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MATRIX METALLOPROTEINASE INHIBITORS

(57) Abstract:

The present invention relates to certain hydroxy propionic acid derivatives and the processes for the synthesis of the same. This invention also relates to pharmacological compositions containing the compounds of the present invention, and methods of treating asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, psoriasis, pulmonary fibrosis, pulmonary inflammation, acute respiratory distress syndrome, periodontitis, multiple sclerosis, gingivitis, atherosclerosis, dry eye, neointimal proliferation, which leads to restenosis and ischemic heart failure, stroke, renal diseases, tumor metastasis, and other inflammatory disorders characterized by over-expression and over activation of a matrix metalloproteinase using the compounds.

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(54) Title: MATRIX METALLOPROTEINASE INHIBITORS

(57) Abstract: The present invention relates to certain hydroxy propionic acid derivatives and the processes for the synthesis of the same. This invention also relates to pharmacological compositions containing the compounds of the present invention, and methods of treating asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, psoriasis, pulmonary fibrosis, pulmonary inflammation, acute respiratory distress syndrome, periodontitis, multiple sclerosis, gingivitis, atherosclerosis, dry eye, neointimal proliferation, which leads to restenosis and ischemic heart failure, stroke, renal diseases, tumor metastasis, and other inflammatory disorders characterized by over-expression and over activation of a matrix metalloproteinase using the compounds.



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MATRIX METALLOPROTEINASE INHIBITORS

Field of the Invention

The present invention relates to certain hydroxy propionic acid derivatives and the processes for the synthesis of the same. This invention also relates to pharmacological compositions containing the compounds of the present invention, and methods of treating
5 asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, psoriasis, pulmonary fibrosis, pulmonary inflammation, acute respiratory distress syndrome, periodontitis, multiple sclerosis, gingivitis, atherosclerosis, dry eye, neointimal proliferation, which leads to restenosis and ischemic heart failure, stroke, renal diseases,
10 tumor metastasis, and other inflammatory disorders characterized by over-expression and over activation of a matrix metalloproteinase using the compounds.

Background of the Invention

Metalloproteinases (MMPs) are a naturally occurring superfamily of proteinases (enzymes) found in most mammals. The superfamily is composed of at least 26 members
15 of zinc-containing enzymes produced by many cell types and sharing structural and functional features. Based on structural and functional considerations, proteinases have been classified into different families and subfamilies (Vartak *et al.*, *J. Drug Targeting*, 15, p. 1-20 (2007); and Hopper, *FEBS*, 354, p. 1-6 (1994)), such as collagenases (MMP-1, -8 and -13), gelatinases (MMP-2, and -9), metalloelastases (MMP-12), the MT-MMPs
20 (MMP-14, -15, -16, -17, -24 and 25), matrilysins (MMP-7 and -26), stromelysins (MMP-3, -10 and -11) and sheddases such as TNF-converting enzymes (TACE, and ACE).

Metalloproteinases are believed to be important in physiological and disease processes that involve remodeling, such as airway diseases, embryonic development, bone formation and uterine remodeling during menstruation. One major biological function of
25 MMPs is to catalyze the breakdown of connective tissues or extra-cellular matrix by their ability to hydrolyze various components of tissue or matrix. Apart from their role in degrading connective tissue, MMPs are involved in the activation of zymogen (pro) forms of other MMPs thereby inducing MMP activation. They are also involved in the biosynthesis of TNF-alpha which is implicated in many pathological conditions.

30 MMP-9, which belongs to the gelatinase family, plays a major role in chronic inflammatory disorders like COPD, asthma and rheumatoid arthritis. The concentration of

MMP-9 has been reported to increase in diseases like asthma, interstitial pulmonary fibrosis (IPF), adult respiratory distress syndrome (ARDS), and in chronic obstructive pulmonary disease (COPD). Because of its proteolytic ability, MMP-9 has been implicated in tissue remodeling of the airways and lungs in chronic inflammatory diseases such as severe asthma and COPD. MMP-9 is also likely to be physiologically important because of its ability to regulate the digestion of components of the extracellular matrix as well as the activity of other proteases and cytokines. MMP-9 is secreted in neutrophils, macrophages, and osteoclasts, which are easily induced by cytokines and growth factors, and plays a role in various physiological and pathological processes.

MMP-12, also known as macrophage elastase or metalloelastase, is expressed in activated macrophages and has been shown to be secreted from alveolar macrophages from smokers, as well as in foam cells in atherosclerotic lesions. MMP-12 knockout mouse studies have shown the development of significant emphysema, thus supporting its role in COPD. MMP-9 (gelatinase B, 92 kDa Type IV collagenase) is one member of the MMP family that is released as a proenzyme and subsequently activated via a protease cascade *in vivo*.

Over-expression or over-activation of an MMP, or an imbalance between an MMP and a natural (*i.e.*, endogenous) tissue inhibitor of a matrix metalloproteinase (TIMP) has been linked to a pathogenesis of diseases characterized by the breakdown of connective tissue or extracellular matrix.

Inhibition of the activity of one or more MMPs may be of benefit in treatment of various inflammatory, autoimmune and allergic diseases, such as, inflammation of the joint, inflammation of the GI tract, inflammation of the skin, collagen remodeling, wound healing disorders, etc.

The design and therapeutic application of MMP inhibitors has revealed that the requirement of a molecule to be an effective inhibitor of MMP class of enzymes is a functional group (*e.g.* carboxylic acid, hydroxamic acid or sulphhydryl) capable of chelating to the active site Zn^{2+} ion (Whittaker *et al.*, *Chem. Rev.*, 99; p. 2735-76 (1999)).

WO 2004/014310 discloses processes for the preparation of peripheral opioid antagonist compounds useful for gastrointestinal motility disorders. WO 02/060888 discloses processes for preparing chromanylbenzoic acids. WO 94/20455 discloses styryl

derivatives as PDE-IV inhibitors useful in the prophylaxis and treatment of diseases such as asthma, where an unwanted inflammatory response or muscular spasm is present. WO 2004/110974 discloses compounds and their physiologically functional derivatives described as inhibitors of matrix metalloproteinase enzymes. WO 2004/113279 discloses
5 inhibitors of matrix metalloproteinase. WO 2005/026120 discloses compounds described as inhibitors of matrix metalloproteinase. U. S. Patent Application No. 2003/0139453 discloses difluorobutyric acid compounds useful for treating diseases associated with zinc metalloprotease activity. WO 2006/090235 describes 5-phenyl-pentanoic acid derivatives described as matrix metalloproteinase inhibitors for the treatment of asthma and other
10 diseases. WO 2008/023336 discloses β -hydroxy and amino-substituted carboxylic acids, which act as matrix metalloproteinase inhibitors.

Research has been carried out into the identification of inhibitors that are selective, *e.g.*, for a few of the MMP subtypes. An MMP inhibitor of improved selectivity would avoid potential side effects associated with inhibition of MMPs that are not involved in the
15 pathogenesis of the disease being treated.

Further, use of more selective MMP inhibitors would require administration of a lower amount of the inhibitor for treatment of disease than would otherwise be required and, after administration, partitioned *in vivo* among multiple MMPs. Still further, the administration of a lower amount of compound would improve the margin of safety
20 between the dose of the inhibitor required for therapeutic activity and the dose of the inhibitor at which toxicity is observed.

Many drugs exist as asymmetric three-dimensional molecules, *i.e.*, chiral, and will therefore have several stereoisomers depending upon the number of chiral centers present. The importance of evaluating new chemical entities having chiral centers as single isomers
25 is to understand their effect on pharmacological and toxicological aspects. There are often pharmacodynamic, pharmacokinetic and/or toxicological differences between enantiomers/diastereomers. Even if natural physiological mediators are achiral, based on their target environment, their receptors/enzymes may demonstrate a preference for only one optically pure enantiomer of agonists, antagonists or inhibitors. From a
30 pharmacokinetics point of view, chirality can have an influence on drug absorption, distribution, metabolism and elimination. Pure single isomers may also offer advantages in terms of these pharmacokinetic parameters thus enabling better developability of such

molecules as drug candidates. It is also known that chirality has a significant effect of the physicochemical properties and crystallinity of a chiral molecule which in turn have profound effects on the pharmacokinetics and developability of the molecule. Besides those mentioned above, regulatory principles guide one to preferably develop single
5 isomers as drug candidates in order to avoid any pharmacological, pharmacokinetic and toxicological problems that may arise due to interactions of an unwanted isomer with undesirable molecular targets.

In this context, synthetic strategies to produce pure single isomers offer advantages over analytical techniques of separation of isomer not only in terms of cost and efficiency
10 but larger amounts of compound can be prepared for elaborate pharmaceutical testing. Thus, compounds of present invention, which are single chiral isomers, have improved potency, improved pharmacokinetics and/or improved physicochemical properties as compared to racemic compounds.

The present invention is directed to overcoming problems encountered in the art.

15

Summary of the Invention

The present invention provides some hydroxy propionic acid derivatives, which act as matrix metalloprotease inhibitors, corresponding processes for the synthesis of and pharmaceutical compositions containing the compounds of the present invention. The present invention relates to matrix metalloproteinase inhibitors useful as effective
20 therapeutic or prophylactic agents in treatment of various inflammatory, autoimmune, and allergic diseases and other inflammatory disorders characterized by the over-expression and over-activation of a matrix metalloproteinase using the compounds.

The present invention discloses a novel class of compounds that are dual MMP-9/12 inhibitors and have desirable activity profiles. The compounds of this invention have
25 beneficial potency and/or selectivity.

Pharmaceutical compositions containing such compounds are provided together with the pharmaceutically acceptable carriers or diluents, which can be used for the treatment or prevention of inflammatory or autoimmune diseases. These pharmaceutical compositions may be administered or coadministered by a wide variety of routes
30 including, for example, oral, topical, rectal, intranasal or by parenteral route. The composition may also be administered or co-administered in slow release dosage forms.

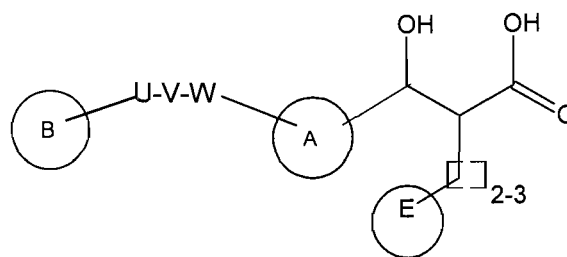
Although the specific enantiomers have been shown by way of examples, the racemates, diastereomers, pharmaceutically acceptable salts, and pharmaceutically acceptable solvates, having the same type of activity, are also provided. Pharmaceutical compositions comprising such compounds, with optionally included excipients are also provided.

Therapeutically effective amounts of one or more compounds of the present invention can be used in combination with one or more other therapeutic agents, for example, other anti-inflammatory agents, beta agonists, antihypertensive agents, immunosuppressive agents and anti-infective agents.

Other objects will be set forth in accompanying description and in the part will be apparent from the description or may be learnt by the practice of the invention.

Detailed Description of The Invention

In accordance with one aspect, there are provided compounds having the structure of Formula I:



Formula I

15

including racemates, enantiomers and diastereomers thereof, or a pharmaceutically acceptable salt thereof wherein,



can be selected from phenyl, fluorophenyl, heteroaryl or heterocyclyl;

U can be a selected from bond, -NH-, -C(=O)-, -(CH₂)_n-, -C(=S)-, -O-, -SO₂- or -S-
 20 - wherein n can be zero or an integer between 1 and 2;

V can be a selected from bond, -NH-, -C(=O)-, -C(=S)- or -SO₂-;

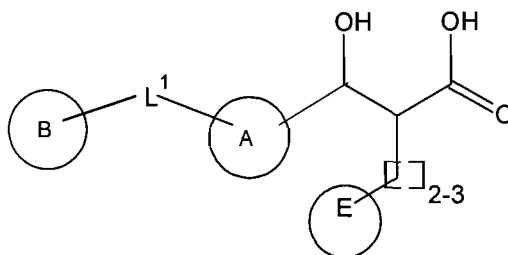
W can be a selected from bond, -NH-, -C(=O)-, (CH₂)_n-, -C(=S)-, -O-, -S- or -SO₂-;

(B) can be selected from aryl, cycloalkyl, heteroaryl or heterocyclyl, each of which can be further substituted by one or more substituent independently selected from R^1

R^1 can be selected from alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno-
 5 C_1 - C_6 alkyl, halogeno- C_1 - C_6 alkoxy, azido, thiol, alkylthiol, $-(CH_2)_n-OR_f$, $-C(=O)-R_f$, $-COOR_f$, $-NR_fR_q$, $-(CH_2)_n-C(=O)NR_fR_q$, $-(CH_2)_n-NHC(=O)-R_f$, $-(CH_2)_n-O-C(=O)-NR_fR_q$, $(CH_2)_n NHC(=O)NR_fR_q$, $-(CH_2)_n-O-C(=O)-R_f$, $-(CH_2)_n-NH-C(=O)-R_f$ or $-(CH_2)_nS(=O)_m-NR_fR_q$ {wherein R_f and R_q are independently selected from hydrogen, alkyl, alkenyl, cycloalkyl aryl, heteroaryl, heterocyclyl, alkylaryl,
 10 alkylheteroaryl and alkylheterocyclyl, n is as defined earlier and m is an integer 0-2};

(E) can be selected from heteroaryl or heterocyclyl.

In accordance with another aspect, there are provided compounds having the structure of Formula Ia:



Formula Ia

15 including racemates, enantiomers and diastereomers thereof, or a pharmaceutically acceptable salt thereof wherein,

(A) can be selected from phenyl, fluorophenyl, heteroaryl or heterocyclyl;

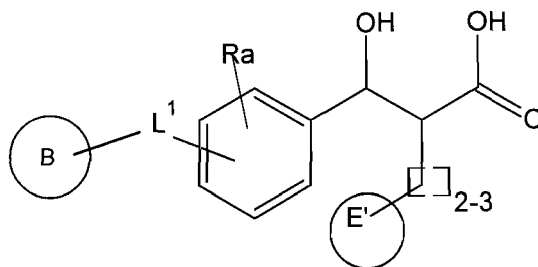
L^1 can be a selected from bond, $-(CH_2)_n$ -, $-NHCO(CH_2)_n$ -, $-(CH_2)_nC(=O)NH$ -, $-NHC(=O)NH$ -, $-SO_2NH$ -, $-NHSO_2$ -, $-SO_2$ -, $-NHC(=O)(O)$ -, $-O-(CH_2)_n$ -, $-(CH_2)_n-O$ -, $-(CH_2)_nOC(=O)NH$ -, $-C(=S)NH$ -, $-NHC(=S)$ - or $-NHC(=S)NH$ - wherein n can be zero or
 20 an integer between 1 and 2;

(B) can be selected from aryl, cycloalkyl, heteroaryl or heterocyclyl, each of which can be further substituted by one or more substituents independently selected from R^1 .

R^1 can be selected from alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno-
 5 C_1 - C_6 alkyl, halogeno- C_1 - C_6 alkoxy, azido, thiol, alkylthiol, $-(CH_2)_n-OR_f$, $-C(=O)-R_f$, $-COOR_f$, $-NR_fR_q$, $-(CH_2)_n-C(=O)NR_fR_q$, $-(CH_2)_n-NHC(=O)-R_f$, $-(CH_2)_n-O-C(=O)-NR_fR_q$, $(CH_2)_n NHC(=O)NR_fR_q$, $-(CH_2)_n-O-C(=O)-R_f$, $-(CH_2)_n-NH-C(=O)-R_f$ or $-(CH_2)_nS(=O)_m-NR_fR_q$ {wherein R_f and R_q are independently selected from hydrogen, alkyl, alkenyl, cycloalkyl aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and
 10 alkylheterocyclyl, n is as defined earlier and m is an integer 0-2};

(E) can be selected from heteroaryl or heterocyclyl.

In yet another aspect, the current invention provides a compound of Formula Ib:

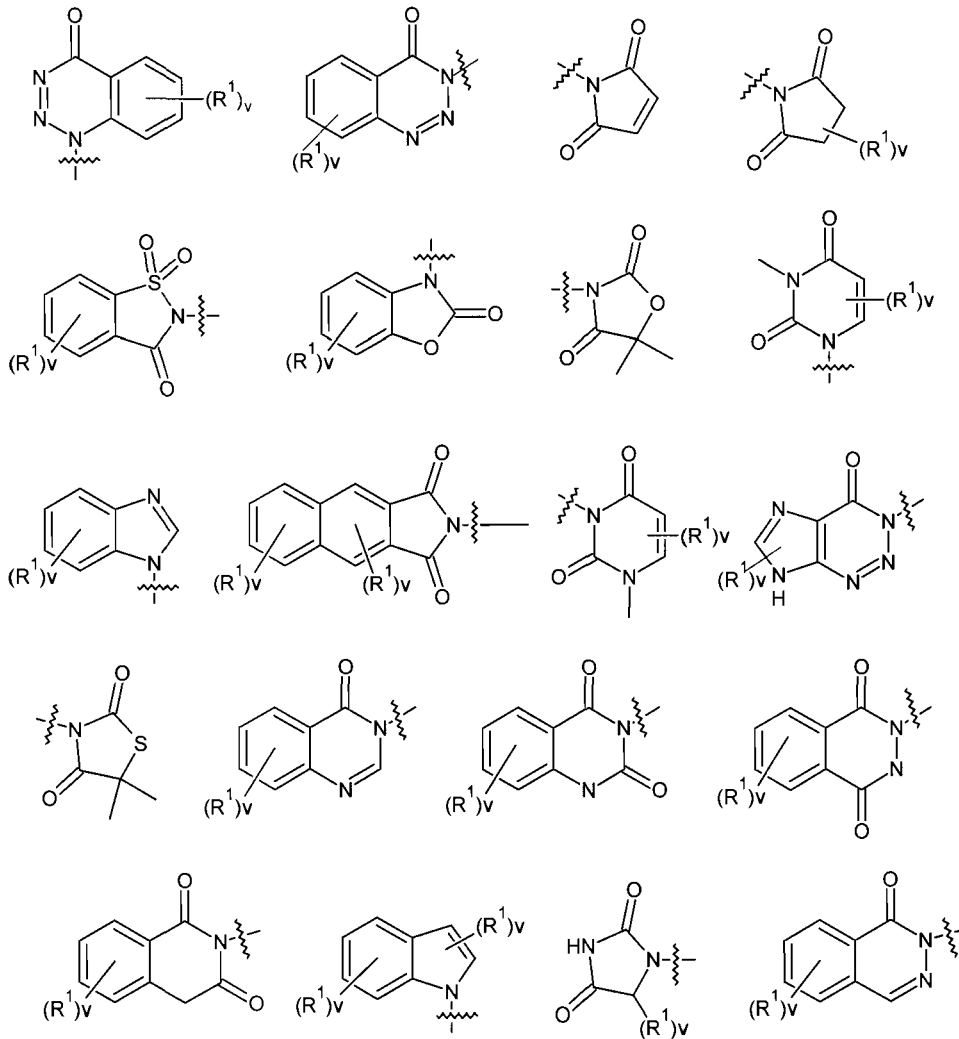


Formula Ib

including racemates, enantiomers and diastereomers thereof, or a pharmaceutically
 15 acceptable salt thereof

wherein,

(E') can be selected from mono, bi or polycyclic heteroaryl or heterocyclyl selected from the following

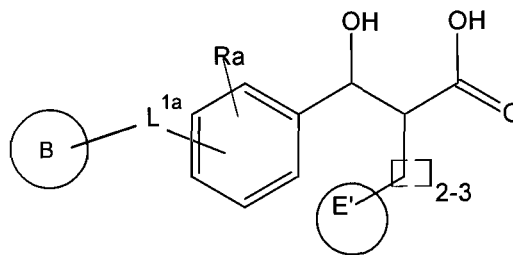


wherein R^1 is as defined earlier and v can be zero or an integer between 1-4.

R_a can be hydrogen or fluorine;

L^1 and \textcircled{B} are as defined earlier.

5 In yet another aspect, the current invention provides a compound of Formula Ic:



Formula Ic

including racemates, enantiomers and diastereomers thereof, or a pharmaceutically acceptable salt thereof, wherein,

L^{1a} is selected from $S(O)_n$, $NHCO(CH_2)_n$ and $NHCO(O)$;

R_a , \textcircled{B} and $\textcircled{E'}$ are as defined earlier.

5 The enantiomers, diastereomers, rotational isomers, *N*-oxides, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates of these compounds, prodrugs and metabolites having the same type of activity are also provided, as well as pharmaceutical compositions comprising the compounds, their metabolites, enantiomers, diastereomers, conformational isomers, *N*-oxides, polymorphs, solvates or
10 pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier and optionally included excipients.

In one embodiment, the invention encompasses compounds of Formula (I), which may include, but are not limited to the following, for example

- 15 (2*S*)-2-[(*S*)-{4-[(4-Chlorophenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 1);
- (2*S*)-2-[(*S*)-{4-[(4-Chlorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 2);
- (2*S*)-2-[(*S*)-{4-[(3,4-Difluorophenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 3);
- 20 (2*S*)-2-[(*S*)-{4-[(2,3-Dichlorophenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 4);
- (2*S*)-2-[(*S*)-{4-[(2,4-Dimethylphenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 5);
- 25 (2*S*)-2-[(*S*)-{4-[(4-Fluorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 6);
- (2*S*)-2-[(*S*)-{4-[(3,4-Difluorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 7);
- 2-[{4-[(2,3-Dichlorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 8);
- 30 (2*S*)-2-[(*S*)-{4-[(2,4-Dimethylphenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 9);
- (2*S*)-2-[(*S*)-(4-{[(4-Ethylphenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 10);
- 35 (2*S*)-2-[(*S*)-(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 11);

- (2*S*)-2-[(*S*)-(4-{[(3,4-Dichlorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 12);
- (2*S*)-2-[(*S*)-Hydroxy(4-{(4-methoxyphenyl)carbonyl]amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 13);
- 5 (2*S*)-2-[(*S*)-Hydroxy(4-{(3-methoxyphenyl)carbonyl]amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 14);
- (2*S*)-2-[(*S*)-Hydroxy(4-{(4-methylphenyl)carbonyl]amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 15);
- 10 (2*S*)-2-[(*S*)-(4-{[(4-Fluorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 16);
- (2*S*)-2-[(*S*)-Hydroxy[4-{(4-methoxy-3-(trifluoromethyl)phenyl)carbonyl]amino}phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 17);
- 15 (2*S*)-2-[(*S*)-Hydroxy(4-{(5-methyl-1,2-oxazol-3-yl)carbonyl]amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 18);
- (2*S*)-2-[(*S*)-(4-{[(3-Chloro-4-fluorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 19);
- 20 (2*S*)-2-[(*S*)-Hydroxy{4-[(phenylcarbonyl)amino]phenyl}methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 20);
- (2*S*)-2-[(*S*)-Hydroxy(4-{(4-propylphenyl)carbonyl]amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 21);
- 25 (2*S*)-2-[(*S*)-Hydroxy{4-[(phenoxycarbonyl)amino]phenyl}methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 22);
- (2*S*)-2-[(*S*)-Hydroxy{4-[(phenylacetyl)amino]phenyl}methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 23);
- (2*S*)-2-[(*S*)-(4-{[(2,4-Dichlorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 24);
- 30 (2*S*)-2-[(*S*)-Hydroxy(4-{(2-methylphenyl)carbonyl]amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 25);
- (2*S*)-2-[(*S*)-(4-{[(2-Fluorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 26);
- 35 (2*S*)-2-[(*S*)-(4-{[(3-Chlorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 27);
- (2*S*)-2-[(*S*)-Hydroxy(4-{(3-methylphenyl)carbonyl]amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 28);
- (2*S*)-2-[(*S*)-(4-{[(3-Fluorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 29);
- 40 (2*S*)-2-[(*S*)-(4-{[(2,6-Dimethoxyphenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 30);

- (2*S*)-2-[(*S*)-{4-[(Cyclopentylcarbonyl)amino]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 31);
- 5 (2*S*)-2-[(*S*)-Hydroxy(4-{(2,4,5-trifluoro-3-methoxyphenyl)carbonyl}amino)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 32);
- (2*S*)-2-[(*S*)-Hydroxy(4-{(2,3,4-trifluorophenyl)carbonyl}amino)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 33);
- (2*S*)-2-[(*S*)-Hydroxy(4-{(2-(trifluoromethyl)phenyl)carbonyl}amino)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 34);
- 10 (2*S*)-2-[(*S*)-(4-{(3,5-Dimethoxyphenyl)carbonyl}amino)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 35);
- (2*S*)-2-[(*S*)-(4-{(2,3-Difluorophenyl)carbonyl}amino)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 36);
- 15 (2*S*)-2-[(*S*)-(4-{(3,5-Dichlorophenyl)carbonyl}amino)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 37);
- (2*S*)-2-[(*S*)-(4-{(2,4-Difluorophenyl)carbonyl}amino)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 38);
- (2*S*)-2-[(*S*)-(4-{(2,6-Difluorophenyl)carbonyl}amino)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 39);
- 20 (2*S*)-2-[(*S*)-Hydroxy(4-{(2-methoxyphenyl)carbonyl}amino)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 40);
- (2*S*)-2-[(*S*)-{4-[(Cyclohexylcarbonyl)amino]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 41);
- (2*S*)-2-[(*S*)-(4-{(4-Ethoxyphenyl)carbonyl}amino)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 42);
- 25 (2*S*)-2-[(*S*)-(4-{(3,4-Difluorophenyl)carbonyl}amino)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 43);
- (2*S*)-2-[(*S*)-Hydroxy(4-{(4-(trifluoromethoxy)phenyl)carbonyl}amino)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 44);
- 30 (2*S*)-2-[(*S*)-Hydroxy(4-{(3-(trifluoromethyl)phenyl)carbonyl}amino)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 45);
- (2*S*)-2-[(*S*)-[4-{(2-Fluoro-4-(trifluoromethyl)phenyl)carbonyl}amino)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 46);
- 35 (2*S*)-2-[(*S*)-(4-{(3-Chloro-2,6-difluorophenyl)carbonyl}amino)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 47);
- (2*S*)-2-[(*S*)-Hydroxy(4-{(4-(trifluoromethyl)phenyl)carbonyl}amino)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 48);
- 40 (2*S*)-2-[(*S*)-(4-{(2,5-Difluorophenyl)carbonyl}amino)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 49);

- (2*S*)-2-[(*S*)-(4-{{(2,3-Difluoro-4-methylphenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 50);
- 5 (2*S*)-2-[(*S*)-[4-({[4-Fluoro-3-(trifluoromethyl)phenyl]carbonyl}amino)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 51);
- (2*S*)-2-[(*S*)-{4-[(Cyclopropylcarbonyl)amino]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 52);
- (2*S*)-2-[(*S*)-(4-{{(2-Ethylphenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 53);
- 10 (2*S*)-2-[(*S*)-Hydroxy(4-{{(4-methoxyphenyl)acetyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 54);
- (2*S*)-2-[(*S*)-{4-[(Cyclobutylcarbonyl)amino]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 55);
- 15 (2*S*)-2-{{(*S*)-Hydroxy[4-(4-methoxyphenoxy)phenyl]methyl}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 56);
- (2*S*)-2-[(*S*)-[4-(3-Chloro-4-fluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 57);
- (2*S*)-2-[(*S*)-[4-(4-Chloro-3-methylphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 58);
- 20 (2*S*)-2-[(*S*)-[4-(4-Chloro-2-fluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 59);
- (2*S*)-2-[(*S*)-[4-(4-Fluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 60);
- (2*S*)-2-[(*S*)-[4-(3,4-Difluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 61);
- 25 (2*S*)-2-[(*S*)-[4-(2-Chlorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 62);
- (2*S*)-2-[(*S*)-[4-(3-Chlorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 63);
- 30 (2*S*)-2-[(*S*)-[4-(2,6-Difluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 64);
- (2*S*)-2-[(*S*)-[4-(2,5-Dichlorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 65);
- (2*S*)-2-[(*S*)-[4-(2-Chloro-4-fluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 66);
- 35 (2*S*)-2-{{(*S*)-Hydroxy[4-(3-methoxyphenoxy)phenyl]methyl}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 67);
- (2*S*)-2-[(*S*)-[4-(2-Chloro-4-methoxyphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 68);

- (2*S*)-2-[(*S*)-[4-(2,4-Difluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 69);
- (2*S*)-2-[(*S*)-[3-Fluoro-4-(4-methylphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 70);
- 5 (2*S*)-2-[(*S*)-[3-Fluoro-4-(3-methylphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 71);
- (2*S*)-2-[(*S*)-[4-(3,4-Dimethylphenoxy)-3-fluorophenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 72);
- 10 (2*S*)-2-[(*S*)-[4-(3,4-Dichlorophenoxy)-3-fluorophenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 73);
- (2*S*)-2-[(*S*)-[4-(4-*tert*-Butylphenoxy)-3-fluorophenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 74);
- (2*S*)-2-[(*S*)-[3-Fluoro-4-(4-methoxyphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 75);
- 15 including racemates, enantiomers and diastereomers thereof, or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein are pharmaceutical compositions comprising therapeutically effective amounts of one or more compounds described herein together with one or more pharmaceutically acceptable carriers, excipients or diluents.

- 20 In another aspect, provided herein are compounds according to Formula I/Ia/Ib/Ic for use in medicine.

In another aspect, provided herein are compounds according to Formula I/Ia/Ib/Ic for use in treating or preventing various inflammatory and allergic diseases comprising administering to a mammal in need thereof.

- 25 In another aspect, provided herein are compounds according to Formula I/Ia/Ib/Ic wherein various inflammatory and allergic diseases are asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, psoriasis, pulmonary fibrosis, pulmonary inflammation, acute respiratory distress syndrome, periodontitis, multiple sclerosis, gingivitis, atherosclerosis, dry eye, neointimal proliferation associated with restenosis and
- 30 ischemic heart failure, stroke, renal disease or tumour metastasis.

In yet another aspect, the present invention relates to the therapeutically effective dose of a compound of Formula I/Ia/Ib/Ic in combination with one or more of other therapeutic agents used for treating various inflammatory and allergic diseases. Examples of such therapeutic agents include, but are not limited to:

- 1) Anti-inflammatory agents, experimental or commercial (i) such as nonsteroidal anti-inflammatory agents piroxicam, diclofenac, propionic acids, fenamates, pyrazolones, salicylates, phosphodiesterase inhibitors including PDE-4 inhibitors, p38 MAP Kinase/Cathepsin inhibitors, CCR-3 antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists, cell adhesion inhibitors (specially ICAM), adenosine 2a agonists, (ii) leukotrienes LTC₄/LTD₄/LTE₄/LTB₄-Inhibitors, 5-lipoxygenase inhibitors and PAF-receptor antagonists, (iii) Cox-2 inhibitors (iv) other MMP inhibitors, (v) interleukin-I inhibitors, (vi) corticosteroids such as alclometasone, amcinonide, amelometasone, beclometasone, betamethasone, budesonide, ciclesonide, clobetasol, cloticasone, cyclomethasone, deflazacort, deprodone, dexbudesonide, diflorasone, difluprednate, fluticasone, flunisolide, halometasone, haloperedone, hydrocortisone, methylprednisolone, mometasone, prednicarbate, prednisolone, rimexolone, tixocortol, triamcinolone, ulobetasol, rofleponide, GW 215864, KSR 592, ST-126, dexamethasone and pharmaceutically acceptable salts, solvates thereof. Preferred corticosteroids include, for example, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, and dexamethasone;
- 2) Beta-agonists, experimental or commercial (i) suitable β 2-agonists include, for example, one or more of albuterol, salbutamol, biltolterol, pirbuterol, levosalbutamol, tulobuterol, terbutaline, bambuterol, metaproterenol, fenoterol, salmeterol, carmoterol, arformoterol, formoterol, and their pharmaceutically acceptable salts or solvates thereof one or more β 2- agonists may be chosen from those in the art or subsequently discovered. (ii) The β 2-agonists may include one or more compounds described in, for example, U.S. Patent Nos. 3,705,233; 3,644,353; 3,642,896; 3,700,681; 4,579,985; 3,994,974; 3,937,838; 4,419,364; 5,126,375; 5,243,076; 4,992,474; and 4,011,258;
- 3) antihypertensive agents, (i) ACE inhibitors, *e.g.*, enalapril, lisinopril, valsartan, telmisartan and quinapril, (ii) angiotensin II receptor antagonists and agonists, *e.g.*, losartan, candesartan, irbesartan, valsartan, and eprosartan, (iii) β -blockers, and (iv) calcium channel blockers;

- 4) immunosuppressive agents, for example, cyclosporine, azathioprine and methotrexate, anti-inflammatory corticosteroids; and
- 5) anti-infective agents (*e.g.*, antibiotics, antivirals).

Definitions

5 The following definitions apply to terms, as used herein:

The term “*alkyl*” refers to a straight or branched fully saturated hydrocarbon chain which is optionally substituted by one or more halo atom, and which has 1 to 20 carbon atoms unless otherwise specified. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *t*-butyl, *n*-hexyl, *n*-decyl, *n*-tetradecyl,
10 trifluoromethyl, chloroethyl, and the like.

The term “*alkenyl*”, unless otherwise specified, refers to a branched or unbranched unsaturated hydrocarbon group containing at least one double bond with *cis* or *trans* geometry and preferably having 2 to 20 carbon atoms. Examples of alkenyl group include ethenyl, 2-propenyl and isopropenyl.

15 The term “*cycloalkyl*” refers to a non aromatic cyclic group having 3 to 20 ring carbon atoms and form one to three rings and may optionally contain one or more olefinic bonds. Polycyclic ring systems may be a spiro, fused or bridged arrangement. Cycloalkyl groups include, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, adamantyl, bicyclo[2.2.1]heptanyl,
20 bicyclo[2.2.2]octane, tricycle[3.3.1.1]decane, and the like.

The term “*aryl*” refers to an aromatic system having from 6 to 14 carbon atoms and up to three rings which may be fused or directly joined. Representative examples of such aryl group include, but are not limited to, phenyl, biphenyl, naphthyl, phenanthrene, anthracenyl, azulenyl, and indanyl. Aryl group may also comprise one or more rings
25 which are not fully aromatic and examples of such system are indane, indene, 2, 3 dihydrobenzofuran and 1,2,3,4-tetrahydronaphthalene

The term “*heteroaryl*” refers to an aromatic system having from 5 to 14 membered carbon atoms and up to three rings, which may be fused or directly joined, and containing from one to eight heteroatoms selected from N, O and S. Examples of heteroaryl groups
30 are pyridinyl, quinolinyl, oxazolyl, imidazolyl, pyrrolyl, thiophenyl, 1,2,3-triazolyl, 1,2,4-

triazolyl, tetrazolyl, thiazolyl, oxadiazolyl, benzoimidazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, and the like.

The term "*heterocyclyl*" refers to a non-aromatic monocyclic or polycyclic ring system, which may be fused spiro or bridged, having 3 to 12 ring atoms and up to eight heteroatoms selected from N, O and S. Examples of heterocyclyl ring systems include piperidine, morpholine, piperazine, isoquinoline, oxazolidine, tetrahydrofuran, dihydrofuran, dihydropyridine, dihydroisoxazole, dihydrobenzofuran, azabicyclohexane, dihydroindole, tetrahydroquinoline, pyrrolidine, azepine, azetidine, aziridine, tetrahydropyridine, benzthiazine, benzoxazinyl, isoindoline, azabicyclo[3.1.0]hexyl, phenoxazine, tetrahydropyran, 1,4-dioxane, and the like.

The terms "*cycloalkylalkyl*", "*arylalkyl*", "*heteroarylalkyl*", "*heterocyclalkyl*", refers respectively, to cycloalkyl, aryl, heteroaryl or heterocyclyl group linked to the remainder of the molecule *via* an alkyl group.

The term "*amino*" refers to -NH₂.

The term "*alkoxy*" denotes the group O-alkyl, wherein alkyl is the same as defined above.

The term "*halogen*" or "*halo*" refers to fluorine, chlorine, bromine or iodine.

The term "*halogeno-C₁-C₆alkyl*" refers to C₁-C₆ alkyl of which one or more hydrogen(s) is/are replaced by halogen.

The term "*halogeno C₁-C₆ alkoxy*" refers to as halogen atom bonded to C₁-C₆ alkoxy group. Examples of such groups include trifluoromethoxy, trichloromethoxy, difluoromethoxy, fluoromethoxy, 2,2,2-trifluoroethoxy, 2-bromoethoxy etc.

The term "*hydroxyl*" or "*hydroxy*" refers to -OH.

The term "*thiol*" refers to the group -SH.

The term "*alkylthiol*" refers to a thiol group when hydrogen is replaced by alkyl, for example, methylthio, ethylthio, propylthio, t-butylthio, cyclopropylthio, and the like.

The term "*cyano*" refers to as C≡N.

The term "*azido*" refers to as N=N=N.

The term “*leaving group*” refers to groups that exhibit or potentially exhibit the properties of being labile under the synthetic conditions and also of being readily separated from synthetic products under defined conditions. Examples of leaving groups include, but are not limited to, halogen (*e.g.*, F, Cl, Br, I), triflates, tosylate, mesylates, alkoxy, thioalkoxy, or hydroxy radicals, and the like.

The term “*protecting groups*” refers to moieties that prevent chemical reaction at a location of a molecule intended to be left unaffected during chemical modification of such molecule. Unless otherwise specified, protecting groups may be used on groups, such as hydroxy, amino, or carboxy. Examples of protecting groups are found in T.W. Greene and P.G.M. Wuts, “Protective Groups in Organic Synthesis”, 2nd Ed., John Wiley and Sons, New York, N.Y. The species of the carboxylic protecting groups, amino protecting groups or hydroxy protecting groups employed are not critical, as long as the derivatised moieties/moiety are/is stable to conditions of subsequent reactions and can be removed without disrupting the remainder of the molecule.

Compounds described herein can contain one or more asymmetric carbon atoms and thus occur as diastereomers. These compounds can also exist as conformers/rotamers. All such isomeric forms of these compounds are included herein. Each stereogenic carbon may be of the *R* or *S* configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are envisioned.

The term “*pharmaceutically acceptable salts*” forming part of this invention includes the salts of carboxylic acid moiety, which may be prepared by reacting the compound with appropriate base to provide corresponding base addition salts. Examples of such bases are alkali metal hydroxide including potassium hydroxide, sodium hydroxide and lithium hydroxide; alkaline earth metal hydroxides such as magnesium hydroxide and calcium hydroxide. Further, the salts of organic bases such as lysine, arginine, guanidine, ethanolamine, choline and the like; inorganic bases *e.g.*, ammonium or substituted ammonium salts are also included. Wherever appropriate, compounds of the present invention may also form the acid addition salts by treating the said compounds with pharmaceutically acceptable organic and inorganic acids, *e.g.*, hydrohalides such as hydrochloride, hydrobromide, hydroiodide; other mineral acids and their corresponding

salts such as sulphate, nitrate, phosphate, etc.; and alkyl and mono-arylsulphonates, such as ethane sulphonate, toluene sulphonate and benzene sulphonate; and other organic acids and their corresponding salts such as acetate, tartarate, maleate, succinate, citrate, etc. The salt forms differ from the compound described herein in certain physical properties such as solubility, but the salts are otherwise equivalent for the purpose of this invention.

The term “*pharmaceutically acceptable solvates*” refers to solvates with water (*i.e.*, hydrates) or pharmaceutically acceptable solvents, for example, solvates with ethanol, and the like. Such solvates are also encompassed within the scope of the disclosure. Furthermore, some of the crystalline forms for compounds described herein may exist as *polymorphs* and as such are intended to be included in the scope of the disclosure.

The term “*polymorphs*” includes all crystalline forms as well as amorphous forms for compounds described herein and as such are included in the present invention.

The term “*pharmaceutically acceptable carriers*” is intended to include non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type.

The term “*pharmaceutically acceptable*” means approved by the regulatory agency of the federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans.

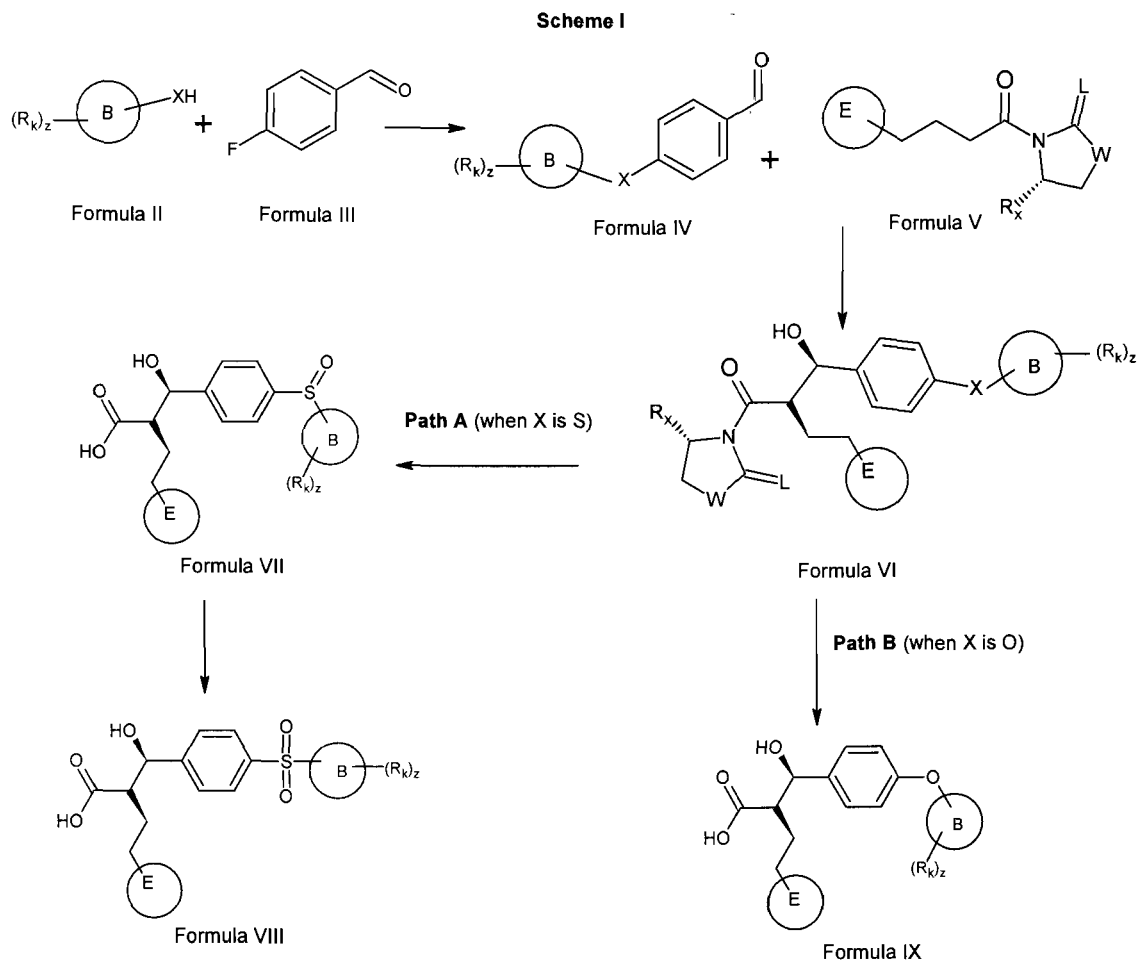
Examples of inflammatory conditions and autoimmune disorders in which the compounds of the invention have potentially beneficial effects in treatment methods may include, but are not limited to diseases of the respiratory tract such as asthma (including allergen-induced asthmatic reactions), cystic fibrosis, bronchitis (including chronic bronchitis), chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), chronic pulmonary inflammation, rhinitis and upper respiratory tract inflammatory disorders (URID), ventilator induced lung injury, silicosis, pulmonary sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, arthritis, *e.g.*, rheumatoid arthritis, osteoarthritis, infectious arthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, Reiter’s syndrome, gouty arthritis and prosthetic joint failure, gout, acute synovitis, spondylitis and non-articular inflammatory conditions, *e.g.*, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitic, fibromyalgic syndrome and other inflammatory conditions associated with

ligamentous sprain and regional musculoskeletal strain, inflammatory disorders of the gastrointestinal tract, *e.g.*, ulcerative colitis, diverticulitis, Crohn's disease, inflammatory bowel diseases, irritable bowel syndrome and gastritis, multiple sclerosis, systemic lupus erythematosus, scleroderma, autoimmune exocrinopathy, autoimmune encephalomyelitis, diabetes, tumor angiogenesis and metastasis, cancer including carcinoma of the breast, colon, rectum, lung, kidney, ovary, stomach, uterus, pancreas, liver, oral, laryngeal and prostate, melanoma, acute and chronic leukemia, periodontal disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy, muscle degeneration, inguinal hernia, retinal degeneration, diabetic retinopathy, macular degeneration, inguinal hernia, ocular inflammation, bone resorption diseases, osteoporosis, osteopetrosis, graft vs. host reaction, allograft rejections, sepsis, endotoxemia, toxic shock syndrome, tuberculosis, usual interstitial and cryptogenic organizing pneumonia, bacterial meningitis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), malaria, leprosy, leishmaniasis, Lyme disease, glomerulonephritis, glomerulosclerosis, renal fibrosis, liver fibrosis, pancreatitis, hepatitis, endometriosis, pain, *e.g.*, that associated with inflammation and/or trauma, inflammatory diseases of the skin, *e.g.*, dermatitis, dermatosis, skin ulcers, psoriasis, eczema, systemic vasculitis, vascular dementia, thrombosis, atherosclerosis, restenosis, reperfusion injury, plaque calcification, myocarditis, aneurysm, stroke, pulmonary hypertension, left ventricular remodeling and heart failure. It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

Compounds disclosed herein may be prepared, for example, by techniques well known in the organic synthesis and familiar to a practitioner ordinarily skilled in art of this invention. In addition, the processes described herein may enable the synthesis of the compounds of the present invention. However, these may not be the only means by which the compounds described in the invention may be synthesized. Further, the various synthetic steps described herein may be performed in alternate sequences in order to furnish the desired compounds.

The compounds of the said invention can be prepared following any of the below Schemes.

The compounds of Formulae VII, VIII and IX can be prepared by following Scheme I.



Accordingly, the compound of Formula II (wherein B is as defined earlier, X is O or S and R_k is H, halo, alkyl, alkoxy, cyano, halogeno- C_1 - C_6 alkyl or halogeno- C_1 - C_6 alkoxy and z is 0-4) can react with a compound of Formula III to give a compound of

Formula IV, which then reacts with a compound of Formula V (wherein E is as defined earlier, L and W are O or S respectively and R_x is alkyl, aryl or aralkyl) to give a compound of Formula VI.

Path A (When X is S): The compound of Formula VI undergoes hydrolysis to give a compound of Formula VII, which then further undergoes oxidation to give a compound of Formula VIII.

Path B (When X is O): The compound of Formula VI undergoes hydrolysis to give a compound of Formula IX.

The reaction of a compound of Formula II with a compound of Formula III to give a compound of Formula IV can be carried out in the presence of a base, for example, potassium carbonate, cesium carbonate, sodium acetate or potassium acetate in a solvent, for example, dimethylformamide, acetonitrile, toluene, tetrahydrofuran, acetone, dioxane, or mixture(s) thereof.

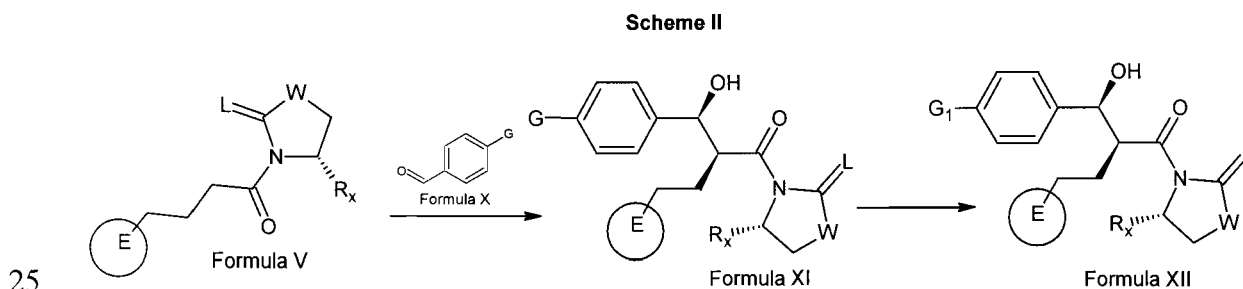
The asymmetric aldol addition of a compound of Formula IV with a compound of Formula V to give a compound of Formula VI can be carried out by generating the enolates with titanium tetrachloride, dibutyl boron triflate, dialkyl boron chloride or tin(II) triflate, in the presence of a base, for example, tetramethylethylenediamine, diisopropylethylamine, tributylamine, *N*-ethylpiperidine, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, tetramethylpropylenediamine or (-) sparteine, in a solvent, for example, dichloromethane or diethyl ether.

Hydrolysis of a compound of Formula VI (Path A, when X is S) to give a compound of Formula VII can be carried out with hydrogen peroxide and lithium hydroxide, in the presence of a solvent, for example, tetrahydrofuran, water, or mixture(s) thereof.

Oxidation of a compound of Formula VII to give a compound of Formula VIII can be carried out with an oxidizing agent, for example, meta chloro perbenzoic acid, oxone or hydrogen peroxide, in a solvent, for example, chloroform, dichloromethane, methanol, water, tetrachloromethane, or mixture(s) thereof.

Hydrolysis of a compound of Formula VI (Path B, when X is O) to give a compound of Formula IX can be carried out in a similar way as the hydrolysis of compound of Formula VI to give a compound of Formula VII.

The compound of Formula XII can be prepared by following Scheme II.

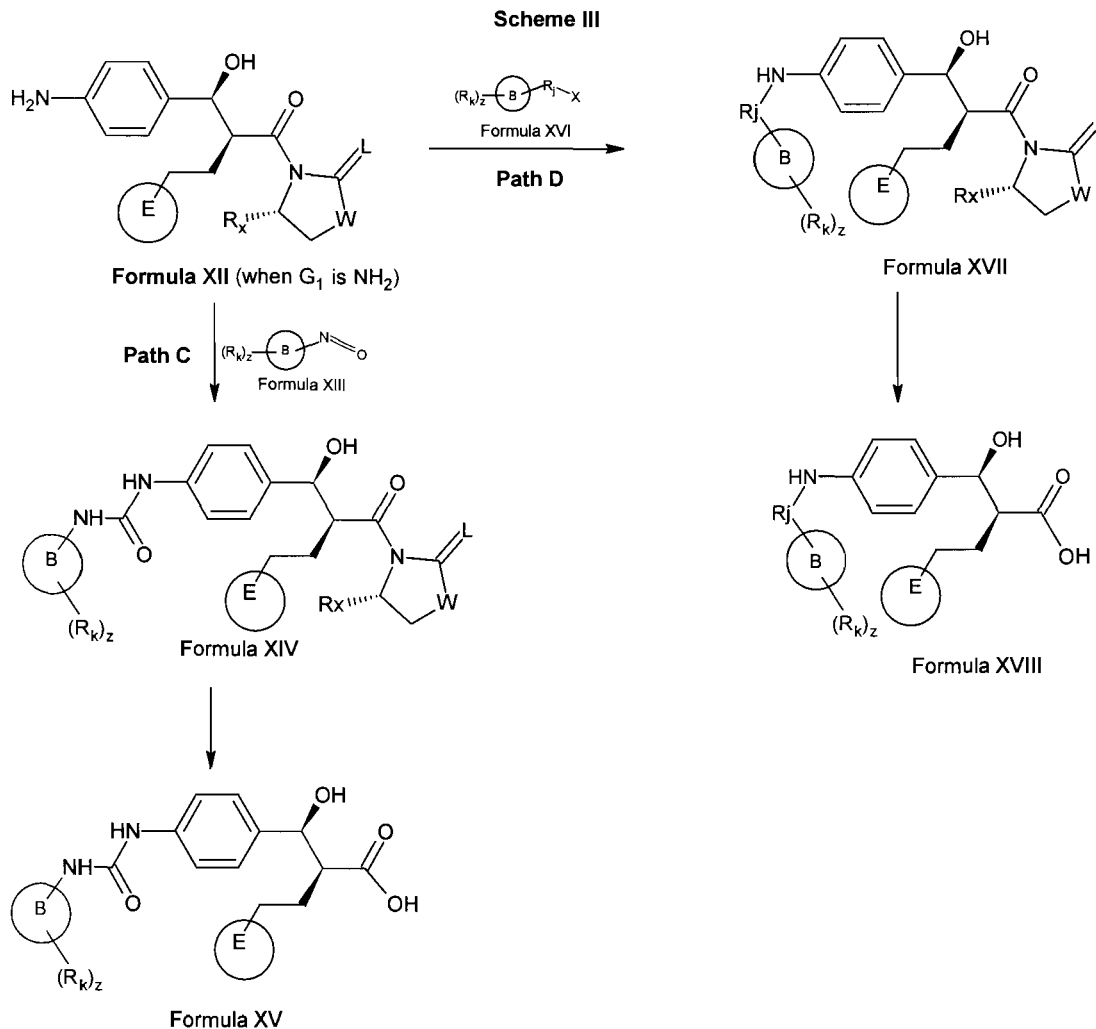


Accordingly, the compound of Formula V (wherein E , L, W and R_x are as defined earlier) undergoes aldol addition with a compound of Formula X (wherein G can be nitro or C(O)O-benzyl) to give a compound of Formula XI, which then can be reduced to give a compound of Formula XII (wherein G_1 can be amino or COOH).

5 Aldol addition of a compound of Formula X to a compound of Formula V to give a compound of Formula XI can be carried out in a similar way as the aldol addition of a compound of Formula IV with a compound of Formula V to give a compound of Formula VI.

10 Reduction of a compound of Formula XI to give a compound of Formula XII can be carried out with one or more reducing agents, for example, palladium-carbon/hydrogen, Raney nickel/hydrogen, platinum/hydrogen or mixture thereof in a solvent, for example, tetrahydrofuran, methanol, ethanol, propanol, isopropanol, or mixtures thereof.

The compound of Formula XV and XVIII can be prepared by following Scheme III.



Accordingly, the compound of Formula XII (when G₁ is amino) can react through two pathways.

Path C: Compound of Formula XII couples with a compound of Formula XIII (wherein R_k and z are as defined earlier) to give a compound of Formula XIV, which then undergoes hydrolysis to give a compound of Formula XV.

Path D: Compound of Formula XII couples with a compound of Formula XVI (wherein X is a leaving group for example halogen and R_j is -(CH₂)₀₋₁-CO-, -C(O)O-, -SO₂-, and R_k is as defined earlier) to give a compound of Formula XVII, which then undergo hydrolysis to give a compound of Formula XVIII.

The coupling of a compound of Formula XII with a compound of Formula XIII to give a compound of Formula XIV (Path C) can be carried out with a suitable base, for example, potassium carbonate, sodium carbonate, triethylamine, diisopropylethyl amine,

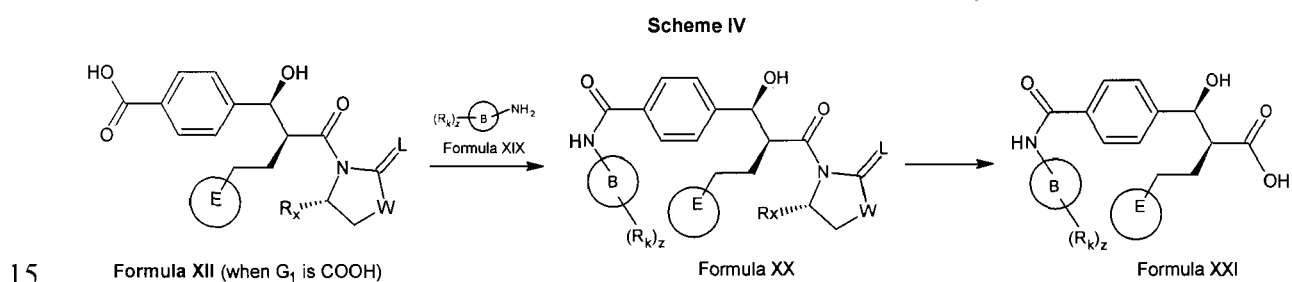
etc. in the presence of solvents like acetonitrile, dimethylformamide, toluene, tetrahydrofuran, acetone or dioxane, etc.

Hydrolysis of compound of Formula XIV to give a compound of Formula XV can be carried out in a similar way as the hydrolysis of compound of Formula VI to give a compound of Formula VII.

The coupling of compound of Formula XII with a compound of Formula XVI to give a compound of Formula XVII (Path D) can be carried out with a base, for example, triethylamine (TEA), *N*-methyl-morpholine (NMM), *N,N*-dimethylaminopyridine (DMAP) or *N,N*-diisopropylethylamine (DIPEA) in a solvent, for example, dichloromethane, tetrahydrofuran, dimethylformamide, dioxane, acetonitrile or acetone.

Hydrolysis of compound of Formula XVII to give a compound of Formula XVIII can be carried out in a similar way as the hydrolysis of compound of Formula VI to give a compound of Formula VII.

The compound of Formula XXI can be synthesized by following Scheme IV.



Accordingly, the compound of Formula XII (when G_1 is COOH) can couple with a compound of Formula XIX to give a compound of Formula XX, which then undergoes hydrolysis to give a compound of Formula XXI.

The coupling of compound of Formula XII with a compound of Formula XIX to give a compound of Formula XX can be carried out in the presence of a coupling agent 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) or *N,N*-dicyclohexylcarbodiimide (DCC) and optionally activating catalyst HOBT and an organic base dimethylaminopyridine, *N*-methylmorpholine or diisopropylethylamine, in an organic solvent, for example, dichloromethane, dichloroethane, chloroform and carbon tetrachloride. Alternatively, XII can also be activated by converting to the corresponding

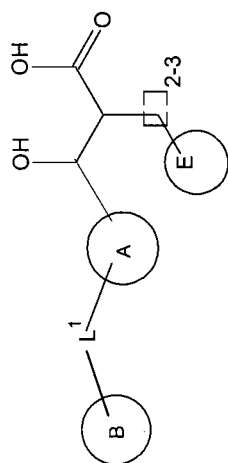
acid chloride (using thionyl chloride, oxalyl chloride, etc.) or the anhydride (pivaloyl chloride, etc.) and coupled with the corresponding anilines.

Hydrolysis of compound of Formula XX to give a compound of Formula XXI can be carried out in a similar way as the hydrolysis of compound of Formula VI to give a
5 compound of Formula VII.

In the above schemes, where specific reagents, for example, bases, acids, solvents, condensing agents, hydrolyzing agents, catalysts etc., as mentioned, is to be understood that other reagents, *e.g.*, other acids, bases, solvents, condensing agents, reducing agents, deprotecting agents, hydrolyzing agents, catalysts, etc., known to one of ordinary skill in
10 the art may be used. Similarly, reaction temperatures and durations may be adjusted according to the desired needs without undue experimentation and well within the abilities of one of ordinary skill in the art.

Table 1 lists the type of compounds synthesized by using the synthetic procedure as demonstrated in Schemes I-IV.

Table I

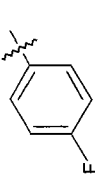
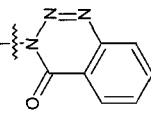
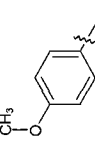
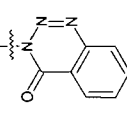
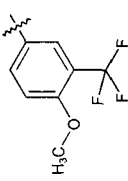
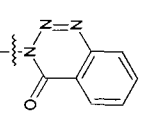

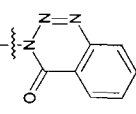
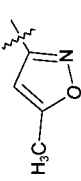
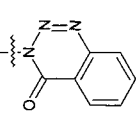
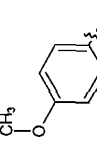
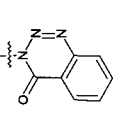
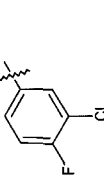
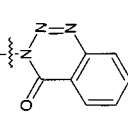
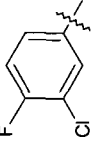
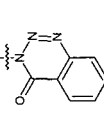
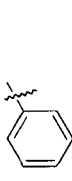
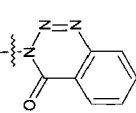
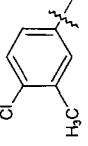
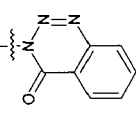
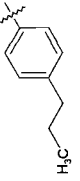
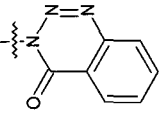
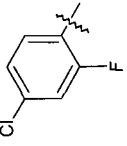
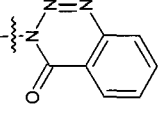


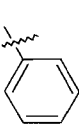
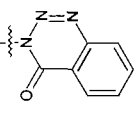
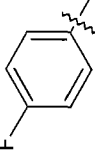
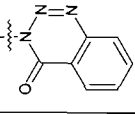
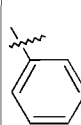
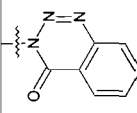
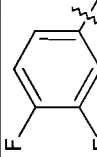
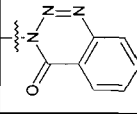
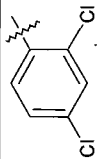
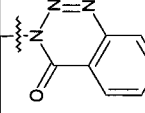
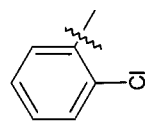
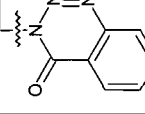
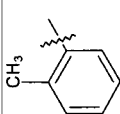
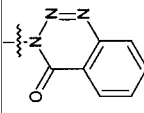
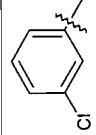
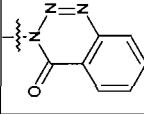
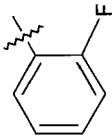
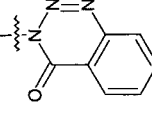
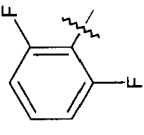
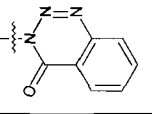
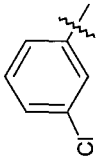
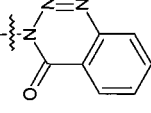
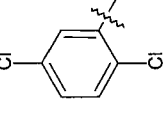
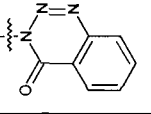
Formula Ia

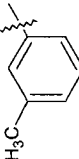
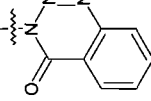
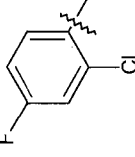
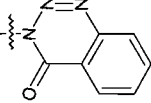
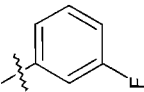
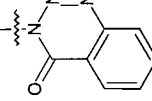
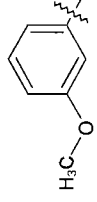
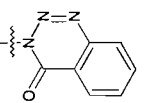
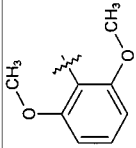
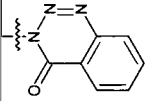
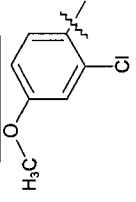
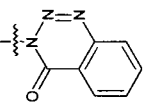
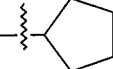
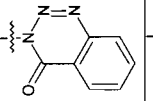
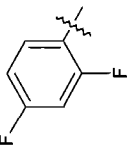
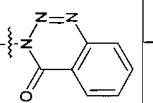
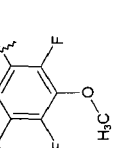
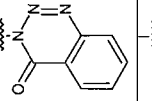
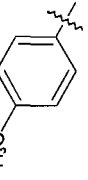
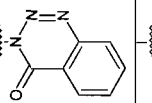
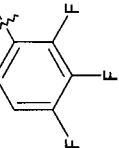
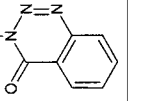
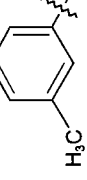
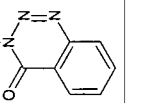
S.No.	B	L ¹	E	S.No.	B	L ¹	E
1		-S(O)-		39		-CONH-	
2		-SO ₂ -		40		-CONH-	
3		-S(O)-		41		-CONH-	

S.No.	B	L ¹	E	S.No.	B	L ¹	E
4		-S(O)-		42		-CONH-	
5		-S(O)-		43		-CONH-	
6		-SO2-		44		-CONH-	
7		-SO2-		45		-CONH-	
8		-SO2-		46		-CONH-	
9		-SO2-		47		-CONH-	

S.No.	B	L ¹	E	S.No.	B	L ¹	E
10		-CONH-		48		-CONH-	
11		-CONH-		49		-CONH-	
12		-CONH-		50		-CONH-	
13		-CONH-		51		-CONH-	
14		-CONH-		52		-CONH-	
15		-CONH-		53		-CONH-	

S.No.	B	L ¹	E	S.No.	B	L ¹	E
16		-CONH-		54		-CH ₂ CONH-	
17		-CONH-		55		-CONH-	
18		-CONH-		56		-O-	
19		-CONH-		57		-O-	
20		-CONH-		58		-O-	
21		-CONH-		59		-O-	

S.No.	B	L ¹	E	S.No.	B	L ¹	E
22		-CONH-		60		-O-	
23		-CH ₂ CONH-		61		-O-	
24		-CONH-		62		-O-	
25		-CONH-		63		-O-	
26		-CONH-		64		-O-	
27		-CONH-		65		-O-	

S.No.	B	L ¹	E	S.No.	B	L ¹	E
28		-CONH-		66		-O-	
29		-CONH-		67		-O-	
30		-CONH-		68		-O-	
31		-CONH-		69		-O-	
32		-CONH-		70		-O-	
33		-CONH-		71		-O-	

S.No.	B	L'	E	S.No.	B	L'	E
34		-CONH-		72		-O-	
35		-CONH-		73		-O-	
36		-CONH-		74		-O-	
37		-CONH-		75		-O-	
38		-CONH-					

The compounds, described herein, may be administered to an animal for treatment orally, topically, rectally, internasally or by parenteral route. Pharmaceutical compositions disclosed herein comprise pharmaceutically effective amounts of compounds described herein formulated together with one or more pharmaceutically acceptable carriers,
5 excipients or diluents.

Solid form preparations for oral administration include capsules, tablets, pills, powder, granules, lozenges, troches, and cachets. For solid form preparations, active compounds can be mixed with one or more inert, pharmaceutically acceptable excipients or carriers, for example, sodium citrate, dicalcium phosphate and/or fillers or extenders (for example,
10 starches, lactose, sucrose, glucose, mannitol, silicic acid, or mixtures thereof); binders, for example, carboxymethylcellulose, alginates, gelatins, polyvinylpyrrolidone, sucrose, acacia or mixtures thereof; disintegrating agents, for example, agar-agar, calcium carbonate, potato starch, alginic acid, certain silicates, sodium carbonate, or mixtures thereof; absorption
15 acceletors, for example, quaternary ammonium compounds; wetting agents, for example, cetyl alcohol, glycerol mono stearate or mixtures thereof; adsorbants, for example, Kaolin; lubricants, for example, talc, calcium stearate, magnesium stearate, solid polyethyleneglycol, sodium lauryl sulfate, or mixtures thereof.

Capsules, tablets or pills may also comprise buffering agents.

Tablets, capsules, pills or granules can be prepared using one or more coatings or
20 shells to modulate the release of active ingredients, for example, enteric coatings or other coatings known to one of ordinary skill in the art.

Liquid form preparations for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups or elixirs. In such liquid form preparations, active compounds can be mixed with water or one or more non-toxic
25 solvents, solubilizing agents or emulsifiers, for example, water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, for example, cottonseed, groundnut, corn, germ, olive, castor and sesame oil, glycerol, fatty acid esters of sorbitan or mixtures thereof. Oral compositions can also include one or more adjuvants, for example, wetting
30 agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, or mixtures thereof.

Injectable preparations, for example, sterile injections, and aqueous suspensions may be formulated according to methods known to one of ordinary skill in the art, and in particular, using one or more suitable dispersing or wetting and suspending agents. Acceptable vehicles and solvents that may be employed include one or more of water,
5 Ringer's solution, isotonic sodium chloride, or mixtures thereof.

Suppositories for rectal administration of the compound of this invention can be prepared by mixing the drug with suitable nonirritating excipients, such as cocoa butter and polyethylene glycols, which are solid at ordinary temperatures but liquid at body temperature and which therefore melt in the rectum and release the drug.

10 Dosage forms for topical or transdermal administration of a compound of the present invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. Active compounds can be admixed under sterile condition with one or more pharmaceutically acceptable carriers and optionally any preservatives or buffers as may be required. Ophthalmic formulations, eardrops, eye ointments, powders
15 and solutions are also encompassed within the scope of this invention.

Pharmaceutical preparations may be in unit dosage form. In unit dosage form, the preparations can be subdivided into unit doses containing appropriate quantities of active components. Unit dosage forms can be packed preparations containing discrete capsules, powders, in vials or ampoules, ointments, capsules, sachets, tablets, gels, creams or any
20 combination and number of such packed forms.

EXPERIMENTAL PROCEDURES

Various solvents, for example, dimethylformamide, benzene, tetrahydrofuran, etc., were dried using various drying reagents according to procedure as described in the literature.

25 Synthesis of starting materials:

Synthesis of 3-[4-((4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl)-4-oxobutyl]-3*H*-benzo[d][1,2,3] triazin-4-one

Synthesis of the title compound was carried out according to reference procedure described in WO 2008/023336, p. 54-55.

30

Synthetic procedures for Scheme I (Path A)

Example I: Synthesis of (2*S*)-2-[(*S*)-{4-[(4-Chlorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(*H*)-yl)butanoic acid (Compound No. 2)

Step 1: Synthesis of 4-[(4-chlorophenyl)sulfanyl]benzaldehyde

5 To a solution of 4-chlorothiophenol (1.0 g, 0.0069 mol) in dimethylformamide (5ml), potassium carbonate (2.8 g, 0.0207 mol) and 4-fluorobenzaldehyde (0.904 g, 0.0072 mol) were added and the reaction mixture was heated to about 100°C for about 4 hours. After completion of reaction, water was added and extracted in ethyl acetate. Organic layer was concentrated, purified by column using 7% ethyl acetate/hexane as
10 eluent to obtain the title compound. (Yield: 0.6g)

Mass-248

LCMS-M+1 (248.97)

**Step 2: Synthesis of 3-{(3*S*)-4-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-3-[(*S*)-{4-[(4-chlorophenyl)sulfanyl]phenyl}(hydroxy)methyl]-4-oxobutyl}-1,2,3-benzotriazin-
15 4(*H*)-one**

To a solution of the 3-{4-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-4-oxobutyl}-1,2,3-benzotriazin-4(*H*)-one (0.2 g, 0.00049 mol) in dichloromethane (5ml) under argon atmosphere cooled to about 0°C, titanium tetrachloride (0.12 g, 0.00063 mol) was added slowly. After about 30 minutes, tetramethylethylenediamine (0.068 g, 0.00058 mol) was
20 added at about 0°C. The reaction mixture was stirred for about 45 minutes at the same temperature and then a solution of 4-[(4-chlorophenyl)sulfanyl]benzaldehyde (0.206 g, 0.00083 mol) in dichloromethane (5 ml) was added very slowly. This reaction mixture was again stirred for about 5 hours at room temperature. On completion, the reaction was quenched with ammonium chloride solution and subsequently by dilute hydrochloric acid
25 and then extracted with dichloromethane and water, purified by column using 8% ethyl acetate/hexane as eluent to obtain the title compound. (Yield: 0.150 g)

Mass-657

LCMS-M+1 (658.02)

Step 3: Synthesis of (2S)-2-[(S)-{4-[(4-chlorophenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound No. 1)

To a solution of the 3-{(3S)-4-[(4S)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-3-[(S)-{4-[(4-chlorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-oxobutyl}-1,2,3-benzotriazin-4(3H)-one (0.1 g, 0.0001 mol) in tetrahydrofuran (5ml) under argon atmosphere at 0°C, hydrogen peroxide solution (0.0102 g, 0.0003 mol) and then lithium hydroxide (0.006 g, 0.00015 mol) were added. The reaction mixture was stirred for about 2 hours at room temperature. The reaction was quenched by acidifying the reaction mixture with sodium bisulfate and extracting in ethyl acetate and water. Organic layer thus obtained was concentrated and purified by preparative TLC using 10% methanol/dichloromethane as eluent to obtain the title compound. (Yield: 0.090 g)

MS-497.95

LCMS-M-1 (496.04)

NMR (DMSO-*d*₆, 400 MHz) δ : 8.04-8.06 (2H, d, *J* = 8.0 Hz), 7.92-7.93 (1H, d, *J* = 4.0Hz), 7.81-7.83 (1H, d, *J* = 8.0 Hz), 7.67-7.69 (2H, d, *J* = 8.0 Hz), 7.57-7.59 (4H, d, *J* = 8 Hz), 7.42-7.44 (2H, d, *J* = 8 Hz), 4.84 (1H, m), 4.38-4.29 (2H, m), 2.54-2.57 (1H, m), 2.07 (1H, m), 1.89 (1H, m).

The following compounds were prepared by following above route of synthesis:

(2S)-2-[(S)-{4-[(3,4-difluorophenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound No. 3);
Mass: 499.48

(2S)-2-[(S)-{4-[(2,3-dichlorophenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound No. 4);
Mass: 532.39

(2S)-2-[(S)-{4-[(2,4-dimethylphenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound No. 5);
Mass: 491.55

Step 4: Synthesis of (2S)-2-[(S)-{4-[(4-chlorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound No. 2)

To a solution of (2S)-2-[(S)-{4-[(4-chlorophenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (0.09 g, 0.00018 mol) in chloroform (5ml) at about 0°C, metachloroperbenzoic acid (0.124 g, 0.00072 mol) was added and the reaction mixture was stirred for about 1 hour at room temperature. On completion, the

reaction was quenched by sodium metabisulphite solution and then extracted in dichloromethane. The organic layer was dried with sodium sulphate and concentrated, purified by preparative TLC and eluted in 10% methanol/dichloromethane to obtain the title compound. (Yield: 0.04 g)

5 MS-513.95

LCMS-M-1 (512.00)

NMR(DMSO_{d6}, 400 MHz) δ : 8.16 (2H, m), 8.08 (1H, m), 7.93-7.95 (4H, d, $J = 8.0$ Hz), 7.82-7.84 (1H, d, $J = 8.0$ Hz), 7.68-7.70 (2H, d, $J = 8$ Hz), 7.53-7.55 (2H, d, $J = 8$ Hz), 4.90 (1H, m), 4.30-4.40 (2H, m), 2.50 (1H, m), 1.90-2.10 (2H, m).

10 The following compounds can be prepared by following above route of synthesis:

(2*S*)-2-[(*S*)-{4-[(4-Fluorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 6)
Mass: 497.49

15 (2*S*)-2-[(*S*)-{4-[(3,4-Difluorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 7)
Mass: 515.48

2-[{4-[(2,3-Dichlorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 8)
Mass: 548.39

20 (2*S*)-2-[(*S*)-{4-[(2,4-Dimethylphenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 9)
Mass: 507.55

Synthetic procedure for Scheme I (Path B)

25 Example II: Synthesis of (2*S*)-2-[(*S*)-Hydroxy[4-(4-methoxyphenoxy)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 56)

Step 1: Synthesis of 4-(4-methoxyphenoxy)benzaldehyde

To a solution of 4-methoxy phenol (1.0 g, 0.0080 mol) in dimethylformamide (5ml), potassium carbonate (3.3 g, 0.024 mol) and 4-fluorobenzaldehyde (1.1 g, 0.0088 mol) were added and the reaction mixture was heated to about 100°C for about 4 hours.

30 On completion of reaction, water was added to it and extracted in ethyl acetate. The organic layer was concentrated, and purified by column using 7% ethyl acetate/hexane as eluent to obtain the title compound. (Yield: 0.9 g)

Step 2: Synthesis of 3-[(3*S*)-4-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-3-[(*S*)-hydroxy[4-(4-methoxyphenoxy)phenyl]methyl]-4-oxobutyl]-1,2,3-benzotriazin-4(3*H*)-one

To a solution of 3-[4-((4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl)-4-oxobutyl]-3*H*-
5 benzo[d][1,2,3]triazin-4-one (5.5 g, 0.013 mol) in dichloromethane (50 ml) under argon
atmosphere at 0°C, titanium tetrachloride (3.19 g, 0.0169 mol) was added slowly. The
reaction mixture was stirred for about 30 minutes and then tetramethylethylenediamine
(3.77 g, 0.0325 mol) at 0°C was added slowly and the reaction mixture continued to stir
for about 45 minutes at the same temperature. Subsequently, a solution of 4-(4-
10 methoxyphenoxy)benzaldehyde (5.2 g, 0.022 mol) in dichloromethane (20 ml) was added
slowly and allowed to stir for about 5 hours. On completion, the reaction was quenched
with ammonium chloride solution and subsequently by dilute hydrochloric acid, extracted
with dichloromethane and water, and purified by column using 8% ethyl acetate/hexane to
obtain the title compound. (Yield: 2.6 g)

15 Step 3: Synthesis of (2*S*)-2-[(*S*)-hydroxy[4-(4-methoxyphenoxy)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 56)

To a solution of the 3-[(3*S*)-4-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-3-[(*S*)-
hydroxy[4-(4-methoxyphenoxy)phenyl]methyl]-4-oxobutyl]-1,2,3-benzotriazin-4(3*H*)-
one (2.6 g, 0.0040 mol) in tetrahydrofuran (30 ml) under argon atmosphere at about 0°C,
20 hydrogen peroxide solution (0.408 g, 0.012 mol) and then lithium hydroxide (0.256 g,
0.0061 mol) were added and this reaction mixture was stirred for about 2 hours. The
reaction was quenched by acidifying the reaction mixture with sodium bisulfate and
extracting with ethyl acetate and water. The organic layer was concentrated, and purified
by column using 8% methanol/dichloromethane as eluent to obtain the title compound.
25 (Yield: 0.9g)

MS-461.46

LCMS-M-1 (460.08)

NMR(DMSO-*d*₆, 400 MHz) δ: 8.19-8.21 (1H, d, *J* = 8.0 Hz), 8.15-8.17 (1H, d, *J* = 8.0
Hz), 8.04-8.08 (1H, d, *J* = 16.0 Hz), 7.89-7.92 (1H, d, *J* = 12.0 Hz), 7.18-7.20 (2H, d, *J* =
30 8 Hz), 6.93 (4H, d), 6.72-6.74 (2H, d, *J* = 8 Hz), 4.77-4.78 (1H, m, *J* = 4 Hz), 4.30-4.40
(2H, m), 3.73 (3H, s), 2.59 (1H, m), 2.03-2.07 (2H, m).

The following compounds were prepared by following above route of synthesis:

- (2*S*)-2-[(*S*)-[4-(3-Chloro-4-fluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 57)
Mass: 482.28
- 5 (2*S*)-2-[(*S*)-[4-(4-Chloro-3-methylphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 58)
Mass: 478.25
- (2*S*)-2-[(*S*)-[4-(4-Chloro-2-fluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 59)
10 Mass: 482.28
- (2*S*)-2-[(*S*)-[4-(4-Fluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 60)
Mass: 448.29
- (2*S*)-2-[(*S*)-[4-(3,4-Difluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 61)
15 Mass: 466.31
- (2*S*)-2-[(*S*)-[4-(2-Chlorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 62)
Mass: 464.26
- (2*S*)-2-[(*S*)-[4-(3-Chlorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 63)
20 Mass: 464.26
- (2*S*)-2-[(*S*)-[4-(2,6-Difluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 64)
25 Mass: 466.31
- (2*S*)-2-[(*S*)-[4-(2,5-Dichlorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 65)
Mass: 498.25 and 500.16
- (2*S*)-2-[(*S*)-[4-(2-Chloro-4-fluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 66)
30 Mass: 482.28
- (2*S*)-2-[(*S*)-Hydroxy[4-(3-methoxyphenoxy)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 67)
Mass: 460.30
- (2*S*)-2-[(*S*)-[4-(2-Chloro-4-methoxyphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 68)
35 Mass: 494.29
- (2*S*)-2-[(*S*)-[4-(2,4-Difluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 69)
40 Mass: 466.31
- (2*S*)-2-[(*S*)-[3-Fluoro-4-(4-methylphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 70)

Mass: 462.36

(2*S*)-2-[(*S*)-[3-Fluoro-4-(3-methylphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 71)

Mass: 462.34

5 (2*S*)-2-[(*S*)-[4-(3,4-Dimethylphenoxy)-3-fluorophenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 72)

Mass: 476.46

(2*S*)-2-[(*S*)-[4-(3,4-Dichlorophenoxy)-3-fluorophenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 73)

10 Mass: 516.33 and 518.29

(2*S*)-2-[(*S*)-[4-(4-*tert*-Butylphenoxy)-3-fluorophenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 74)

Mass: 504.44

15 (2*S*)-2-[(*S*)-[3-Fluoro-4-(4-methoxyphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 75)

Mass: 478.38

Synthetic Procedure For Scheme II

Example III: Synthesis of 3-[(3*S*,4*S*)-4-(4-Aminophenyl)-3-{[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl}-4-hydroxybutyl]-1,2,3-benzotriazin-4(3*H*)-one

20 **Step 1: Synthesis of 3-[(3*S*)-4-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-3-[(*S*)-hydroxy(4-nitrophenyl)methyl]-4-oxobutyl]-1,2,3-benzotriazin-4(3*H*)-one**

To a solution of 3-{4-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-4-oxobutyl}-1,2,3-benzotriazin-4(3*H*)-one (20 g, 0.049 mol) in dichloromethane (350 ml) at about 0°C, titanium tetrachloride (58.8 ml, 0.311 mol) was added and the reaction mixture was stirred
 25 for about 20 minutes at room temperature (~25°C). To this, tetramethylethylenediamine (18.5 ml, 0.122 mol) was added at 0°C and the reaction mixture was allowed to stir for about 20 minutes. At the same temperature, 4-nitrobenzaldehyde (12.6 g, 0.083 mol) in dichloromethane (50 ml) was added and allowed to stir for about 2 hours at room
 30 temperature (~25°C). On completion, saturated solution of ammonium chloride and subsequently dilute hydrochloric acid were added to the reaction mixture. Organic layer was extracted in dichloromethane, concentrated, purified on silica gel (60-120 mesh) using 25% ethyl acetate:hexane as eluent to get the desired product. (Yield: 18.2g)

MS: 560.15 (M+1)

Step 2: Synthesis of 3-[(3*S*,4*S*)-4-(4-aminophenyl)-3-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl]-4-hydroxybutyl]-1,2,3-benzotriazin-4(3*H*)-one

To a solution of 3-[(3*S*,4*S*)-4-(4-aminophenyl)-3-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-3-[(*S*)-hydroxy(4-nitrophenyl)methyl]-4-oxobutyl]-1,2,3-benzotriazin-4(3*H*)-one (18 g, 0.032 mol) in tetrahydrofuran (100 ml) and methanol (100 ml), 10% Pd/C (6.0 g) was added at room temperature (~25°C) and H₂ was supplied in Parr apparatus at 50 psi for about one hour. The reaction mixture was filtered through celite and the residue was washed with 10% methanol/dichloromethane. The filtrate was concentrated, purified on silica gel (60-120 mesh) column using 60% ethyl acetate:hexane as eluent to get desired product. (Yield: 14.57 g)

MS: 512.02 (M-18)

Synthetic procedure for Scheme III

Example IV: Synthesis of (2*S*)-2-[(*S*)-[4-([2-fluoro-4-(trifluoromethyl)phenyl]carbonyl)amino]phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 46)

Step 1: Synthesis of *N*-{4-[(1*S*,2*S*)-2-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl]-1-hydroxy-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butyl]phenyl}-2-fluoro-4-(trifluoromethyl)benzamide

To a solution of 3-[(3*S*,4*S*)-4-(4-aminophenyl)-3-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl]-4-hydroxybutyl]-1,2,3-benzotriazin-4(3*H*)-one (0.3 g, 0.00057 mol) in dichloromethane (40 ml), triethylamine (0.24 ml, 0.0017 mol) was added at about 0°C. To this reaction mixture, 2-fluoro-4-trifluoromethyl benzoylchloride (0.19 g, 0.00086 mol) was added under nitrogen atmosphere and the reaction mixture was allowed to stir for about 2 hours at room temperature. On completion, water was added and the organic layer was extracted and concentrated to get crude product. (Yield: 153 mg)

Step 2: Synthesis of (2*S*)-2-[(*S*)-[4-([2-fluoro-4-(trifluoromethyl)phenyl]carbonyl)amino]phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 46)

To the solution of *N*-{4-[(1*S*,2*S*)-2-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl]-1-hydroxy-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butyl]phenyl}-2-fluoro-4-

(trifluoromethyl) benzamide (0.153 g, 0.000213 mol) in tetrahydrofuran (20 ml), hydrogen peroxide (0.022 g, 0.00064 mol), lithium hydroxide (0.0134 g, 0.000032 mol) and water (2.0 ml) were added and the reaction mixture was stirred for about one hour at room temperature. The organic layer was extracted with ethyl acetate, dried over anhydrous sodium sulphate, and concentrated to get crude product. Purification was done on preparative TLC using 10% methanol:dichloromethane as eluent to get the title product. (Yield: 61.0 mg)

MS: 545.16 (M+1)

NMR (DMSO-*d*₆, 400 MHz), δ : 10.56 (1H, s), 8.22-8.17 (2H, m), 8.07 (1H, t, $J = 7.44$ Hz), 7.92-7.87 (3H, m), 7.73 (1H, d, $J = 8.04$ Hz), 7.56 (2H, d, $J = 8.4$ Hz), 7.25 (2H, d, $J = 8.4$ Hz), 4.82 (1H, d, $J = 6.04$ Hz), 4.40-4.32 (2H, m), 2.75-2.60 (1H, m), 2.30-2.0 (2H, m)

Example V: Synthesis of (2*S*)-2-[(*S*)-(4-[(4-ethylphenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(*H*)-yl)butanoic acid (Compound No. 10)

Step 1: Synthesis of 3-[(3*S*)-4-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-3-[(*S*)-hydroxy(4-nitrophenyl)methyl]-4-oxobutyl]-1,2,3-benzotriazin-4(*H*)-one

To a solution of 3-{4-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-4-oxobutyl}-1,2,3-benzotriazin-4(*H*)-one (1 g, 0.0025 mol) in dichloromethane (20 ml) at 0 °C, titanium tetrachloride (2.94 ml, 0.0029 mol) was added drop wise and the reaction mixture was stirred for about 40 minutes at room temperature (~25 °C). To this, tetramethylethylenediamine (0.712 g, 0.0061 mol) was added at about 0 °C and the reaction mixture was allowed to stir for another 30 minutes. At same temperature, a solution of 4-nitrobenzaldehyde (0.64 g, 0.0042 mol) in dichloromethane (50 ml) was added to the reaction mixture and allowed to stir for about 2 hours at room temperature (~25 °C). On completion, saturated solution of ammonium chloride was added and the reaction mixture was worked up by dichloromethane and water. Purification was done on silica gel (60-120 mesh) using 30% ethyl acetate:hexane as eluent to get the title product. (Yield: 0.62g)

MS: 559.91 (M+1)

Step 2: Synthesis of 3-[(3*S*,4*S*)-4-(4-aminophenyl)-3-[[4*S*]-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl]-4-hydroxybutyl]-1,2,3-benzotriazin-4(3*H*)-one

To a solution of 3-[(3*S*,4*S*)-4-(4-aminophenyl)-3-[[4*S*]-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-3-[(*S*)-hydroxy(4-nitrophenyl)methyl]-4-oxobutyl]-1,2,3-benzotriazin-4(3*H*)-one (0.61 g, 0.0011 mol) in tetrahydrofuran (20 ml), 10% Pd/C (0.5 g) at room temperature (~25°C) was added and H₂ was supplied using balloon for about 2 hours. The reaction mixture was filtered through celite and the residue was washed with 10% methanol:dichloromethane. The filtrate was concentrated to get the desired compound. (Yield: 0.6g)

MS: 511.94 (M-18)

10 Step 3: Synthesis of *N*-{4-[(1*S*,2*S*)-2-[[4*S*]-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl]-1-hydroxy-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butyl]phenyl}-4-ethylbenzamide

To a solution of 3-[(3*S*,4*S*)-4-(4-aminophenyl)-3-[[4*S*]-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl]-4-hydroxybutyl]-1,2,3-benzotriazin-4(3*H*)-one (0.6 g, 0.0011 mol) in dichloromethane (20 ml), triethylamine (0.47 ml, 0.0034 mol) was added at about 0°C. Afterwards, 4-ethyl benzoylchloride (0.29 g, 0.0017 mol) was added and the reaction mixture was stirred for about 30 minutes at 0°C. The reaction was worked up with dichloromethane and water to get crude product. (Yield: 680 mg)

MS: 662.04 (M+1)

20 Step 4: Synthesis of (2*S*)-2-[(*S*)-(4-[[4-ethylphenyl]carbonyl]amino)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 10)

To the solution of *N*-{4-[(1*S*,2*S*)-2-[[4*S*]-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl]-1-hydroxy-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butyl]phenyl}-4-ethylbenzamide (0.35 g, 0.00053 mol) in tetrahydrofuran (10 ml), hydrogen peroxide (0.3ml, 2.65 moles) was added and reaction mixture was stirred for about 15 minutes at 0°C. Subsequently, lithium hydroxide (0.033 g, 0.00079 mol) and water (5 ml) were added to it and again stirred for about 2 hours at room temperature. On completion, the reaction was quenched by adding water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated and purified by preparative

TLC using 10% methanol:dichloromethane as eluent to get the title product. (Yield: 84.0 mg)

MS: 485.17 (M-1)

NMR (DMSO-*d*₆, 400 MHz), δ : 10.06 (1H, s), 8.20-8.15 (2H, m), 8.06-8.02 (1H, m),
5 7.89-7.85 (3H, m), 7.61 (2H, d, *J* = 8.4 Hz), 7.35 (2H, d, *J* = 8.4 Hz), 7.21 (2H, d, *J* = 8.4 Hz), 4.80-4.78 (1H, m), 4.40-4.32 (2H, m), 2.70-2.65 (3H, m), 2.20-2.00 (2H, m).

The following compounds were prepared by following above route of synthesis:

- 10 (2*S*)-2-[(*S*)-(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 11)
Mass: 492.91
- (2*S*)-2-[(*S*)-(4-{{(3,4-Dichlorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 12)
Mass: 528.84
- 15 (2*S*)-2-[(*S*)-Hydroxy(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 13)
Mass: 489.97
- (2*S*)-2-[(*S*)-Hydroxy(4-{{(3-methoxyphenyl)carbonyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 14)
Mass: 489.97
- 20 (2*S*)-2-[(*S*)-Hydroxy(4-{{(4-methylphenyl)carbonyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 15)
Mass: 473.01
- 25 (2*S*)-2-[(*S*)-(4-{{(4-Fluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 16)
Mass: 477.96
- (2*S*)-2-[(*S*)-Hydroxy(4-{{[4-methoxy-3-(trifluoromethyl)phenyl]carbonyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 17)
Mass: 557.94
- 30 (2*S*)-2-[(*S*)-Hydroxy(4-{{(5-methyl-1,2-oxazol-3-yl)carbonyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 18)
Mass: 464.96
- 35 (2*S*)-2-[(*S*)-(4-{{(3-Chloro-4-fluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 19)
Mass: 510.80
- (2*S*)-2-[(*S*)-Hydroxy(4-[(phenylcarbonyl)amino]phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 20)
Mass: 459.95

- (2*S*)-2-[(*S*)-Hydroxy(4-{{(4-propylphenyl)carbonyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 21)
Mass: 501.92
- 5 (2*S*)-2-[(*S*)-Hydroxy{4-[(phenoxy)carbonyl]amino}phenyl}methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 22)
Mass: 475.92
- (2*S*)-2-[(*S*)-Hydroxy{4-[(phenyl)acetyl]amino}phenyl}methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 23)
Mass: 473.94
- 10 (2*S*)-2-[(*S*)-(4-{{(2,4-Dichlorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 24)
Mass: 526.84
- (2*S*)-2-[(*S*)-Hydroxy(4-{{(2-methylphenyl)carbonyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 25)
15 Mass: 472.92
- (2*S*)-2-[(*S*)-(4-{{(2-Fluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 26)
Mass: 476.88
- (2*S*)-2-[(*S*)-(4-{{(3-Chlorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 27)
20 Mass: 492.85
- (2*S*)-2-[(*S*)-Hydroxy(4-{{(3-methylphenyl)carbonyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 28)
Mass: 472.92
- 25 (2*S*)-2-[(*S*)-(4-{{(3-Fluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 29)
Mass: 476.88
- (2*S*)-2-[(*S*)-(4-{{(2,6-Dimethoxyphenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 30)
30 Mass: 518.92
- (2*S*)-2-[(*S*)-{4-[(Cyclopentyl)carbonyl]amino}phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 31)
Mass: 450.94
- (2*S*)-2-[(*S*)-Hydroxy(4-{{(2,4,5-trifluoro-3-methoxyphenyl)carbonyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 32)
35 Mass: 543.09
- (2*S*)-2-[(*S*)-Hydroxy(4-{{(2,3,4-trifluorophenyl)carbonyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 33)
40 Mass: 513.06
- (2*S*)-2-[(*S*)-Hydroxy{4-{{[2-(trifluoromethyl)phenyl]carbonyl}amino}phenyl}methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 34)
Mass: 527.11

- (2*S*)-2-[(*S*)-(4-{{(3,5-Dimethoxyphenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 35)
Mass: 519.13
- 5 (2*S*)-2-[(*S*)-(4-{{(2,3-Difluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 36)
Mass: 495.04
- (2*S*)-2-[(*S*)-(4-{{(3,5-Dichlorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 37)
Mass: 526.99
- 10 (2*S*)-2-[(*S*)-(4-{{(2,4-Difluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 38)
Mass: 495.04
- (2*S*)-2-[(*S*)-(4-{{(2,6-Difluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 39)
15 Mass: 495.10
- (2*S*)-2-[(*S*)-Hydroxy(4-{{(2-methoxyphenyl)carbonyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 40)
Mass: 489.16
- 20 (2*S*)-2-[(*S*)-{4-[(Cyclohexylcarbonyl)amino]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 41)
Mass: 465.20
- (2*S*)-2-[(*S*)-(4-{{(4-Ethoxyphenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 42)
25 Mass: 503.20
- (2*S*)-2-[(*S*)-(4-{{(3,4-Difluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 43)
Mass: 495.16
- (2*S*)-2-[(*S*)-Hydroxy[4-({[4-(trifluoromethoxy)phenyl]carbonyl}amino)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 44)
30 Mass: 545.15
- (2*S*)-2-[(*S*)-Hydroxy[4-({[3-(trifluoromethyl)phenyl]carbonyl}amino)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 45)
Mass: 527.15
- 35 (2*S*)-2-[(*S*)-(4-{{(3-Chloro-2,6-difluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 47)
Mass: 529.13
- (2*S*)-2-[(*S*)-Hydroxy[4-({[4-(trifluoromethyl)phenyl]carbonyl}amino)phenyl]methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 48)
40 Mass: 527.16
- (2*S*)-2-[(*S*)-(4-{{(2,5-Difluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 49)
Mass: 495.15

(2*S*)-2-[(*S*)-(4-{{(2,3-Difluoro-4-methylphenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 50)
Mass: 509.18

5 (2*S*)-2-[(*S*)-[4-{{[4-Fluoro-3-(trifluoromethyl)phenyl]carbonyl}amino}phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 51)
Mass: 545.15

10 (2*S*)-2-[(*S*)-{4-[(Cyclopropylcarbonyl)amino]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 52)
Mass: 423.19

(2*S*)-2-[(*S*)-(4-{{(2-Ethylphenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 53)
Mass: 485.19

15 (2*S*)-2-[(*S*)-Hydroxy(4-{{(4-methoxyphenyl)acetyl}amino}phenyl)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 54)
Mass: 503.20

(2*S*)-2-[(*S*)-{4-[(Cyclobutylcarbonyl)amino]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 55)
Mass: 437.21

20

Assay for Matrix Metalloproteinases (MMPs)

New chemical entities of the present invention and corresponding standards used in the present invention were prepared (stock 10 mM) in 100% DMSO and subsequent dilutions were made in MMP assay buffer [50 mM HEPES, 10 mM CaCl₂, 150 nM NaCl, 25 1 μM Zinc Acetate, 600 μM CHAPS (pH 7.4)]. Assays used human MMPs expressed either as full length or catalytic domain. The Collagenase (MMP-1), Gelatinase (MMP-9), Elastase (MMP-12) and membrane type-1 (MMP-14) were cleaved and activated using reagent APMA (4-amino phenyl mercuric acetate) to obtain active catalytic domains. In a typical 100 μl reaction assay mixture, 1.0 μl of desired MMP enzyme was incubated in 30 buffered solution in absence or presence of 1.0 μl of NCEs/standards for 30 minutes. Reaction was started with desired furogenic substrate – FAM-TAMRA (FAM-Thr-Pro-Gly-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-Arg-Lys-TAMRA-NH₂) at a final concentration of 10 μM per well and reaction was allowed to proceed for 45 minutes and rate of velocity was monitored (increase in RFUs) at excitation wavelength of 495 nm and emission 525 35 nm. Blank reaction rate (without enzyme) was subtracted from each value. The percent control was calculated using the following formula:

Percent activity = (inhibited rate/control rate) × 100.

IC₅₀ values were calculated using least square regression analysis method by Graph-Pad prism version 4.2 software; using a 5-6 point dose response curve in presence of inhibitor. IC₅₀ values were averaged for duplicate assay data and values tabulated.

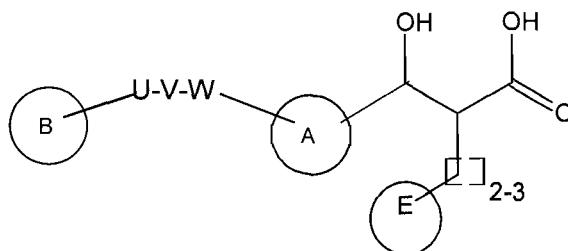
- 5 The present invention relates to compounds that act as dual MMP-9/12 inhibitors, which have desirable activity profiles.

MMP-9 activities of the compounds disclosed in the invention, provided IC₅₀ values from about 10 micromolar to about 1 nM, or from about 1 micromolar to about 1 nM, or from about 650 nM to about 1 nM, or from about 300 nM to about 1 nM, or from
10 about 100 nM to about 1 nM, or from about 50 nM to about 1 nM, or from about 30 nM to about 1 nM, or from about 20 nM to about 1 nM, or from about 12 nM to about 1 nM, as compared to about 1.4 nM to 3.2 nM for marimastat.

MMP-12 activities of the compounds disclosed in the invention, provided IC₅₀ values from about 10 micromolar to about 1 nM, or from about 1 micromolar to about 1
15 nM, or from about 300 nM to about 1 nM, or from about 100 nM to about 1 nM, or from about 50 nM to about 1 nM, or from about 30 nM to about 1 nM, or from about 20 nM to about 1 nM, or from about 15 nM to about 1 nM, or from about 7 nM to about 1 nM as compared to 0.2 nM to 0.9 nM for marimastat.

We claim:

1. A compound of Formula I:



Formula I

including racemates, enantiomers and diastereomers thereof, or a pharmaceutically acceptable salt thereof, wherein,



is phenyl, fluorophenyl, heteroaryl or heterocyclyl;

U is a bond, -NH-, -C(=O)-, -(CH₂)_n-, -C(=S)-, -O-, -SO₂- or -S- wherein n is zero or an integer between 1 and 2;

V is a bond, -NH-, -C(=O)-, -C(=S)- or -SO₂-;

W is a bond, -NH-, -C(=O)-, -(CH₂)_n-, -C(=S)-, -O-, -S- or -SO₂-;



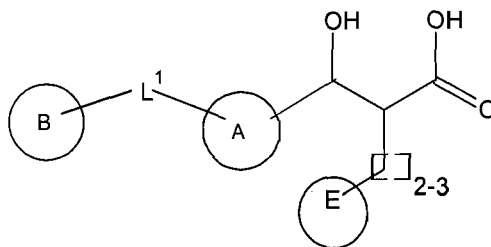
is aryl, cycloalkyl, heteroaryl or heterocyclyl, each of which can be further substituted by one or more substituent independently selected from R¹

R¹ is alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno-C₁-C₆ alkyl, halogeno-C₁-C₆ alkoxy, azido, thiol, alkylthiol, -(CH₂)_n-OR_f, -C(=O)-R_f, -COOR_f, -NR_fR_q, -(CH₂)_n-C(=O)NR_fR_q, -(CH₂)_n-NHC(=O)-R_f, -(CH₂)_n-O-C(=O)-NR_fR_q, (CH₂)_n NHC(=O)NR_fR_q, -(CH₂)_n-O-C(=O)-R_f, -(CH₂)_n-NH-C(=O)-R_f or -(CH₂)_nS(=O)_m-NR_fR_q {wherein R_f and R_q are independently selected from hydrogen, alkyl, alkenyl, cycloalkyl aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and alkylheterocyclyl, n is as defined earlier and m is an integer 0-2};



is selected from heteroaryl or heterocyclyl.

- 1 2. A compound according to claim 1, having the structure of Formula Ia



Formula Ia

2

3 including racemates, enantiomers and diastereomers thereof, or a pharmaceutically
4 acceptable salt thereof wherein,

5 $\textcircled{\text{A}}$ is phenyl, fluorophenyl, heteroaryl or heterocyclyl;

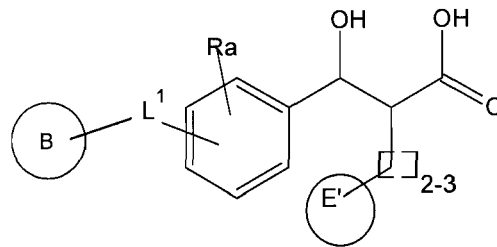
6 L^1 is a bond, $-(\text{CH}_2)_n-$, $-\text{NHCO}(\text{CH}_2)_n-$, $-(\text{CH}_2)_n\text{C}(=\text{O})\text{NH}-$, $-\text{NHC}(=\text{O})\text{NH}-$, $-$
7 $\text{SO}_2\text{NH}-$, $-\text{NHSO}_2-$, $-\text{SO}_2-$, $-\text{NHC}(=\text{O})(\text{O})-$, $-\text{O}-(\text{CH}_2)_n-$, $-(\text{CH}_2)_n\text{O}-$, $-$
8 $(\text{CH}_2)_n\text{OC}(=\text{O})\text{NH}-$, $-\text{C}(=\text{S})\text{NH}-$, $-\text{NHC}(=\text{S})-$ or $-\text{NHC}(=\text{S})\text{NH}-$ wherein n is zero
9 or an integer between 1 and 2;

10 $\textcircled{\text{B}}$ is aryl, cycloalkyl, heteroaryl or heterocyclyl each of which can be further
11 substituted by one or more substituents independently selected from R^1 ;

12 R^1 is alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno- C_1 - C_6 alkyl,
13 halogeno- C_1 - C_6 alkoxy, azido, thiol, alkylthiol, $-(\text{CH}_2)_n\text{-OR}_f$, $-\text{C}(=\text{O})\text{-R}_f$, $-\text{COOR}_f$, $-$
14 NR_fR_q , $-(\text{CH}_2)_n\text{-C}(=\text{O})\text{NR}_f\text{R}_q$, $-(\text{CH}_2)_n\text{-NHC}(=\text{O})\text{-R}_f$, $-(\text{CH}_2)_n\text{-O-C}(=\text{O})\text{-NR}_f\text{R}_q$,
15 $(\text{CH}_2)_n\text{NHC}(=\text{O})\text{NR}_f\text{R}_q$, $-(\text{CH}_2)_n\text{-O-C}(=\text{O})\text{-R}_f$, $-(\text{CH}_2)_n\text{-NH-C}(=\text{O})\text{-R}_f$ or
16 $-(\text{CH}_2)_n\text{S}(=\text{O})_m\text{-NR}_f\text{R}_q$ {wherein R_f and R_q are independently selected from hydrogen,
17 alkyl, alkenyl, cycloalkyl aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and
18 alkylheterocyclyl, n is as defined earlier and m is an integer 0-2};

19 $\textcircled{\text{E}}$ is heteroaryl or heterocyclyl.

1 3. A compound according to claim 1, having the structure of Formula Ib

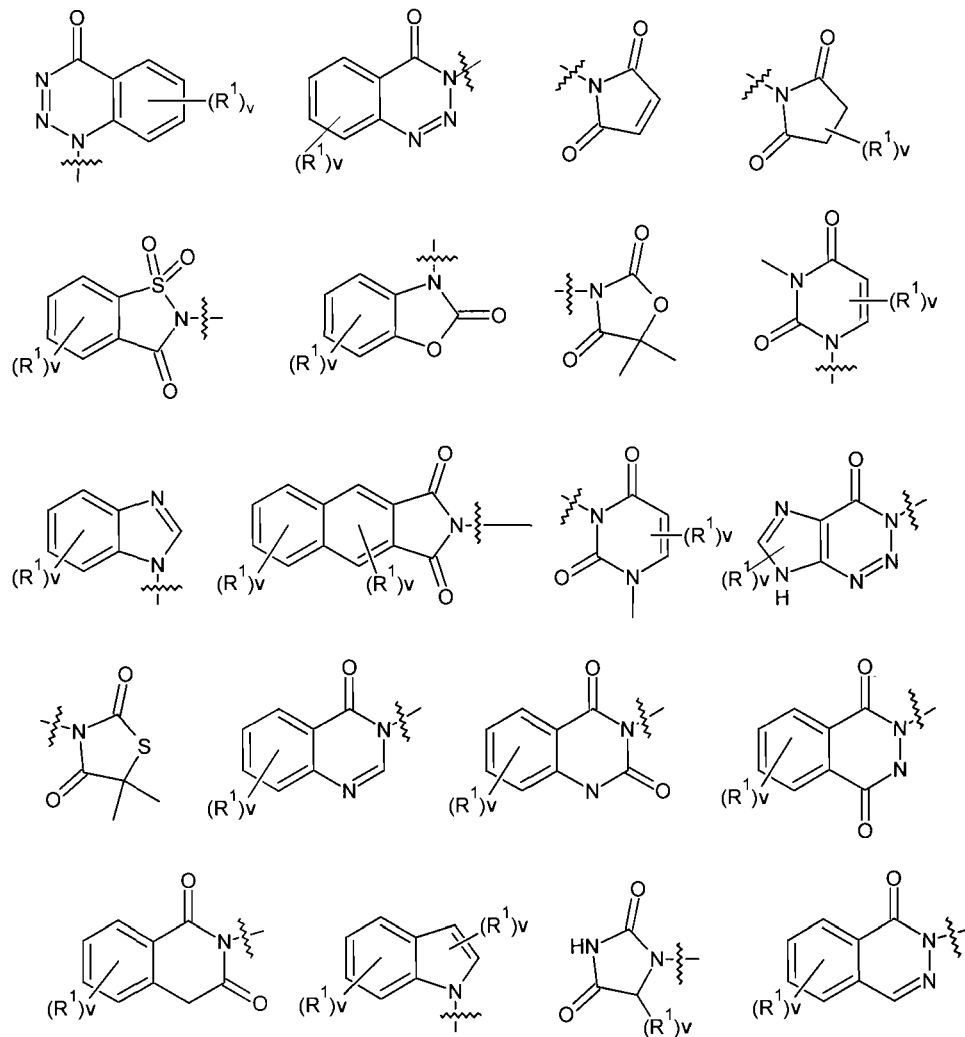


2 **Formula Ib**

3 including racemates, enantiomers and diastereomers thereof, or a pharmaceutically
4 acceptable salt thereof wherein,



5 is mono, bi or polycyclic heteroaryl or heterocyclyl selected from the
6 following:



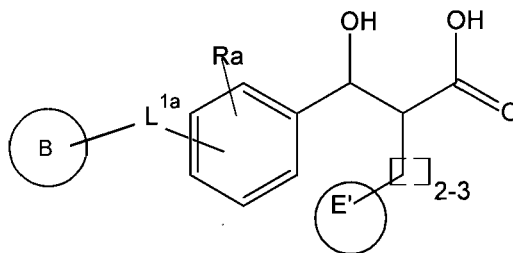
7

8 v is zero or an integer between 1-4.

9 Ra is hydrogen or fluorine;

10 R^1 , L^1 and \textcircled{B} are as defined in claim 1.

1 4. A compound according to claim 1, having the structure of Formula Ic



2 **Formula Ic**

3 including racemates, enantiomers and diastereomers thereof, or a pharmaceutically
4 acceptable salt thereof, wherein,

5 L^{1a} is $S(O)_n$, $NHCO(CH_2)_n$ and $NHCO(O)$;

6 Ra, \textcircled{B} and $\textcircled{E'}$ are as defined in claim 1.

1 5. A compound of Formula I, which is:

2 (2*S*)-2-[(*S*)-{4-[(4-Chlorophenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-
3 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 1);

4 (2*S*)-2-[(*S*)-{4-[(4-Chlorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-
5 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 2);

6 (2*S*)-2-[(*S*)-{4-[(3,4-Difluorophenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-
7 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 3);

8 (2*S*)-2-[(*S*)-{4-[(2,3-Dichlorophenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-
9 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 4);

10 (2*S*)-2-[(*S*)-{4-[(2,4-Dimethylphenyl)sulfinyl]phenyl}(hydroxy)methyl]-4-(4-oxo-
11 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 5);

12 (2*S*)-2-[(*S*)-{4-[(4-Fluorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-
13 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 6);

14 (2*S*)-2-[(*S*)-{4-[(3,4-Difluorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-
15 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 7);

16 2-[{4-[(2,3-Dichlorophenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-1,2,3-
17 benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 8);

- 18 (2*S*)-2-[(*S*)-{4-[(2,4-Dimethylphenyl)sulfonyl]phenyl}(hydroxy)methyl]-4-(4-oxo-
19 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 9);
- 20 (2*S*)-2-[(*S*)-(4-{[(4-Ethylphenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-
21 oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 10);
- 22 (2*S*)-2-[(*S*)-(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-
23 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 11);
- 24 (2*S*)-2-[(*S*)-(4-{[(3,4-Dichlorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-
25 (4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 12);
- 26 (2*S*)-2-[(*S*)-Hydroxy(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)methyl]-4-(4-
27 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 13);
- 28 (2*S*)-2-[(*S*)-Hydroxy(4-{[(3-methoxyphenyl)carbonyl]amino}phenyl)methyl]-4-(4-
29 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 14);
- 30 (2*S*)-2-[(*S*)-Hydroxy(4-{[(4-methylphenyl)carbonyl]amino}phenyl)methyl]-4-(4-
31 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 15);
- 32 (2*S*)-2-[(*S*)-(4-{[(4-Fluorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-
33 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 16);
- 34 (2*S*)-2-[(*S*)-Hydroxy{4-({[4-methoxy-3-(trifluoromethyl)phenyl]carbonyl}amino
35 phenyl)methyl}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound
36 No. 17);
- 37 (2*S*)-2-[(*S*)-Hydroxy(4-{[(5-methyl-1,2-oxazol-3-yl)carbonyl]amino}phenyl)
38 methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 18);
- 39 (2*S*)-2-[(*S*)-(4-{[(3-Chloro-4-fluorophenyl)carbonyl]amino}phenyl)(hydroxy)
40 methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 19);
- 41 (2*S*)-2-[(*S*)-Hydroxy{4-[(phenylcarbonyl)amino]phenyl}methyl]-4-(4-oxo-1,2,3-
42 benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 20);
- 43 (2*S*)-2-[(*S*)-Hydroxy(4-{[(4-propylphenyl)carbonyl]amino}phenyl)methyl]-4-(4-
44 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 21);
- 45 (2*S*)-2-[(*S*)-Hydroxy{4-[(phenoxycarbonyl)amino]phenyl}methyl]-4-(4-oxo-1,2,3-
46 benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 22);
- 47 (2*S*)-2-[(*S*)-Hydroxy{4-[(phenylacetyl)amino]phenyl}methyl]-4-(4-oxo-1,2,3-
48 benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 23);
- 49 (2*S*)-2-[(*S*)-(4-{[(2,4-Dichlorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-
50 (4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 24);
- 51 (2*S*)-2-[(*S*)-Hydroxy(4-{[(2-methylphenyl)carbonyl]amino}phenyl)methyl]-4-(4-
52 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 25);
- 53 (2*S*)-2-[(*S*)-(4-{[(2-Fluorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-
54 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 26);
- 55 (2*S*)-2-[(*S*)-(4-{[(3-Chlorophenyl)carbonyl]amino}phenyl)(hydroxy)methyl]-4-(4-
56 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 27);

- 57 (2*S*)-2-[(*S*)-Hydroxy(4-{{(3-methylphenyl)carbonyl}amino}phenyl)methyl]-4-(4-
58 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 28);
- 59 (2*S*)-2-[(*S*)-(4-{{(3-Fluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-
60 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 29);
- 61 (2*S*)-2-[(*S*)-(4-{{(2,6-Dimethoxyphenyl)carbonyl}amino}phenyl)(hydroxy)
62 methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 30);
- 63 (2*S*)-2-[(*S*)-{4-[(Cyclopentylcarbonyl)amino]phenyl}(hydroxy)methyl]-4-(4-oxo-
64 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 31);
- 65 (2*S*)-2-[(*S*)-Hydroxy(4-{{(2,4,5-trifluoro-3-methoxyphenyl)carbonyl}amino}
66 phenyl)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound
67 No. 32);
- 68 (2*S*)-2-[(*S*)-Hydroxy(4-{{(2,3,4-trifluorophenyl)carbonyl}amino}phenyl)methyl]-4-
69 (4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 33);
- 70 (2*S*)-2-[(*S*)-Hydroxy[4-({[2-(trifluoromethyl)phenyl]carbonyl}amino)phenyl]
71 methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 34);
- 72 (2*S*)-2-[(*S*)-(4-{{(3,5-Dimethoxyphenyl)carbonyl}amino}phenyl)(hydroxy)methyl]
73 -4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 35);
- 74 (2*S*)-2-[(*S*)-(4-{{(2,3-Difluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-
75 (4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 36);
- 76 (2*S*)-2-[(*S*)-(4-{{(3,5-Dichlorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-
77 (4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 37);
- 78 (2*S*)-2-[(*S*)-(4-{{(2,4-Difluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-
79 (4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 38);
- 80 (2*S*)-2-[(*S*)-(4-{{(2,6-Difluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-
81 (4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 39);
- 82 (2*S*)-2-[(*S*)-Hydroxy(4-{{(2-methoxyphenyl)carbonyl}amino}phenyl)methyl]-4-(4-
83 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 40);
- 84 (2*S*)-2-[(*S*)-{4-[(Cyclohexylcarbonyl)amino]phenyl}(hydroxy)methyl]-4-(4-oxo-
85 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 41);
- 86 (2*S*)-2-[(*S*)-(4-{{(4-Ethoxyphenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-
87 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 42);
- 88 (2*S*)-2-[(*S*)-(4-{{(3,4-Difluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-
89 (4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 43);
- 90 (2*S*)-2-[(*S*)-Hydroxy[4-({[4-(trifluoromethoxy)phenyl]carbonyl}amino)phenyl]
91 methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 44);
- 92 (2*S*)-2-[(*S*)-Hydroxy[4-({[3-(trifluoromethyl)phenyl]carbonyl}amino)phenyl]
93 methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 45);
- 94 (2*S*)-2-[(*S*)-[4-({[2-Fluoro-4-(trifluoromethyl)phenyl]carbonyl}amino)phenyl]
95 (hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound
96 No. 46);

- 97 (2*S*)-2-[(*S*)-(4-{{(3-Chloro-2,6-difluorophenyl)carbonyl}amino}phenyl)(hydroxy)
98 methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 47);
- 99 (2*S*)-2-{{(*S*)-Hydroxy[4-({[4-(trifluoromethyl)phenyl]carbonyl}amino)phenyl]
100 methyl}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 48);
- 101 (2*S*)-2-[(*S*)-(4-{{(2,5-Difluorophenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-
102 (4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 49);
- 103 (2*S*)-2-[(*S*)-(4-{{(2,3-Difluoro-4-methylphenyl)carbonyl}amino}phenyl)(hydroxy)
104 methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 50);
- 105 (2*S*)-2-[(*S*)-[4-({[4-Fluoro-3-(trifluoromethyl)phenyl]carbonyl}amino)phenyl]
106 (hydroxy)methyl]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound
107 No. 51);
- 108 (2*S*)-2-[(*S*)-{4-[(Cyclopropylcarbonyl)amino]phenyl}(hydroxy)methyl]-4-(4-oxo-
109 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 52);
- 110 (2*S*)-2-[(*S*)-(4-{{(2-Ethylphenyl)carbonyl}amino}phenyl)(hydroxy)methyl]-4-(4-
111 oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 53);
- 112 (2*S*)-2-[(*S*)-Hydroxy(4-{{(4-methoxyphenyl)acetyl}amino}phenyl)methyl]-4-(4-
113 oxo-1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 54);
- 114 (2*S*)-2-[(*S*)-{4-[(Cyclobutylcarbonyl)amino]phenyl}(hydroxy)methyl]-4-(4-oxo-
115 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 55);
- 116 (2*S*)-2-{{(*S*)-Hydroxy[4-(4-methoxyphenoxy)phenyl]methyl}-4-(4-oxo-1,2,3-
117 benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 56);
- 118 (2*S*)-2-[(*S*)-[4-(3-Chloro-4-fluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-
119 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 57);
- 120 (2*S*)-2-[(*S*)-[4-(4-Chloro-3-methylphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-
121 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 58);
- 122 (2*S*)-2-[(*S*)-[4-(4-Chloro-2-fluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-
123 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 59);
- 124 (2*S*)-2-[(*S*)-[4-(4-Fluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-
125 benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 60);
- 126 (2*S*)-2-[(*S*)-[4-(3,4-Difluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-
127 benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 61);
- 128 (2*S*)-2-[(*S*)-[4-(2-Chlorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-
129 benzotriazin-3(4*H*)-yl)butanoic acid(Compound No. 62);
- 130 (2*S*)-2-[(*S*)-[4-(3-Chlorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-
131 benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 63);
- 132 (2*S*)-2-[(*S*)-[4-(2,6-Difluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-
133 benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 64);
- 134 (2*S*)-2-[(*S*)-[4-(2,5-Dichlorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-
135 benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 65);

- 136 (2*S*)-2-[(*S*)-[4-(2-Chloro-4-fluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-
137 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 66);
- 138 (2*S*)-2-[(*S*)-Hydroxy[4-(3-methoxyphenoxy)phenyl]methyl]-4-(4-oxo-1,2,3-
139 benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 67);
- 140 (2*S*)-2-[(*S*)-[4-(2-Chloro-4-methoxyphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-
141 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 68);
- 142 (2*S*)-2-[(*S*)-[4-(2,4-Difluorophenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-1,2,3-
143 benzotriazin-3(4*H*)-yl)butanoic acid (Compound No. 69);
- 144 (2*S*)-2-[(*S*)-[3-Fluoro-4-(4-methylphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-
145 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 70);
- 146 (2*S*)-2-[(*S*)-[3-Fluoro-4-(3-methylphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-
147 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 71);
- 148 (2*S*)-2-[(*S*)-[4-(3,4-Dimethylphenoxy)-3-fluorophenyl](hydroxy)methyl]-4-(4-oxo-
149 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 72);
- 150 (2*S*)-2-[(*S*)-[4-(3,4-Dichlorophenoxy)-3-fluorophenyl](hydroxy)methyl]-4-(4-oxo-
151 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 73);
- 152 (2*S*)-2-[(*S*)-[4-(4-*tert*-Butylphenoxy)-3-fluorophenyl](hydroxy)methyl]-4-(4-oxo-
153 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 74);
- 154 (2*S*)-2-[(*S*)-[3-Fluoro-4-(4-methoxyphenoxy)phenyl](hydroxy)methyl]-4-(4-oxo-
155 1,2,3-benzo triazin-3(4*H*)-yl)butanoic acid (Compound No. 75);
- 156 including racemates, enantiomers and diastereomers thereof, or a pharmaceutically
157 acceptable salt.

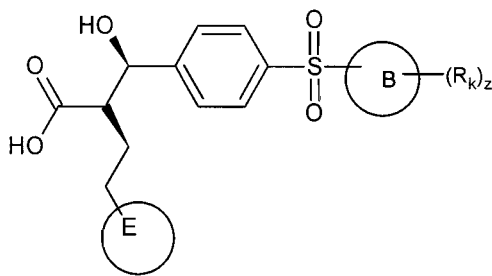
- 1 6. A pharmaceutical composition comprising a therapeutically effective amount of a
2 compound according to any one of claims 1 to 5, together with a pharmaceutically
3 acceptable carrier, excipient or diluent.
- 1 7. A compound according to any one of claims 1 to 5, for use in the treatment or
2 prophylaxis of an animal or a human suffering from an inflammatory or allergic
3 disease.
- 1 8. A compound according to claim 7, wherein the inflammatory disease or allergic
2 disease is asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic
3 arthritis, psoriasis, pulmonary fibrosis, pulmonary inflammation, acute respiratory
4 distress syndrome, periodontitis, multiple sclerosis, gingivitis, atherosclerosis, dry
5 eye, neointimal proliferation associated with restenosis and ischemic heart failure,
6 stroke, renal disease or tumour metastasis.

- 1 9. A pharmaceutical composition according to claim 6, further comprising one or
2 more additional active ingredients selected from:
- 3 (a) Anti-inflammatory agents, (i) such as nonsteroidal anti-inflammatory agents
4 piroxicam, diclofenac, propionic acids, fenamates, pyrazolones, salicylates,
5 phosphodiesterase inhibitors including PDE-4 inhibitors, p38 MAP
6 Kinase/Cathepsin inhibitors, CCR-3 antagonists, iNOS inhibitors, tryptase
7 and elastase inhibitors, beta-2 integrin antagonists, Cell adhesion inhibitors
8 (specially ICAM), adenosine 2a agonists, (ii) leukotrienes
9 LTC4/LTD4/LTE4/LTB4-Inhibitors, 5-lipoxygenase inhibitors and PAF-
10 receptor antagonists, (iii) Cox-2 inhibitors (iv) other MMP inhibitors, (v)
11 interleukin-I inhibitors, (vi) corticosteroids such as alclometasone,
12 amcinonide, amelometasone, beclometasone, betamethasone, budesonide,
13 ciclesonide, clobetasol, cloticasone, cyclomethasone, deflazacort, deprodone,
14 dexbudesonide, diflorasone, difluprednate, fluticasone, flunisolide,
15 halometasone, haloperedone, hydrocortisone, methylprednisolone,
16 mometasone, prednicarbate, prednisolone, rimexolone, tixocortol,
17 triamcinolone, ulobetasol, rofleponide, GW 215864, KSR 592, ST-126,
18 dexamethasone and pharmaceutically acceptable salts, solvates thereof.
19 Preferred corticosteroids include, for example, flunisolide, beclomethasone,
20 triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, and
21 dexamethasone;
- 22 (b) beta-agonists, suitable β 2-agonists include, for example, one or more of
23 albuterol, salbutamol, biltolterol, pirbuterol, levosalbutamol, tulobuterol,
24 terbutaline, bambuterol, metaproterenol, fenoterol, salmeterol, carmoterol,
25 arformoterol, formoterol, and their pharmaceutically acceptable salts or
26 solvates thereof one or more β 2- agonists;
- 27 (c) antihypertensive agents, (i) ACE inhibitors, *e.g.*, enalapril, lisinopril,
28 valsartan, telmisartan and quinapril, (ii) angiotensin II receptor antagonists
29 and agonists, *e.g.*, losartan, candesartan, irbesartan, valsartan, and eprosartan,
30 (iii) β -blockers, and (iv) calcium channel blockers;

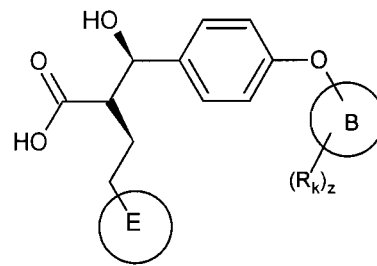
31 (d) immunosuppressive agents, - cyclosporine, azathioprine and methotrexate,
 32 anti-inflammatory corticosteroids; and

33 (e) anti-infective agents.

1 10. A process for preparing a compound of Formula VIII (Formula I when Ring A is
 2 phenyl, U is $-\text{SO}_2-$, V and W are bonds) and Formula IX (Formula I when Ring A is
 3 phenyl, U is $-\text{O}-$, V and W are bonds)



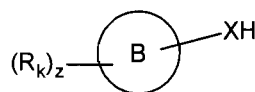
4 Formula VIII



5 Formula IX

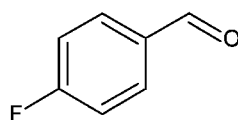
6 comprising:

7 a) reacting compound of Formula II



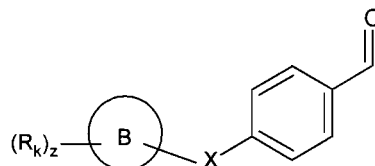
8 Formula II

9 with a compound of Formula III



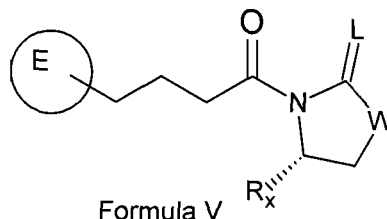
10 Formula III

11 to give a compound of Formula IV



12 Formula IV

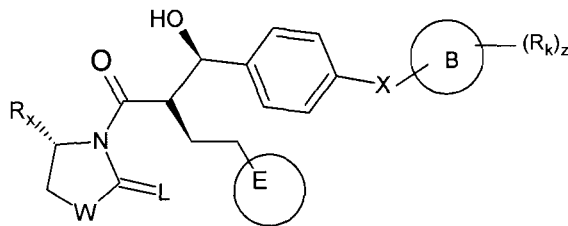
13 b) reacting a compound of Formula IV with a compound of Formula V,



13

14

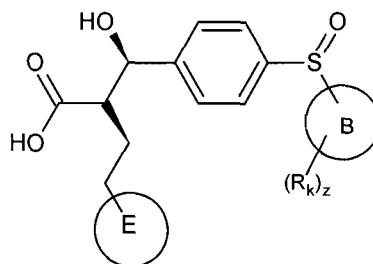
to give a compound of Formula VI,



15

16

- c) hydrolysing a compound of Formula VI (when X is S) to give a compound of
17 Formula VII



18

19

- d) oxidizing a compound of Formula VII to give a compound of Formula VIII

20

or

21

- e) hydrolysing a compound of Formula VI (when X is O) to give a compound of
22 Formula IX

23

wherein,




24

is aryl, cycloalkyl, heteroaryl or heterocyclyl each of which can be
25 further substituted by one or more substituent independently selected from
26 R^1 .

27

R^1 is alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno- C_1 - C_6 alkyl,
28 halogeno- C_1 - C_6 alkoxy, azido, thiol, alkylthiol, $-(CH_2)_n-OR_f$, $-C(=O)-R_f$, -

29 COOR_f, -NR_fR_q, -(CH₂)_n-C(=O)NR_fR_q, -(CH₂)_n-NHC(=O)-R_f, -(CH₂)_n-O-
 30 C(=O)-NR_fR_q, (CH₂)_n NHC(=O)NR_fR_q, -(CH₂)_n-O-C(=O)-R_f, -(CH₂)_n-NH-
 31 C(=O)-R_f or -(CH₂)_nS(=O)_m-NR_fR_q {wherein R_f and R_q are independently
 32 selected from hydrogen, alkyl, alkenyl, cycloalkyl aryl, heteroaryl, heterocyclyl,
 33 alkylaryl, alkylheteroaryl and alkylheterocyclyl, n is as defined earlier and m is
 34 an integer 0-2};

35  is selected from heteroaryl or heterocyclyl;

36 X is O or S ;

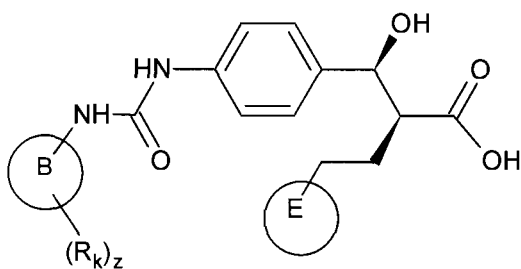
37 R_k is H, halo, alkyl, alkoxy, cyano, halogeno-C₁-C₆ alkyl or halogeno-C₁-C₆
 38 alkoxy;

39 z is 0-4;

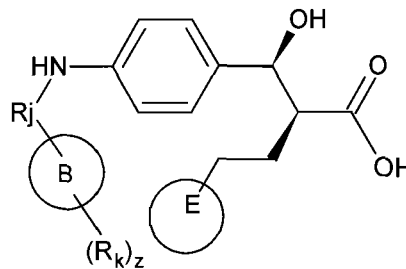
40 L and W are O or S respectively; and

41 R_x is alkyl, aryl or aralkyl.

- 1 11. A process for preparing a compound of Formula XV (Formula I when Ring A is
 2 phenyl, U is -NH-, V is -CO- and W is -NH-) and XVIII (Formula I when Ring A is
 3 phenyl, U is -NH-, V and W combined together are R_j)



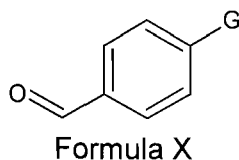
4 Formula XV



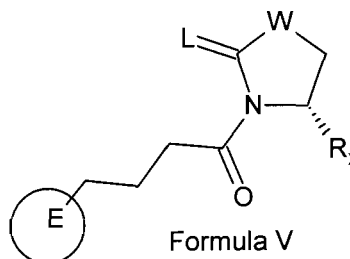
5 Formula XVIII

6 comprising

- 7 a) Aldol addition of a compound of Formula X with a compound of Formula V

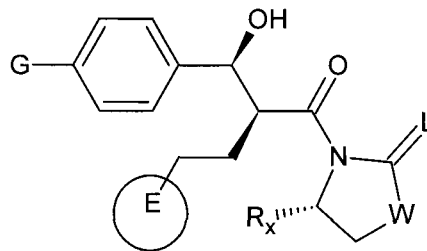


8 Formula X



9 Formula V

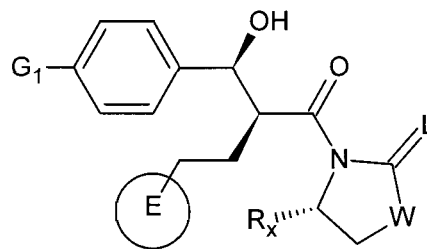
8 to give a compound of Formula XI



Formula XI

9

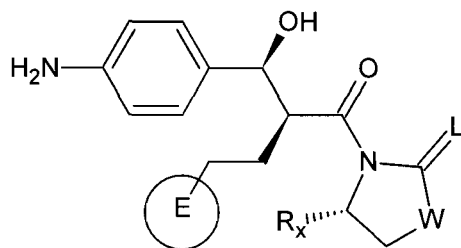
10 b) reducing a compound of Formula XI to give a compound of Formula XII



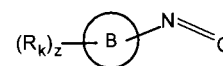
Formula XII

11

12 c) coupling a compound of Formula XII (when G₁ is amino) with a compound
13 of Formula XIII



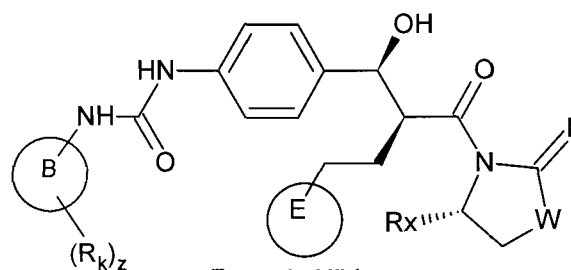
Formula XII (when G₁ is NH₂)



Formula XIII

14

15 to give a compound of Formula XIV



Formula XIV

16

17 d) hydrolyzing a compound of Formula XIV to give a compound of Formula
18 XV

18

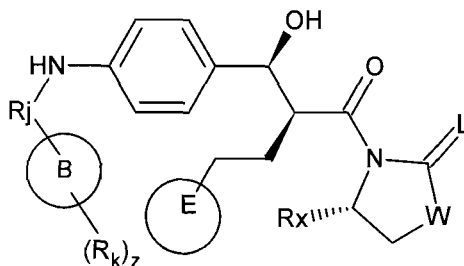
19 or

20 e) coupling a compound of Formula XII with a compound of Formula XVI



21 Formula XVI

22 to give a compound of Formula XVII,



23 Formula XVII

24 f) hydrolyzing a compound of Formula XVII to give a compound of Formula
25 XVIII

26 wherein,

27 B is aryl, cycloalkyl, heteroaryl or heterocyclyl, each of which can be
28 further substituted by one or more substituents independently selected from
29 R^1 ;

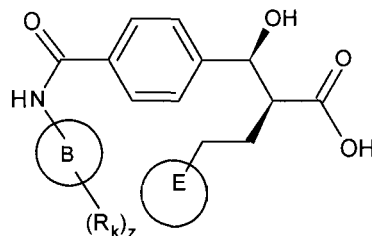
30 R^1 is alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno- C_1 - C_6 alkyl,
31 halogeno- C_1 - C_6 alkoxy, azido, thiol, alkylthiol, $-(CH_2)_n$ - OR_f , $-C(=O)$ - R_f ,
32 $COOR_f$, $-NR_fR_q$, $-(CH_2)_n$ - $C(=O)NR_fR_q$, $-(CH_2)_n$ - $NHC(=O)$ - R_f , $-(CH_2)_n$ - O -
33 $C(=O)$ - NR_fR_q , $(CH_2)_n$ $NHC(=O)NR_fR_q$, $-(CH_2)_n$ - O - $C(=O)$ - R_f , $-(CH_2)_n$ - NH -
34 $C(=O)$ - R_f or $-(CH_2)_n$ $S(=O)_m$ - NR_fR_q {wherein R_f and R_q are independently
35 selected from hydrogen, alkyl, alkenyl, cycloalkyl aryl, heteroaryl, heterocyclyl,
36 alkylaryl, alkylheteroaryl and alkylheterocyclyl, n is as defined earlier and m is
37 an integer 0-2};

38 E is selected from heteroaryl or heterocyclyl;

39 R_k is H, halo, alkyl, alkoxy, cyano, halogeno- C_1 - C_6 alkyl or halogeno- C_1 -
40 C_6 alkoxy;

- 41 z is 0-4;
 42 L and W are O or S respectively;
 43 Rx is alkyl, aryl or aralkyl;
 44 G is nitro or C(O)O-benzyl;
 45 G₁ is amino or COOH;
 46 X is a leaving group for example halogen; and
 47 R_j is -(CH₂)₀₋₁-CO-, -C(O)O-, -SO₂-.

- 1 12. A process for preparing a compound of Formula XXI (Formula I when Ring A is
 2 phenyl, U is -CO-V is -NH-, and W is a bond)



Formula XXI

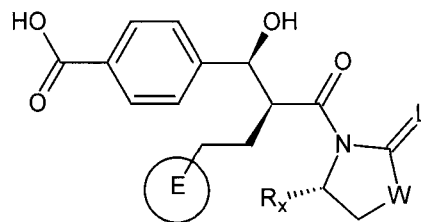
3

4

Comprising:

5

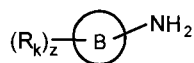
- a) coupling a compound of Formula XII (when G₁ is COOH)

Formula XII (when G₁ is COOH)

6

7

with a compound of Formula XIX

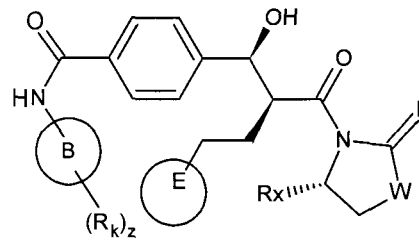


Formula XIX

8

9

to give a compound of Formula XX



Formula XX

10

11 b) hydrolyzing a compound of Formula XX to give a compound of Formula
 12 XXI,

13 wherein,

14 $\textcircled{\text{B}}$ is aryl, cycloalkyl, heteroaryl or heterocyclyl, each of which can be
 15 further substituted by one or more substituent independently selected from
 16 R^1 ;

17 R^1 is alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno-C₁-C₆ alkyl,
 18 halogeno-C₁-C₆ alkoxy, azido, thiol, alkylthiol, $-(\text{CH}_2)_n\text{-OR}_f$, $-\text{C}(=\text{O})\text{-R}_f$, $-\text{COOR}_f$, $-\text{NR}_f\text{R}_q$, $-(\text{CH}_2)_n\text{-C}(=\text{O})\text{NR}_f\text{R}_q$, $-(\text{CH}_2)_n\text{-NHC}(=\text{O})\text{-R}_f$, $-(\text{CH}_2)_n\text{-O-C}(=\text{O})\text{-NR}_f\text{R}_q$, $(\text{CH}_2)_n\text{NHC}(=\text{O})\text{NR}_f\text{R}_q$, $-(\text{CH}_2)_n\text{-O-C}(=\text{O})\text{-R}_f$, $-(\text{CH}_2)_n\text{-NH-C}(=\text{O})\text{-R}_f$ or $-(\text{CH}_2)_n\text{S}(=\text{O})_m\text{-NR}_f\text{R}_q$ {wherein R_f and R_q are independently
 22 selected from hydrogen, alkyl, alkenyl, cycloalkyl aryl, heteroaryl, heterocyclyl,
 23 alkylaryl, alkylheteroaryl and alkylheterocyclyl, n is as defined earlier and m is
 24 an integer 0-2};

25 $\textcircled{\text{E}}$ is selected from heteroaryl or heterocyclyl;

26 R_k is H, halo, alkyl, alkoxy, cyano, halogeno-C₁-C₆ alkyl or halogeno-C₁-
 27 C₆ alkoxy;

28 z is 0-4;

29 L and W are O or S respectively;

30 Rx is alkyl, aryl or aralkyl.