethyl]-1-[(4-methylbenzene)sulfonyl]urea;
4-{[(IS)-1-(((5-chloro-2-(3-fluorophenoxy)pyridin-3-yl)carbonyl)amino)ethyl]benzoic acid;
4-((4-(5-methoxypyridin-2-yl)phenoxy)methyl)-5-methyl-N-(o-tolylsulfonyl)furan-2-carboxamide;
4-{1-[(2,5-dimethyl-4-[4-(trifluoromethyl)benzyl]-3-thienyl]carbonyl}[amino]cyclopropyl} benzoic acid, or a pharmaceutically acceptable salt thereof.

[Claim 5] The use of Claim 4, wherein the compound of (I), (II), (III) or (IV) is selected from:
3-[2-(4-[2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl]phenylethyl]-1-[(4-methylbenzene)sulfonyl]urea;
4-{[(IS)-1-(((5-chloro-2-(3-fluorophenoxy)pyridin-3-yl)carbonyl)amino)ethyl]benzoic acid;
4-((4-(5-methoxypyridin-2-yl)phenoxy)methyl)-5-methyl-N-(o-tolylsulfonyl)furan-2-carboxamide;
4-[(1S)-1-[(2,5-dimethyl-4-[4-(trifluoromethyl)benzyl]-3-thienyl]carbonyl]amino)cyclopropyl} benzoic acid, or a pharmaceutically acceptable salt thereof.

[Claim 6] The use of any one of Claims 2 to 5, wherein the compound of the formula (I), (II), (III), (IV), (Va) or (Vb), or the pharmaceutically acceptable salt is used in combination with one or more additional compounds known to be useful in the treatment or prevention of cartilage disease or the symptoms thereof.

[Claim 7] The use of Claim 6, wherein the one or more additional compounds known to be useful in the treatment or prevention of cartilage disease or the symptoms thereof are selected from NSAIDs, COX-2 inhibitors, steroids, matrix metalloproteinase inhibitors and hyaluronic acid.

[Claim 8] A pharmaceutical composition for the treatment of cartilage disease which comprises a therapeutically effective amount of a compound of
the formula (I), (II), (III), (IV), (Va) or (Vb) in Claim 2 or a pharmaceutically acceptable salt thereof.

[Claim 9] The pharmaceutical composition of Claim 8, which further comprises a therapeutically effective amount of one or more additional compounds known to be useful in the treatment or prevention of cartilage disease or the symptoms thereof.

[Claim 10] A method for the treatment of cartilage diseases in an animal subject including a mammalian subject, which comprises administering to the animal subject including a mammalian subject a compound of the formula (I), (II), (III), (IV), (Va) or (Vb) in Claim 2 or a pharmaceutically acceptable salt thereof.

[Claim 11] The method of Claim 10, which further comprises administering a therapeutically effective amount of one or more additional compounds known to be useful in the treatment or prevention of cartilage disease thereof.

[Claim 12] A method for the treatment of cartilage diseases, which comprises administering to an animal subject including a mammalian subject in need a therapeutically effective amount of a compound of the formula (I), (II), (III), (IV), (Va) or (Vb) in Claim 2 or a pharmaceutically acceptable salt thereof.

[Claim 13] The method of Claim 12, which further comprises administering a therapeutically effective amount of one or more additional compounds known to be useful in the treatment or prevention of cartilage disease thereof.

[Claim 14] A compound of the formula (I), (II), (III), (IV), (Va) or (Vb) in Claim 2 or a pharmaceutically acceptable salt thereof for use in the treatment of cartilage diseases in an animal subject including a mammalian subject.
# INTERNATIONAL SEARCH REPORT

**INTERNATIONAL APPLICATION No.**

PCT/JP2014/001597

## A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)


Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

- Published examined utility model applications of Japan 1992-1996
- Published unexamined utility model applications of Japan 1971-2014
- Registered utility model specifications of Japan 1996-2014
- Published registered utility model applications of Japan 1994-2014

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAplus/MEDLINE/EMBASE/BIOSIS (STN), JSTPlus / JMEDPlus / JST/ bibU (JDream1U)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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☑ Further documents are listed in the continuation of Box C.  ☐ See patent family annex.

* Special categories of cited documents:
  - “A” document defining the general state of the art which is not considered to be of particular relevance
  - “E” earlier application or patent but published on or after the international filing date
  - “L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - “O” document referring to an oral disclosure, use, exhibition or other means
  - “P” document published prior to the international filing date but later than the priority date claimed

“\(\uparrow\)” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“\(\times\)” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“\(\uparrow\)” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Date of the actual completion of the international search | 11.06.2014 |
Date of mailing of the international search report | 24.06.2014 |

Name and mailing address of the ISA/JP

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Form PCT/ISA/210 (extra sheet) (July 2009)
INTERNATIONAL SEARCH REPORT

International application No.
PCT/ JP2 014/001597

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos. :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos. :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)
D1 discloses use of an EP4 antagonist for the treatment of cartilage diseases by showing that the said antagonist reversed inhibition of proteoglycan synthesis and that it inhibited release of aggrecan fragments in cartilage (p.5086 right column - p.5087 left column). Therefore, claim 1 lacks novelty over D1, and involves no special technical features. Thus, claims of this application are divided into 7 inventions with respective special technical features as shown below. Note that claim 1, which involves no special technical features, is grouped into Invention 1.

(Invention 1) claims 1

(Invention 2) claims 2-14(partial)
A compound of the formula (I) and use thereof in the manufacture of a medicament for the treatment of cartilage diseases.
Claims 2-14 whose subject matter relates to a compound of the formula (I) or the use thereof do not comprise all parts specifying the claim 1 though they are in the same category with it. Moreover, searches are unable to be completed with no additional burden for claims 2-14 whose subject matter relates to a compound of the formula (I) or the use thereof after searches are done and decisions are made for claim 1. Furthermore, no other reasons are to be found under which it is possible to do searches efficiently both for claims 2-14 whose subject matter relates to a compound of the formula (I) or the use thereof and for claim 1 together. Therefore, claims 2-14 whose subject matter relates to a compound of the formula (I) or the use thereof cannot be grouped into Invention 1.

(Invention 3) claims 2-14(partial)
A compound of the formula (II) and use thereof in the manufacture of a medicament for the treatment of cartilage diseases.
Claims 2-14 whose subject matter relates to a compound of the formula (II) or the use thereof do not comprise all parts specifying the claim 1 though they are in the same category with it. Moreover, searches are unable to be completed with no additional burden for claims 2-14 whose subject matter relates to a compound of the formula (II) or the use thereof after searches are done and decisions are made for claim 1 or for claims 2-14 of Invention 2. Furthermore, no other reasons are to be found under which it is possible to do searches efficiently both for claims 2-14 whose subject matter relates to a compound of the formula (II) or the use thereof and for claim 1 or for 2-14 of Invention 2 together. Therefore, claims 2-14 whose subject matter relates to a compound of the formula (II) or the use thereof cannot be grouped into Invention 1 or 2.

(Invention 4) claims 2-14(partial)
A compound of the formula (III) and use thereof in the manufacture of a medicament for the treatment of cartilage diseases.
Claims 2-14 whose subject matter relates to a compound of the formula (III) or the use thereof do not comprise all parts specifying the claim 1 though they are in the same category with it. Moreover, searches are unable to be completed with no additional burden for claims 2-14 whose subject matter relates to a compound of the formula (III) or the use thereof after searches are done and decisions are made for claim 1 or for claims 2-14 of Invention 2 or 3. Furthermore, no other reasons are to be found under which it is possible to do searches efficiently both for claims 2-14 whose subject matter relates to a compound of the formula (III) or the use thereof and for claim 1 or claims 2-14 of Invention 2 or 3 together. Therefore, claims 2-14 whose subject matter relates to a compound of the formula (III) or the use thereof cannot be grouped into Invention 1, 2 or 3.

(Invention 5) claims 2-14(partial)
A compound of the formula (IV) and use thereof in the manufacture of a medicament for the treatment of cartilage diseases.

(continued to the extra sheet)
Claims 2-14 whose subject matter relates to a compound of the formula (IV) or the use thereof do not comprise all parts specifying the claim 1 though they are in the same category with it. Moreover, searches are unable to be completed with no additional burden for claims 2-14 whose subject matter relates to a compound of the formula (IV) or the use thereof after searches are done and decisions are made for claim 1 or for claims 2-14 of Invention 2, 3 or 4. Furthermore, no other reasons are to be found under which it is possible to do searches efficiently both for claims 2-14 whose subject matter relates to a compound of the formula (IV) or the use thereof and for claim 1 or claims 2-14 of Invention 2, 3 or 4 together. Therefore, claims 2-14 whose subject matter relates to a compound of the formula (IV) or the use thereof cannot be grouped into Invention 1, 2, 3 or 4.

(Invention 6) claims 2-14(partial)
A compound of the formula (Va) and use thereof in the manufacture of a medicament for the treatment of cartilage diseases.

Claims 2-14 whose subject matter relates to a compound of the formula (Va) or the use thereof do not comprise all parts specifying the claim 1 though they are in the same category with it. Moreover, searches are unable to be completed with no additional burden for claims 2-14 whose subject matter relates to a compound of the formula (Va) or the use thereof after searches are done and decisions are made for claim 1 or for claims 2-14 of Invention 2, 3, 4 or 5. Furthermore, no other reasons are to be found under which it is possible to do searches efficiently both for claims 2-14 whose subject matter relates to a compound of the formula (Va) or the use thereof and for claim 1 or claims 2-14 of Invention 2, 3, 4 or 5 together. Therefore, claims 2-14 whose subject matter relates to a compound of the formula (Va) or the use thereof cannot be grouped into Invention 1, 2, 3, 4 or 5.

(Invention 7) claims 2-14(partial)
A compound of the formula (Vb) and use thereof in the manufacture of a medicament for the treatment of cartilage diseases.

Claims 2-14 whose subject matter relates to a compound of the formula (Vb) or the use thereof do not comprise all parts specifying the claim 1 though they are in the same category with it. Moreover, searches are unable to be completed with no additional burden for claims 2-14 whose subject matter relates to a compound of the formula (Vb) or the use thereof after searches are done and decisions are made for claim 1 or claims 2-14 of Invention 2, 3, 4, 5 or 6. Furthermore, no other reasons are to be found under which it is possible to do searches efficiently both for claims 2-14 whose subject matter relates to a compound of the formula (Vb) or the use thereof and for claim 1 or claims 2-14 of Invention 2, 3, 4, 5 or 6 together. Therefore, claims 2-14 whose subject matter relates to a compound of the formula (Vb) or the use thereof cannot be grouped into Invention 1, 2, 3, 4, 5 or 6.