

MATRIX METALLOPROTEINASE INHIBITORS

Field of the Invention

The present invention relates to certain sulfone acetic acid derivatives as MMP inhibitor and processes for its syntheses. The 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 scleriosis, gingivitis, atherosclerosis, dry eye, and neointimal proliferation which leads to restenosis and ischemic heart failure, stroke, renal disease,
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; 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 (MMP-14,
20 -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 disease processes that involve remodeling such as embryonic development, bone formation and uterine remodeling during menstruation. One major biological function of MMPs is to catalyze
25 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.

MMP-9 (gelatinase B) has been implicated in pathogenesis of COPD, MS and other inflammatory disorders. MMP-9 is secreted as proenzyme and upon activation, exhibits distinct roles in the progression of both disease states. For example, leukocyte mediated activation of MMP-9 exhibits during the inflammatory response associated with
5 COPD, marks the onset of processes linked to airway obstruction. MMP-9 is the primary pro-inflammatory mediator of the inflammation and its expression goes higher in all inflammatory diseases, like COPD, MS, arthritis, psoriasis, etc. Other MMPs are also involved in some vital and regulatory functions of the cell, so an MMP-9 selective inhibitor would only target the inflammation component of the disease and would be free
10 of undesirable toxicity.

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.

15 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
20 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 sulphydryl) capable of chelating to the active site Zn^{2+} ion (Whittaker *et al.*, *Chem. Rev.*, 99; p. 2735-76 (1999)).

WO 03/82841 discloses new 5-substituted 1,1-dioxo-1,2,5-thiazolidine-3-one derivatives as protein tyrosine phosphatase inhibitors used for treating, *e.g.*, diabetes,
25 metabolic disorders, obesity and ischemic disease. EP 0 507 238 discloses *R*- and *S*-carboxylic acids in the treatment of diabetes, especially diabetes mellitus. EP 0 279 162 discloses new 2-substituted thio-alkanoic acid derivatives useful for treating diabetes, atherosclerosis, and diseases of lipid metabolism.

Research has been carried out into the identification of inhibitors that are selective,
30 *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 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 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 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 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 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 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.

Summary of the Invention

The present invention provides sulfone acetic acid derivatives as matrix metalloproteinase-9 inhibitors which are effective therapeutic or prophylactic agents for the treatment of various inflammatory and allergic diseases. Also provides are processes for synthesizing such compounds.

The compounds of the present invention are useful for the treatment of inflammatory and autoimmune diseases.

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 and autoimmune diseases. These pharmaceutical compositions may be administered or co-administered by a wide variety of routes 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.

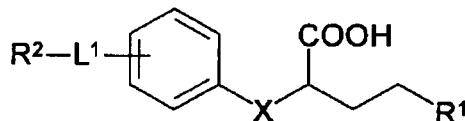
Although, the specific enantiomers have been shown by way of examples, racemates, diastereomers, and pharmaceutically acceptable salts are also provided. Pharmaceutical compositions comprising such compounds, their racemates, enantiomers, diastereomers, and pharmaceutically acceptable salts are also included.

The therapeutically effective amount of one or more compounds of the present invention can be used in combination with one or more other therapeutic agents, for example, protein synthesis inhibitors, amino glycosides, cell wall synthesis inhibitor (glycopeptides, beta-lactams, etc.), RNA, and DNA synthesis inhibitors or fatty acid synthesis inhibitors.

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

Detailed Description of the Invention

In accordance with one aspect there is provided a compounds having structure of Formula I:



Formula I

including racemates, enantiomers and diastereomers, thereof or a pharmaceutically acceptable salts thereof.

5 Wherein,

X can be S, SO or SO₂;

L¹ can be selected from bond, -O-, -S-, -SO-, -SO₂-, -CH₂-, -NR⁴-, -NHCO(CH₂)_n-,
 -(CH₂)_nCONH-, -NHCONH-, -SO₂NH-, -NHCO(O)-, -O-(CH₂)_n-,
 -(CH₂)_n-O-, -OC(O)NH-, -C(S)NH-, -NHC(S)-, -NHC(S)NH-, -COO- wherein n
 10 can be zero or an integer between 1 and 2;

R¹ can be -OCONHR³, OCSNHR³, OCH₂R³;

When **R**¹ is OCONHR³ or OCSNHR³ then **R**² can be hydrogen, C₁-C₆alkyl,
 hydroxyl, C₁-C₆alkoxy, cyano, nitro, halogen, halogeno C₁-C₆alkyl, C₆-C₁₂ aryl,
 C₃-C₈cycloalkyl, C₅-C₁₂ heteroaryl wherein C₆-C₁₂ aryl, C₃-C₈cycloalkyl, C₅-C₁₂
 15 heteroaryl is optionally substituted with one or more times with **R**⁵;

When **R**¹ is OCH₂R³, then **R**² can be C₆-C₁₂ aryl, C₃-C₈ cycloalkyl, C₆-C₁₂
 heteroaryl;

R³ is alkyl, alkenyl, alkynyl, C₆-C₁₂ aryl, C₃-C₈ cycloalkyl, C₅-C₁₂ heteroaryl, C₃-
 C₁₂ heterocyclyl which may optionally be substituted one or more times with **R**⁵;

20 **R**⁴ can be H, C₁₋₆alkyl, C₁₋₄alkylaryl;

R⁵ can be selected from 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)-
 25 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 define earlier and m is an integer 0-2};

In one aspect the invention encompasses compounds that include, for example,

- 4-{[(4-Chlorophenyl)carbamoyl]oxy}-2-[(4-chlorophenyl)sulfanyl]butanoic acid (Compound no. 1);
- 5 2-[(4-Chlorophenyl)sulfanyl]-4-{[(4-fluorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 2);
- 4-{[(4-Chlorophenyl)carbamoyl]oxy}-2-[(4-chlorophenyl)sulfonyl]butanoic acid (Compound no. 3);
- 2-[(4-Chlorophenyl)sulfonyl]-4-{[(4-fluorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 4);
- 10 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(4-fluorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 5);
- 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(2-fluoro-5-(trifluoromethyl)phenyl)carbamoyl]oxy}butanoic acid (Compound no. 6);
- 15 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(3,5-dimethoxyphenyl)carbamoyl]oxy}butanoic acid (Compound no. 7);
- 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(5-fluoro-2-methylphenyl)carbamoyl]oxy}butanoic acid (Compound no. 8);
- 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(2-fluorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 9);
- 20 4-{[(3-Chloro-4-methoxyphenyl)carbamoyl]oxy}-2-[(4-{[(4-chlorophenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 10);
- 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(3-ethoxyphenyl)carbamoyl]oxy}butanoic acid (Compound no. 11);
- 25 4-{[(3-Chlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-chlorophenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 12);
- 4-{[(4-Chlorophenyl)carbamothioyl]oxy}-2-[(4-{[(4-chlorophenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 13);
- 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(3-cyanophenyl)carbamothioyl]oxy}butanoic acid (Compound no. 14);
- 30 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfonyl]-4-{[(4-fluorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 15);
- 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfonyl]-4-{[(2-fluoro-5-(trifluoromethyl)phenyl)carbamoyl]oxy}butanoic acid (Compound no. 16);
- 35 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfonyl]-4-{[(5-fluoro-2-methylphenyl)carbamoyl]oxy}butanoic acid (Compound no. 17);
- 4-{[(3-Chloro-4-methoxyphenyl)carbamoyl]oxy}-2-[(4-{[(4-chlorophenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 18);
- 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfonyl]-4-{[(2-fluorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 19);

- 4-{{(3-Chlorophenyl)carbamoyl}oxy}-2-[(4-{{(4-chlorophenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 20);
- 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfonyl]-4-{{(3-cyanophenyl)carbamothioyl}oxy}butanoic acid (Compound no. 21);
- 5 4-(Benzyloxy)-2-[(4-{{(4-methylphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 22);
- 4-(Benzyloxy)-2-[(4-{{(3-fluorophenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 23);
- 10 4-(Benzyloxy)-2-[(4-{{(3-chlorophenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 24);
- 4-(Benzyloxy)-2-[(4-{{(4-ethylphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 25);
- 4-(Benzyloxy)-2-[(4-{{(3-methoxyphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 26);
- 15 4-(Benzyloxy)-2-[(4-{{(2-fluorophenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 27)
- 4-(Benzyloxy)-2-[(4-nitrophenyl)sulfonyl]butanoic acid (Compound no. 28);
- 4-{{(2-Fluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methylphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 29);
- 20 4-{{(3-Fluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methylphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 30);
- 4-{{(3-Fluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methylphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 31);
- 25 4-{{(4-Chlorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 32);
- 4-{{(4-Ethylphenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 33);
- 2-[(4-{{(4-Methoxyphenyl)carbonyl}amino}phenyl)sulfanyl]-4-{{(4-(trifluoromethyl)phenyl)carbamoyl}oxy}butanoic acid (Compound no. 34);
- 30 4-{{(2,6-Dichlorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 35);
- 2-[(4-{{(4-Methoxyphenyl)carbonyl}amino}phenyl)sulfanyl]-4-{{(2-methylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 36);
- 35 4-{{(4-Methoxyphenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 37);
- 4-{{(tert-Butylcarbamoyl)oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 38);
- 4-{{(2,4-Difluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 39);

- 4-{{(2-Fluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 40);
- 4-{{(3-Fluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 41);
- 5 4-{{(3,4-Dichlorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 42);
- 4-{{(3,4-Dichlorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methylphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 43);
- 10 4-{{(2,4-Difluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methylphenyl)carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 44);
- 4-{{(4-Chlorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 45);
- 4-{{(4-Ethylphenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 46);
- 15 2-[(4-{{(4-Methoxyphenyl)carbonyl}amino}phenyl)sulfonyl]-4-{{(4-(trifluoromethyl)phenyl)carbamoyl}oxy}butanoic acid (Compound no. 47);
- 4-{{(2,6-Dichlorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}aminophenyl})sulfonyl]butanoic acid (Compound no. 48);
- 20 2-[(4-{{(4-Methoxyphenyl)carbonyl}amino}phenyl)sulfonyl]-4-{{(2-methylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 49);
- 4-[(*tert*-Butylcarbamoyl)oxy]-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 50);
- 4-{{(2,4-Difluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 51);
- 25 4-{{(2-Fluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 52);
- 4-{{(3-Fluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 53);
- 30 4-{{(5-Chloro-2-methoxyphenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 54);
- 4-{{(3,4-Dichlorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methoxyphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 55);
- 4-{{(3,4-Dichlorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methylphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 56);
- 35 4-{{(2,4-Difluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methylphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 57);
- 4-{{(2-Fluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methylphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 58);
- 40 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(2-fluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 59);

- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-ethylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 60);
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{[4-(propan-2-yl)phenyl]carbamoyl}oxy}butanoic acid (Compound no. 61);
- 5 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-methoxyphenyl)carbamoyl}oxy}butanoic acid (Compound no. 62);
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(2-methylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 63);
- 10 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(3-fluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 64);
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-methylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 65);
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{[4-(trifluoromethyl)phenyl]carbamoyl}oxy}butanoic acid (Compound no. 66);
- 15 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(2,4-difluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 67);
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-fluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 68);
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(2,6-dichlorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 69);
- 20 4-[(*tert*-Butylcarbamoyl)oxy]-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfanyl)butanoic acid (Compound no. 70);
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(3,4-dichlorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 71);
- 25 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-[(pentylcarbamoyl)oxy]butanoic acid (Compound no. 72);
- 4-{{(3-Chlorophenyl)carbamoyl}oxy}-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfanyl)butanoic acid (Compound no. 73);
- 30 4-[(Butylcarbamoyl)oxy]-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfanyl)butanoic acid (Compound no. 74);
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(2-fluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 75);
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(4-ethylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 76);
- 35 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(2-methylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 77);
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(4-methylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 78);
- 40 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{[4-(trifluoromethyl)phenyl]carbamoyl}oxy}butanoic acid (Compound no. 79);

- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(2,4-difluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 80);
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(4-fluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 81);
- 5 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(2,6-dichlorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 82);
- 4-[(*tert*-Butylcarbamoyl)oxy]-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfonyl)butanoic acid (Compound no. 83);
- 10 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(3,4-dichlorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 84);
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-[(pentylcarbamoyl)oxy]butanoic acid (Compound no. 85);
- 4-{{(3-Chlorophenyl)carbamoyl}oxy}-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfonyl)butanoic acid (Compound no. 86);
- 15 4-[(Butylcarbamoyl)oxy]-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfonyl)butanoic acid (Compound no. 87);
- 2-[(4-{{(2-Fluorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 88);
- 20 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 89);
- 2-[(4-{{(2,6-Dimethoxyphenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 90);
- 2-({4-[(Cyclopropylcarbonyl)amino]phenyl}sulfanyl)-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 91);
- 25 2-[(4-{{(2-Methylphenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 92);
- 2-[(4-{{(2-Ethoxyphenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 93);
- 30 2-[(4-{{(2,3-Difluorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 94);
- 2-[(4-{{(3,4-Dichlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 95);
- 2-[(4-{{(4-Ethoxyphenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 96);
- 35 2-({4-[(Cyclohexylcarbonyl)amino]phenyl}sulfanyl)-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 97);
- 2-[(4-{{(2,4-Dichlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 98).

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.

5 In another aspect, provided herein are methods for treating or preventing various inflammatory and allergic diseases comprising administering to a mammal in need thereof therapeutically effective amount of one or more compounds of Formula 1 described herein.

10 In yet another aspect, the present invention relates to the therapeutically effective amount of compounds of Formula I in combination with one or more of other therapeutic agents used in treating various inflammatory and allergic diseases. Examples of such therapeutic agents includes but are not limited to:

- 15 a) anti-inflammatory agents, experimental or commercial (i) such as nonsteroidal anti-inflammatory agents piroxicam, diclofenac, propionic acids, fenamates, pyrazolones, salicylates, PDE-4/p38 MAP Kinase/Cathepsin inhibitors, (ii) leukotrienes LTC₄/LTD₄/LTE₄/LTB₄-Inhibitors, 5-lipoxygenase inhibitor and PAF-receptor antagonists, (iii) Cox-2 inhibitors, (iv) MMP inhibitors, and (v) interleukin-I inhibitors;
- 20 b) 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.
- c) immunosuppressive agents such as cyclosporine, azathioprine and methotrexate, and anti inflammatory corticosteroids.

The following definitions apply to terms as used herein.

25 The term "alkyl" unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term can be exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-decyl, tetradecyl, and the like.

The term "alkenyl" unless otherwise specified, refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group having from 2 to 20 carbon atoms with cis, trans or geminal geometry.

5 The term "alkynyl" unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, having from 2 to 20 carbon atoms.

The term "cycloalkyl" unless otherwise specified, refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which may optionally contain one or more olefinic bonds, unless otherwise constrained by the definition. Such cycloalkyl groups can include, for example, single ring structures,
10 including cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like or multiple ring structures, including adamantanyl, and bicyclo [2.2.1] heptane or cyclic alkyl groups to which is fused an aryl group, for example, indane, and the like. Spiro and fused ring structures can also be included.

The term "aryl" unless otherwise specified, refers to aromatic system having 6 to
15 14 carbon atoms, wherein the ring system can be mono-, bi- or tricyclic and are carbocyclic aromatic groups. For example, aryl groups include, but are not limited to, phenyl, biphenyl, anthryl or naphthyl ring and the like, optionally substituted with 1 to 3 substituents selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, CF₃, cyano, nitro, COOR_ψ, NHC(=O)R_λ, -NR_λR_π,
20 -C(=O)NR_λR_π, -NHC(=O)NR_λR_π, -O-C(=O)NR_λR_π, -SO_mR_ψ, carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or amino carbonyl amino, mercapto, haloalkyl, optionally substituted aryl, optionally substituted heterocyclylalkyl, thioalkyl, -CONHR_π, -OCOR_π, -COR_π, -NHSO₂R_π or -SO₂NHR_π (wherein R_λ, R_π, m and R_ψ are the same as defined earlier). Aryl groups optionally may be fused with a cycloalkyl group,
25 wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S. Groups such as phenyl, naphthyl, anthryl, biphenyl, and the like exemplify this term.

The term "aralkyl" unless otherwise specified, refers to alkyl-aryl linked through an alkyl portion (wherein alkyl is as defined above) and the alkyl portion contains 1-6 carbon atoms and aryl is as defined above. Examples of aralkyl groups include benzyl,
30 ethylphenyl, propylphenyl, naphthylmethyl, and the like.

The term “aryloxy” denotes the group O-aryl wherein aryl is the same as defined above.

The term “heteroaryl” unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms or a bicyclic or tricyclic aromatic group having from
5 8 to 10 ring atoms, with one or more heteroatom(s) independently selected from N, O or S. Unless otherwise constrained by the definition, the substituents are attached to a ring atom, *i.e.*, carbon or heteroatom in the ring. Examples of heteroaryl groups include oxazolyl, imidazolyl, pyrrolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, oxadiazolyl, benzoimidazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl,
10 isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzthiazinyl, benzthiazinonyl, benzoxazinyl, benzoxazinonyl, quinazonyl, carbazolyl phenothiazinyl, phenoxazinyl, benzothiazolyl or benzoxazolyl, and the like.

The term “heterocyclyl” unless otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms wherein 1 to 4 carbon atoms
15 in a ring are replaced by heteroatoms selected from O, S or N, and optionally are benzofused or fused heteroaryl having 5-6 ring members. Examples of heterocyclyl groups include benzotriazinone, isoindoledione, pyrimidinedione, aza-spiro[4.5]decanedione, benzo-oxazinedione, imidazolidinedione, phthalazinone, oxazolidinyl, tetrahydrofuranyl, dihydrofuranyl, benzoxazinyl, benzthiazinyl, imidazolyl,
20 benzimidazolyl, tetrazolyl, carbazolyl, indolyl, phenoxazinyl, phenothiazinyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, thiazolidinyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl, tetrahydropyranyl, piperazinyl, 3*H*-imidazo[4,5-*b*]pyridine, isoquinolinyl, 1*H*-pyrrolo[2,3-*b*]pyridine or piperazinyl, and the like.

25 The term “cycloalkylalkyl” refers to cycloalkyl group linked through alkyl portion, wherein the alkyl having 1 to 6 carbon atoms and cycloalkyl are the same as defined earlier.

The term “heteroarylalkyl” refers to heteroaryl group linked through alkyl portion, wherein the alkyl having 1 to 6 carbon atoms and heteroaryl are the same as defined
30 earlier.

The term "heterocyclylalkyl" refers to heterocyclyl group linked through alkyl portion, wherein the alkyl having 1 to 6 carbon atoms and heterocyclyl are the same as defined earlier.

The term "amino" refers to —NH_2

5 The term "halogen or Halo" refers to fluorine, chlorine, bromine or iodine;

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,
10 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
15 P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd Ed., John Wiley and Sons, New York, N.Y., which is incorporated herein by reference. 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 is/are stable to conditions of subsequent reactions and can be removed without disrupting the remainder of the
20 molecule.

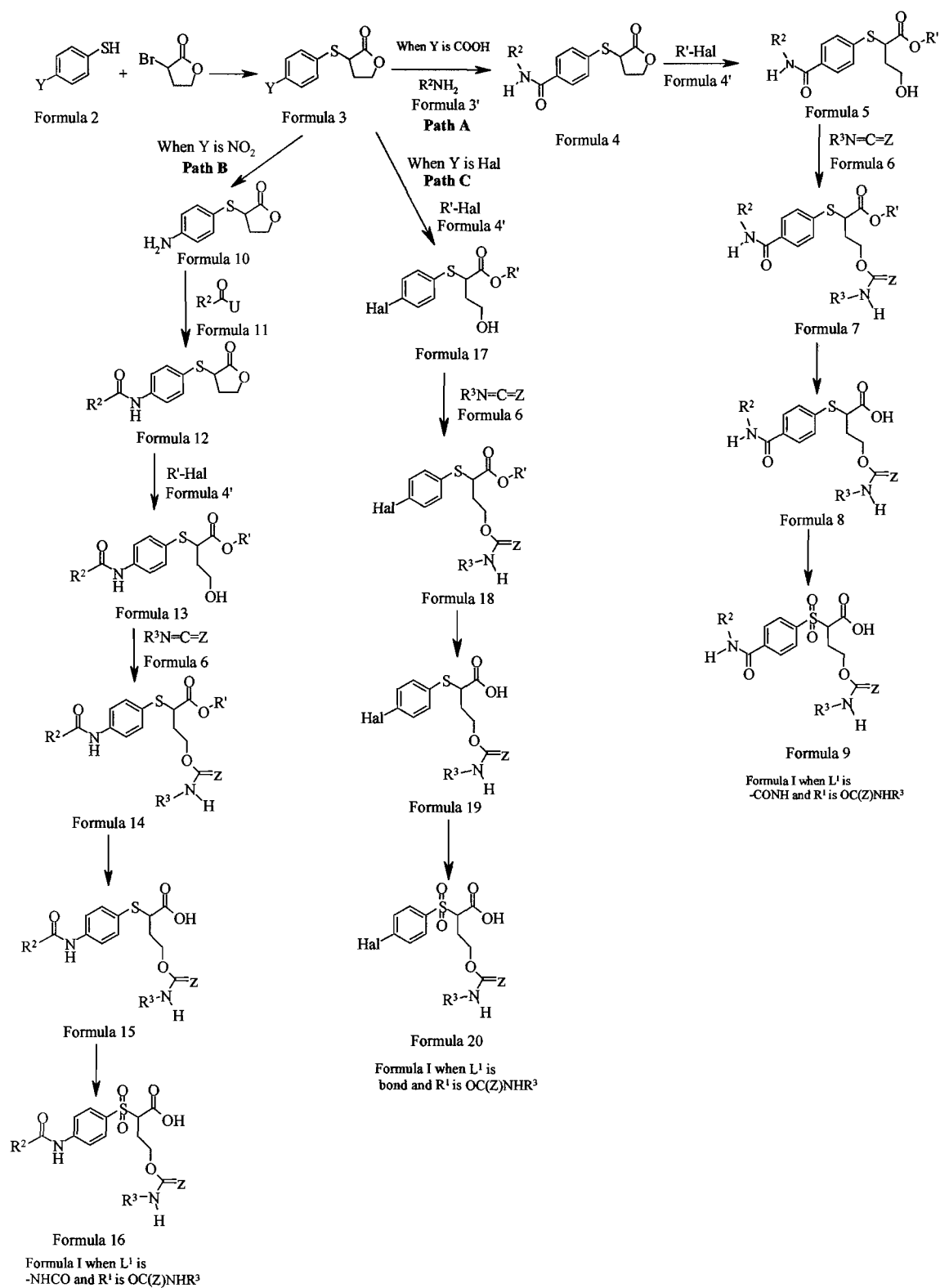
The compounds of this invention can contain one asymmetric carbon atom and thus may occur as racemic mixtures, enantiomers and diastereomers. These compounds can also exist as conformers/rotamers. All such isomeric forms of these compounds are included in the present invention. Each stereogenic carbon atom may be of the *R* or *S*
25 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 mixture thereof are envisioned as part of the invention.

The term "pharmaceutically acceptable salts" forming part of this invention
30 includes the salts of carboxylic acids moiety, which can be prepared by reacting the compound with appropriate base to provide corresponding base addition salts. Examples

of such base 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
5 ammonium salts are also included. Wherever appropriate, compounds with pharmaceutically acceptable organic and inorganic acids, *e.g.*, hydro halides, 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
10 and their corresponding salts, such as acetate, tartaratae, maleate, succinate, citrate, etc.

In another aspect, the compounds disclosed herein may be prepared by following reaction sequences as depicted in Schemes I, and II.

Scheme I



The compound of Formula 8 (Path A), Formula 9 (Path A), Formula 15 (Path B), Formula 16 (Path B), Formula 19 (Path C) and Formula 20 (Path C) can be prepared according to Scheme I. Thus, reacting a compound of Formula 2 (wherein Y is NO₂, Hal and COOH) with alpha bromo lactone gives a compound of Formula 3. The compound of
5 Formula 3 can react in three ways to give a compound of Formula 8, Formula 9, Formula 15, Formula 16, Formula 19 and Formula 20.

Path A (when Y is COOH): The reaction of a compound of Formula 3 with a compound of Formula 3' (where R² is same as defined earlier) to give a compound of Formula 4 which upon reaction with a compound of Formula 4' (wherein R' is alkyl, allyl, benzyl, *t*-
10 butyl, silyl and Hal is F, Cl, Br, I) gives a compound of Formula 5. The reaction of a compound of Formula 5 with a compound of Formula 6 (where R³ is same as defined earlier and Z is O or S) gives a compound of Formula 7. The hydrolysis of a compound of Formula 7 gives a compound of Formula 8 which upon oxidation gives a compound of Formula 9.

Path B (when Y is NO₂): The reduction of a compound of Formula 3 gives a compound of Formula 10 which upon reaction with a compound of Formula 11 (wherein R² is same as defined earlier and U is a leaving group such as halide, alkyloxy, aryloxy) gives a compound of Formula 12. The compound of Formula 12 upon reaction with a compound of Formula 4' (wherein R' and Hal are same as defined earlier) gives a compound of
20 Formula 13. The reaction of a compound of Formula 13 with a compound of Formula 6 (wherein R³ and Z are same as defined earlier) gives a compound of Formula 14. The hydrolysis of a compound of Formula 14 gives a compound of Formula 15 which upon oxidation gives a compound of Formula 16.

Path C (when Y is halogen): The reaction of a compound of Formula 3 with a compound of Formula 4' (wherein R' and Hal is same as defined earlier) gives a compound of
25 Formula 17 which upon reaction with a compound of Formula 6 (wherein R³ and Z are same as defined as earlier) gives a compound of Formula 18. The hydrolysis of a compound of Formula 18 gives a compound of Formula 19 which upon oxidation gives a compound of Formula 20.

30 The reaction of a compound of Formula 2 with alpha bromo lactone to give a compound of Formula 3 can be carried out in the presence of organic base, for example,

triethylamine, pyridine, *N,N'*-dimethylaminopyridine, 2,6-lutidine, 1-methylpiperidine, *N*-ethyl-diisopropylamine or *N*-methylmorpholine in a solvent selected from, dichloromethane, dichloroethane, chloroform, carbon tetrachloride, or mixture(s) thereof.

5 The reaction of a compound of Formula 3 (Path A) with a compound of Formula 3' to give a compound of Formula 4 can be carried out using base selected from triethylamine, pyridine, *N,N*-dimethylaminopyridine, 2,6-lutidine, 1-methylpiperidine, *N*-ethyl-diisopropylamine or *N*-methylmorpholine, in the presence of a additives, for example, hydroxybenzotriazole, 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine, 2-hydroxypyridine, *N*-hydroxysuccinimide or 1-hydroxy-7-azabenzotriazole, with a suitable
10 condensing agent, for example, dicyclohexyl carbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, chlorotripyrrolidinophosphonium hexafluorophosphate or (benzotriazol-1-yloxy)*tris*-(dimethylamino)phosphonium hexafluorophosphate.

The reaction of a compound of Formula 4 with a compound of Formula 4' to give a compound of Formula 5 can be carried out in the presence of 18-crown-6 using one or
15 more inorganic base selected from sodium bicarbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide in the presence of a solvent, selected from, *N*, *N'*-dimethylformamide, methanol, ethanol, propanol, butanol, tetrahydrofuran, acetonitrile, water, or mixture thereof.

The reaction of a compound of Formula 5 with a compound of Formula 6 to give a
20 compound of Formula 7 can be carried out in the presence of organic base selected from, for example, triethylamine, pyridine, *N,N'*-dimethylaminopyridine, 2,6-lutidine, 1-methylpiperidine, *N*-ethyl-diisopropylamine or *N*-methylmorpholine in a solvent selected from tetrahydrofuran, dimethylsulfoxide, acetonitrile, *N*, *N'*-dimethylformamide, or mixture(s) thereof.

25 The hydrolysis of a compound of Formula 7 to give a compound of Formula 8 can be carried out in the presence of inorganic base selected from, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide in solvents for example, tetrahydrofuran, acetonitrile, methanol, ethanol, propanol, dimethylsulfoxide, or mixture(s) thereof.

30 The oxidation of a compound of Formula 8 to give a compound of Formula 9 can be carried out with oxidizing agents, for example, meta-chloroperbenzoic acid or oxone in

a solvent, selected from, chloroform, dichloromethane, methanol, water, carbon tetrachloride, or mixture(s) thereof.

The reduction of a compound of Formula 3 (Path B) to give a compound of Formula 10 can be carried out using reducing agent selected from, for example, Pd/C,
5 lithium aluminum hydride, Raney Nickel in the presence of hydrazine hydrate, zinc, tin or iron in the presence of hydrochloric acid in a solvent selected from tetrahydrofuran, methanol, ethanol, dichloromethane, or mixture(s) thereof.

The reaction of a compound of Formula 10 with a compound of Formula 11 to give a compound of Formula 12 can be carried out in the presence of organic base, for
10 example, triethylamine, pyridine, *N,N'*-dimethylaminopyridine, 2,6-lutidine, 1-methylpiperidine, *N*-ethyldiisopropylamine or *N*-methylmorpholine in a solvent selected from, dichloromethane, dichloroethane, chloroform, carbon tetrachloride, or mixture(s) thereof.

The ring opening of a compound of Formula 12 with a compound of Formula 4' to
15 give a compound of Formula 13 can be carried out under similar conditions as described for the reaction of a compound of Formula 4 with a compound of Formula 4' to give a compound of Formula 5.

The reaction of a compound of Formula 13 with a compound of Formula 6 to give a compound of Formula 14 can be carried out under similar conditions as described for the
20 reaction of a compound of Formula 5 with a compound of Formula 6 to give a compound of Formula 7.

The hydrolysis of a compound of Formula 14 to give a compound of Formula 15 can be carried out under similar conditions as described for the reaction of a compound of Formula 7 to give a compound of Formula 8.

25 The oxidation of a compound of Formula 15 to give a compound of Formula 16 can be carried out under similar conditions as described for the compound of Formula 8 to give a compound of Formula 9.

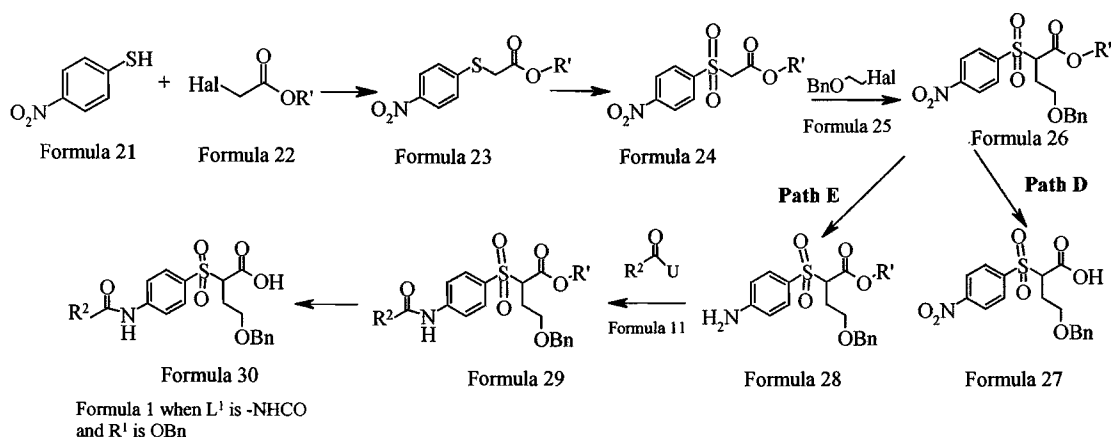
The reaction of a compound of Formula 3 (Path C) with a compound of Formula 4' to give a compound of Formula 17 can be carried out under similar conditions as described
30 for the reaction of compound of Formula 4 with a compound of Formula 4' to give a compound of Formula 5.

The reaction of a compound of Formula 17 with a compound of Formula 6 to give a compound of Formula 18 can be carried out under similar conditions as described for the reaction of a compound of Formula 5 with a compound of Formula 6 to give a compound of Formula 7.

- 5 The hydrolysis of a compound of Formula 18 to give a compound of Formula 19 can be carried out under similar conditions as described for the hydrolysis of a compound of Formula 7 to give a compound of Formula 8.

- 10 The oxidation of a compound of Formula 19 to give a compound of Formula 20 can be carried out under similar conditions as described for the compound of Formula 8 to give a compound of Formula 9.

Scheme II



- 15 The compound of Formula 27 (Path D) and Formula 30 (Path E) can be prepared according to Scheme II. Thus, reaction of a compound of Formula 21 with a compound of Formula 22 (wherein R' and Hal are same as defined earlier) gives a compound of Formula 23 which upon oxidation gives a compound of Formula 24. The reaction of a compound of Formula 24 with a compound of Formula 25 (Bn is benzyl group and Hal is same as defined earlier) forms a compound of Formula 26. The compound of Formula 26 can be reacted in two ways to give a compound of Formula 27 and Formula 30.

Path D: The hydrolysis of a compound of Formula 26 gives a compound of Formula 27.

Path E: The reduction of a compound of Formula 26 gives a compound of Formula 28 which upon reaction with a compound of Formula 11 (wherein R² and U are same as

defined earlier) gives a compound of Formula 29. The compound of Formula 29 upon hydrolysis gives a compound of Formula 30.

The reaction of a compound of Formula 21 with a compound of Formula 22 to give a compound of Formula 23 can be carried out in the presence of organic base selected from, for example, triethylamine, pyridine, *N,N'*-dimethylaminopyridine, 2,6-lutidine, 1-methylpiperidine, *N*-ethyl-diisopropylamine or *N*-methylmorpholine in a solvent selected from dichloromethane, dichloroethane, carbon tetrachloride, chloroform, tetrahydrofuran, dimethylsulfoxide, acetonitrile, *N, N'*-dimethylformamide, or mixture(s) thereof.

The oxidation of a compound of Formula 23 to form a compound of Formula 24 can be carried out under similar conditions as described for the compound of Formula 8 to give a compound of Formula 9.

The reaction of a compound of Formula 24 with a compound of Formula 25 to give a compound of Formula 26 can be carried out using tetrabutylammonium iodide in the presence of inorganic base selected from lithium carbonate, sodium carbonate, potassium carbonate, barium carbonate using a solvent selected from, *N,N'*-dimethylformamide, acetonitrile, tetrahydrofuran, dimethylsulfoxide, or mixture(s) thereof.

The hydrolysis of a compound of Formula 26 (Path D) to give a compound of Formula 27 can be carried out under similar conditions as described for the compound of Formula 7 to give a compound of Formula 8.

The reduction of a compound of Formula 26 (Path E) to give a compound of Formula 28 can be carried out using reducing agent selected from, for example, lithium aluminum hydride, Raney Nickel in hydrazine hydrate or ammonium formate, zinc, tin or iron in the presence or in the absence of hydrochloric acid.

The reaction of a compound of Formula 28 with a compound of Formula 11 to give a compound of Formula 29 can be carried out under similar conditions as described for the reaction of a compound of Formula 10 with a compound of Formula 11 to give a compound of Formula 12.

The hydrolysis of a compound of Formula 29 to give a compound of Formula 30 can be carried out under similar conditions as described for the compound of Formula 7 to give a compound of Formula 8.

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 agent, deprotecting agent, hydrolyzing agents, catalysts, etc., known to one of ordinary skill in 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.

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, excipients or diluents.

Solid form preparations for oral administration include capsules, tablets, pills, powder, granules, lozenges, troches, cachets and suppositories. For solid form preparations, active compounds can be mixed with one or more inert, pharmaceutically acceptable excipients or carrier. Tablets and capsules for oral administration may contain conventional excipients, such as binding agents and/or dissolution enhancers, for example, polyvinyl pyrrolidone, cellulose, mucilage of starch, gelatin, sorbitol, syrup, acacia or tragacanth; fillers or bulking agents, for example, microcrystalline cellulose, sugar, maize-starch, calcium phosphate, sorbitol or lactose; lubricants, for example, talc, silica, polyethyleneglycol, magnesium stearate or stearic acid; disintegrating agents and binder, for example, croscarmellose sodium, pregelatinized starch, sodium starch glycolate or potato starch; glidants, for example, colloidal silicon dioxide or talc; antiadherants, for example, magnesium stearate or sodium lauryl sulfate; and coating materials.

Capsules, tablets or pills may also comprise buffering agents.

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

General Example

A formulation of a tablet could typically contain from 0.01 mg to 500 mg of active compound whilst tablet fill weight may range from 50 mg to 1000 mg. An example is illustrated below.

5	Ingredients	Amount % w/w
	Active Compound	0.01 to 20 mg
	Microcrystalline Cellulose	about 50% to about 90%
	Croscarmellose Sodium	about 1% to about 10%
	Pregelatinized Starch	about 1% to about 15%
10	Polyvinyl Pyrrolidone (K-30)	about 5% to about 12%
	Talc	about 0.1% to about 2%
	Magnesium Stearate	about 0.1% to about 2%
	Colloidal Silicon Dioxide	about 0.1% to about 2%

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 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 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, 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 coca 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.

5 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
10 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 packaged preparations containing discrete capsules, powders, in vials or ampoules, ointments, capsules, sachets, tablets, gels, creams
15 or any combination and number of such packaged forms.

The following examples are set forth to demonstrate general synthetic procedures for the preparation of representative compounds of the present invention. The examples are provided to illustrate particular aspect of the disclosure and do not limit the scope of the present invention.

20 **Experimental**

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

Example 1: Synthesis of 2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-fluoro phenyl)carbamoyl}oxy}butanoic acid (Compound no. 68) (Scheme I, Path A, Formula 8)
25

Step a: Preparation of 4-[(2-oxotetrahydrofuran-3-yl)sulfanyl]benzoic acid

To an ice cooled solution of 4-mercaptobenzoic acid (0.5 g, 0.003 moles) in dichloromethane (5 mL) under argon atmosphere were added triethylamine (0.909 g,
30 0.009 moles) and a solution of bromo lactone (0.53 g, 0.003 moles) in dichloromethane (5

mL) drop wise. The reaction mixture was allowed to stir for about 30 minutes. After completion, reaction mixture was diluted by adding water and extracting in dichloromethane. The combined organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product which was purified by silica gel column using 70% ethyl acetate in hexane as eluent to get desired compound.

Yield: 0.800 g

LCMS: 239.16 (M+1)

Step b: Preparation of *N*-(4-chlorophenyl)-4-[(2-oxotetrahydrofuran-3-yl)sulfanyl]benzamide

To the solution of compound obtained from Step *a* (15.0 g, 0.0630 moles) in dichloromethane (150 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI, 18.0 g, 0.0942 moles), hydroxybenzotriazole (HOBT 10.2 g, 0.0689 moles), 4-dimethylaminopyridine (DMAP 1.5 g, 0.0122 moles) and stirred for about 30 minutes under argon atmosphere. After 30 minutes, 4-chloroaniline (8.0 g, 0.0630 moles) was added and again stirred for about 12 hours at room temperature. After completion, reaction mixture was diluted by adding water and extracting in dichloromethane. The combined organic layer was dried over anhydrous sodium sulphate and concentrated to get crude compound which was purified by column chromatography using 40% ethyl acetate in hexane as eluent to get desired compound.

Yield: 13.0 g

LCMS: 348.05 (M+1)

Step c: Preparation of methyl 2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-hydroxybutanoate

To a solution of compound obtained from Step *b* (13.0 g, 0.037 mole) in *N,N*-dimethylformamide (52 mL) and water (13 mL) was added sodium hydroxide (1.70 g, 0.044 moles). The reaction mixture was allowed to stir for about 30 minutes at room temperature. After 30 minutes, sodium bicarbonate (3.7 g, 0.044 moles), 18 crown 6 (0.970 g, 0.0037 moles) and methyl iodide (7.80 g, 0.055 moles) were added and stirred for overnight. After completion, reaction mixture was diluted by adding water and extracting in ethyl acetate. The combined organic layer was dried over anhydrous sodium

sulphate and concentrated to get crude product which was purified by silica gel column using 30% ethyl acetate in hexane as eluent to get desired compound.

Yield: 8.0 g

**Step d: Preparation of methyl 2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-
5 {[(4-fluorophenyl)carbamoyl]oxy}butanoate**

To a solution of compound obtained from Step *c* (0.500 g, 0.0013 moles) in tetrahydrofuran (5 mL) under argon atmosphere were added triethylamine (0.393 g, 0.0038 moles) and 4-fluoro-isocyanate (0.213 g, 0.0016 moles) and stirred for about 2 hours at room temperature. After completion, reaction mixture was diluted by adding water and
10 extracting in ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product which was purified by silica gel column using 30% ethyl acetate in hexane as eluent to afford desired compound.

Yield: 0.3 g

**Step e: Preparation of 2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-
15 {[(4-fluorophenyl)carbamoyl]oxy}butanoic acid**

To a solution of compound obtained from Step *d* (0.300 g, 0.0005 moles) in tetrahydrofuran (5ml)/methanol (5ml) was added a solution of lithium hydroxide (0.036 g, 0.0006 moles) in water (1 mL) and stirred for about one hour at room temperature. After completion, reaction mixture was acidify by adding sodium bisulphite solution and
20 extracted in ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and concentrated to get a compound which was purified by preparative TLC eluted using 10% methanol in dichloromethane.

Yield: 0.050 g

LCMS: 501.15 (M-1)

¹H NMR (400 MHz, DMSO-*d*₆)-δ: 10.28 - 10.35 (1H, s), 9.67 (1H, s), 7.76 - 7.78 (4H, m),
25 7.53 - 7.55 (2H, m), 7.32 - 7.44 (3H, m), 7.07 - 7.20 (3H, m), 4.18 - 4.21 (2H, m), 3.98 - 4.02 (1H, m), 1.90 - 2.23 (2H, m).

The following compounds can be prepared by following the above synthetic route.

2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-
30 {[(2-fluorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 59);

- LCMS: 501.17 (M-1)
2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-ethylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 60);
- 5 LCMS: 511.22 (M-2)
2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{[4-(propan-2-yl)phenyl]carbamoyl}oxy}butanoic acid (Compound no. 61);
- LCMS: 525.19 (M-2)
2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-methoxyphenyl)carbamoyl}oxy}butanoic acid (Compound no. 62);
- 10 LCMS: 513.18 (M-1)
2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(2-methylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 63);
- LCMS: 497.18 (M-1)
2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(3-fluoro phenyl)carbamoyl}oxy}butanoic acid (Compound no. 64);
- 15 LCMS: 501.16 (M-1)
2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-methylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 65);
- LCMS: 417.17 (M-1)
2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{[4-(trifluoromethyl)phenyl]carbamoyl}oxy}butanoic acid (Compound no. 66);
- 20 LCMS: 551.09 (M-1)
2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(2,4-difluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 67);
- 25 LCMS: 519.15 (M-1)
2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(2,6-dichlorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 69);
- LCMS: 553.06 (M)
4-[(*tert*-Butylcarbamoyl)oxy]-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfanyl)butanoic acid (Compound no. 70);
- 30 LCMS: 463.20 (M-1)
2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(3,4-dichlorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 71);
- LCMS: 553.03 (M)
2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-[(pentylcarbamoyl)oxy]butanoic acid (Compound no. 72);
- 35 LCMS: 477.19 (M-1)

4-{{(3-Chlorophenyl)carbamoyl}oxy}-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfanyl)butanoic acid (Compound no. 73);

LCMS: 519.10 (M)

5 4-[(Butylcarbamoyl)oxy]-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfanyl)butanoic acid (Compound no. 74);

LCMS: 463.17 (M-1)

Example 2: Synthesis of 2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(4-fluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 81) (Scheme I, Path A, Formula 9)

10 To an ice-cooled solution of 2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-fluorophenyl)carbamoyl}oxy}butanoic acid (0.050 g, 0.00009 moles) in chloroform (5 mL) was added metachloroperbenzoic acid (0.065 g, 0.00037 moles) and stirred for 1 hour at room temperature. The reaction mixture was quenched by adding sodium metabisulphite solution and then extracted in dichloromethane. The combined organic
15 layer was dried over anhydrous sodium sulphate and concentrated to get crude product which was purified by preparative TLC eluted in 12% methanol in dichloromethane.

Yield: 0.030 g

LCMS: 533.18 (M-1)

¹H NMR (400 MHz, DMSO-*d*₆) -δ: 10.63 - 10.71 (1H, s), 9.10 (1H, s), 8.10 - 8.12 (2H, d, *J* = 8.0 Hz), 7.96 - 7.98 (2H, d, *J* = 8.0 Hz), 7.83 - 7.86 (2H, m), 7.41 - 7.44 (4H, m), 7.10 - 7.21 (2H, m), 4.17 (2H, m), 3.86 (1H, m), 2.11 (2H, m).

The following compounds can be prepared by following the above synthetic route.

2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(2-fluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 75);

25 LCMS: 533.21 (M-1)

2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(4-ethylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 76);

LCMS: 543.24 (M-2)

2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(2-methylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 77);

30 LCMS: 529.22 (M-1)

2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(4-methylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 78);

LCMS: 529.20 (M-1)

- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-({4-(trifluoromethyl)phenyl}carbamoyl)oxy}butanoic acid (Compound no. 79);
LCMS: 583.21 (M-1)
- 5 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(2,4-difluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 80);
LCMS: 551.19 (M-1)
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(2,6-dichlorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 82);
LCMS: 541.11 (M-44)
- 10 4-[(*tert*-Butylcarbamoyl)oxy]-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfonyl)butanoic acid (Compound no. 83);
LCMS: 451.19 (M-45)
- 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(3,4-dichlorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 84);
LCMS: 585.09 (M)
- 15 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-[(pentylcarbamoyl)oxy]butanoic acid (Compound no. 85);
LCMS: 509.24 (M-1)
- 20 4-{{(3-Chlorophenyl)carbamoyl}oxy}-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfonyl)butanoic acid (Compound no. 86);
LCMS: 551.11 (M)
- 4-[(Butylcarbamoyl)oxy]-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}sulfonyl)butanoic acid (Compound no. 87);
LCMS: 495.24
- 25 Example 3: Synthesis of 2-[(4-{{(4-chlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-{{(4-fluoro phenyl)carbamoyl}oxy}butanoic acid (Compound no. 5) (Scheme I, Path B, Formula 15)

Step a: Preparation of 3-[(4-nitrophenyl)sulfanyl]dihydrofuran-2(3*H*)-one

- To an ice-cooled solution of *p*-nitro thiophenol (10.0 g, 0.0645 moles) in
30 dichloromethane (75 mL) under argon atmosphere were added triethylamine (19.4 g, 0.1935 moles) and a solution of bromo-lactone (11.1 g, 0.067 moles) in dichloromethane (75 mL) drop wise. The reaction mixture was allowed to stir for about 30 minutes at room temperature. After completion, reaction mixture was diluted with water and extracted in dichloromethane. The combined organic layer was dried over anhydrous sodium sulphate

and concentrated to get a crude product. The crude product so obtained was purified by silica gel column using 30% ethyl acetate in hexane as eluent to get title compound.

Yield: 11 g

Step b: Preparation of 3-[(4-aminophenyl)sulfanyl]dihydrofuran-2(3H)-one

5 To the solution of compound obtained from Step *a* (10.0 g, 0.04184 moles) in tetrahydrofuran/methanol (100 mL:100 mL) was added Pd/C (4 g) under vacuum and hydrogen pressure was applied using balloon. The reaction mixture was allowed to stir for about 2 hours at room temperature. After completion, reaction mixture was filtered through celite and concentrated to get desired compound.

10 Yield: 5.0 g

LCMS: 210 (M+1)

Step c: Preparation of 4-chloro-*N*-{4-[(2-oxotetrahydrofuran-3-yl)sulfanyl]phenyl} benzamide

To a solution of compound obtained from Step *b* (4.86 g, 0.0232 moles) in
15 dichloromethane (100 mL) under argon atmosphere was added triethylamine (7.04 g, 0.0697 moles) and cooled to 0°C and then 4-chlorobenzoyl chloride (4.27 g, 0.024 moles) was added slowly drop wise. The reaction mixture was allowed to stir for 10 minutes at room temperature. After completion, reaction mixture was diluted with water and extracting in dichloromethane. The organic layer was washed with sodium bicarbonate
20 and separated. The organic layer was dried over anhydrous sodium sulphate and concentrated to obtain a crude product. The crude product obtained was purified by silica gel column using 10% ethyl acetate in hexane as eluent.

Yield: 4.0 g

LCMS: 348 (M+1)

25 **Step d: Preparation of methyl 2-[(4-[(4-chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-hydroxybutanoate**

To a solution of compound obtained from Step *c* (8.2 g, 0.0236 moles) in *N,N*-dimethylformamide (32 mL) and water (8 mL) was added sodium hydroxide (1.12 g, 0.0283 moles). The reaction mixture was allowed to stir for about 30 minutes at room

temperature. After 30 minutes, sodium bicarbonate (2.3 g, 0.0283 moles), 18 crown 6 (0.620 g, 0.0023 moles) and methyl iodide (5.02 g, 0.0354 moles) were added to reaction mixture and stirred for overnight at room temperature. After completion, reaction mixture was diluted by adding water and extracting in ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to get a crude product which was purified by silica gel column using 8% ethyl acetate in hexane as eluent.

Yield: 8.0 g

Step e: Preparation of methyl 4-[[[(4-chlorophenyl)carbamoyl]oxy]-2-[(4-[(4-chlorophenyl)carbonyl]amino}phenyl)sulfanyl]butanoate

To a solution of compound obtained from Step d (0.500 g, 0.00131 moles) in tetrahydrofuran (10 mL) under argon atmosphere were added triethylamine (0.266 g, 0.0026 moles) and 1-chloro-4-isocyanatobenzene (0.211 g, 0.0015 moles) and stirred for about 2 hours at room temperature. After completion, reaction mixture was diluted by adding water and extracting in ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product which was purified by silica gel column using 15% ethyl acetate in hexane as eluent.

Yield: 0.4 g

Step f: Preparation of 4-[[[(4-chlorophenyl)carbamoyl]oxy]-2-[(4-[(4-chlorophenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid

To a solution of compound obtained from Step e (0.300 g, 0.0005 moles) in tetrahydrofuran /methanol (5 mL:5 mL) was added a solution of lithium hydroxide (0.034 g, 0.0008 moles) in water and stirred at room temperature for about one hour. After completion, reaction mixture was acidify with sodium bisulphite solution and then extracted in ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product which was purified by preparative TLC using 10% methanol/dichloromethane as eluent.

Yield: 0.080 g

LCMS: 503 (M+1), 520 (M+18)

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.4 (1H, s), 9.66 (1H, s), 7.95 - 7.97 (2H, d, *J* = 8.4 Hz), 7.73 - 7.76 (2H, d, *J* = 8.4 Hz), 7.59 - 7.61 (2H, d, *J* = 8.4 Hz), 7.43 - 7.49 (4H, d, *J* =

8.4 Hz), 7.06 - 7.15 (2H, d, $J = 4.0$ Hz), 5.7 (1H, s), 4.12 - 4.23 (2H, m), 3.72 - 3.76 (1H, m), 2.07 - 2.12 (1H, m), 1.89 - 1.96 (1H, m).

The following compounds can be prepared by following the above synthetic route.

- 5 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[2-fluoro-5-(trifluoro methyl)phenyl]carbamoyl}oxy}butanoic acid (Compound no. 6);
LCMS: 571.11 (M+1)
- 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(3,5-dimethoxyphenyl)carbamoyl]oxy}butanoic acid (Compound no. 7);
LCMS: 545.11 (M)
- 10 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(5-fluoro-2-methylphenyl)carbamoyl]oxy}butanoic acid (Compound no. 8);
LCMS: 517.17 (M+1)
- 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(2-fluorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 9);
15 LCMS: 503.11 (M+1)
- 4-{[(3-Chloro-4-methoxyphenyl)carbamoyl]oxy}-2-[(4-{[(4-chlorophenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 10);
LCMS: 549.03 (M)
- 20 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(3-ethoxyphenyl)carbamoyl]oxy}butanoic acid (Compound no. 11);
LCMS: 529.15 (M), 546.19 (M+17)
- 4-{[(3-Chlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-chlorophenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 12);
LCMS: 519.07 (M), 536.11 (M+17)
- 25 4-{[(4-Chlorophenyl)carbamothioyl]oxy}-2-[(4-{[(4-chlorophenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 13);
LCMS: 535.03 (M)
- 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(3-cyanophenyl)carbamothioyl]oxy}butanoic acid (Compound no. 14);
30 LCMS: 527.12 (M+1)
- 4-{[(2-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 29) ;
LCMS: 483.14 (M+1)
- 35 4-{[(3-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 30);
LCMS: 483.21 (M+1)

- 4-{[(4-Chlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 32);
LCMS: 513.22 (M-1)
- 5 4-{[(4-Ethylphenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 33);
LCMS: 507.28 (M-1)
- 2-[(4-{[(4-Methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 34);
LCMS: 547.20 (M-1)
- 10 4-{[(2,6-Dichlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 35);
LCMS: 547.3 (M-2)
- 2-[(4-{[(4-Methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(2-methylphenyl)carbamoyl]oxy}butanoic acid (Compound no. 36);
- 15 LCMS: 493.22 (M-1)
- 4-{[(4-Methoxyphenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 37);
LCMS: 509.26 (M-1)
- 20 4-[(*tert*-Butylcarbamoyl)oxy]-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 38);
LCMS: 459.24 (M-1)
- 4-{[(2,4-Difluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 39);
LCMS: 515.20 (M-1)
- 25 4-{[(2-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 40);
LCMS: 497.25 (M-1)
- 4-{[(3-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 41);
- 30 LCMS: 497.25 (M-1)
- 4-{[(3,4-Dichlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 42);
LCMS: 547.14 (M-2)
- 35 4-{[(3,4-Dichlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 43);
LCMS: 535.09 (M+2)
- 4-{[(2,4-Difluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 44);

- LCMS: 501.15 (M+1)
 2-[(4-{[(2-Fluorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 88);
 LCMS: 535.27 (M-1)
- 5 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 89);
 LCMS: 551.27 (M-1)
 2-[(4-{[(2,6-Dimethoxyphenyl)carbonyl]amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 90);
- 10 LCMS: 577.29 (M-1)
 2-({4-[(Cyclopropylcarbonyl)amino]phenyl}sulfanyl)-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 91);
 LCMS: 483.19 (M+1)
- 15 2-[(4-{[(2-Methylphenyl)carbonyl]amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 92);
 LCMS: 531.25 (M-1)
 2-[(4-{[(2-Ethoxyphenyl)carbonyl]amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 93);
 LCMS: 561.27 (M-1)
- 20 2-[(4-{[(2,3-Difluorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 94);
 LCMS: 553.21 (M-1)
 2-[(4-{[(3,4-Dichlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 95);
- 25 LCMS: 585.21 (M-2)
 2-[(4-{[(4-Ethoxyphenyl)carbonyl]amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 96);
 LCMS: 561.28
- 30 2-({4-[(Cyclohexylcarbonyl)amino]phenyl}sulfanyl)-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 97);
 LCMS: 523.33 (M-1)
 2-[(4-{[(2,4-Dichlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 98);
 LCMS: 585.19 (M-2), 587.15 (M).
- 35 Example 4: Synthesis of 2-[(4-{[(4-chlorophenyl)carbonyl]amino}phenyl)sulfanyl]-4-
 {[4-(4-fluorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 15) (Scheme I, Path B,
 Formula 16)

To an ice-cooled solution of 4-{{(4-fluorophenyl)carbamoyl}oxy}-2-{{(4-chlorophenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (0.080 g, 0.00015 moles) was added meta-chloroperbenzoic acid (0.101 g, 0.00059 moles) and stirred for about one hour at room temperature. After completion, reaction mixture was quenched by adding sodium metabisulphite solution and then extracted in dichloromethane. The organic layer was dried over anhydrous sodium sulphate and concentrated to obtain a crude product which was purified by preparative TLC using 10% methanol in dichloromethane as eluent. Yield: 0.020 g

LCMS: 535 (M+1), 557 (M+23)

10 NMR (400 MHz, DMSO-*d*₆) δ 11.00 (1H, s), 9.67 (1H, s), 7.98 - 8.05 (4H, d, *J* = 8.4 Hz), 7.78 - 7.80 (2H, d, *J* = 9.2 Hz), 7.57 - 7.60 (2H, d, *J* = 8.4 Hz), 7.42 - 7.45 (2H, d, *J* = 8.8 Hz), 7.05 - 7.10 (2H, d, *J* = 8.8 Hz), 4.17 - 4.19 (1H, m), 3.97 - 4.03 (1H, m), 3.70 - 3.79 (1H, m), 2.07 - 2.11 (2H, m).

The following compounds can be prepared by following the above synthetic route.

- 15 2-[[4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfonyl]-4-{{(2-fluoro-5-(trifluoromethyl)phenyl)carbamoyl}oxy}butanoic acid (Compound no. 16);
LCMS: 603.22 (M+1), 620.22 (M+18)
- 2-[[4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfonyl]-4-{{(5-fluoro-2-methylphenyl)carbamoyl}oxy}butanoic acid (Compound no. 17);
- 20 LCMS: 548.03 (M)
- 4-{{(3-Chloro-4-methoxyphenyl)carbamoyl}oxy}-2-[[4-{{(4-chlorophenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 18);
LCMS: 581.33 (M), 603.08 (M+1)
- 25 2-[[4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfonyl]-4-{{(2-fluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 19);
LCMS: 535.22 (M+1), 552.28 (M+18)
- 4-{{(3-Chlorophenyl)carbamoyl}oxy}-2-[[4-{{(4-chlorophenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 20);
LCMS: 552.01 (M+1), 573.14 (M+22)
- 30 2-[[4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfonyl]-4-{{(3-cyanophenyl)carbamothioyl}oxy}butanoic acid (Compound no. 21);
LCMS: 564.12 (M+6), 542.24 (M-16)
- 4-{{(3-Fluorophenyl)carbamoyl}oxy}-2-[[4-{{(4-methylphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 31);

- LCMS: 515.09 (M+1)
4-{[(4-Chlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 45);
LCMS: 547.20 (M+1)
- 5 4-{[(4-Ethylphenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 46);
LCMS: 540.25 (M)
2-[(4-{[(4-Methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]-4-({[4-(trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 47);
- 10 LCMS: 579.24 (M-1)
4-{[(2,6-Dichlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 48);
LCMS: 579.18 (M-20)
- 15 2-[(4-{[(4-Methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]-4-{[(2-methylphenyl)carbamoyl]oxy}butanoic acid (Compound no. 49);
LCMS: 525.24 (M-1)
4-[(*tert*-Butylcarbamoyl)oxy]-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 50);
LCMS: 491.29 (M-1)
- 20 4-{[(2,4-Difluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 51);
LCMS: 547.22 (M-1)
4-{[(2-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 52);
- 25 LCMS: 529.22 (M-1)
4-{[(3-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 53);
LCMS: 529.25 (M-1)
- 30 4-{[(5-Chloro-2-methoxyphenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 54);
LCMS: 575.23 (M-2), 577.17 (M)
4-{[(3,4-Dichlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 55);
LCMS: 579.14 (M-2), 581.16 (M)
- 35 4-{[(3,4-Dichlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 56);
LCMS: 565.06 (M)

4-{{(2,4-Difluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methylphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 57);

LCMS: 533.10 (M+1)

5 4-{{(2-Fluorophenyl)carbamoyl}oxy}-2-[(4-{{(4-methylphenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 58);

LCMS: 515.15 (M+1)

Example 5: Synthesis of 4-{{(4-chlorophenyl)carbamoyl}oxy}-2-[(4-chlorophenyl)sulfonyl]butanoic acid (Compound no. 1) (Scheme I, Path C, Formula 19)

Step a: Preparation of 3-[(4-chlorophenyl)sulfonyl]dihydrofuran-2(3H)-one

10 To an ice cooled solution of *p*-chloro thiophenol (10.0 g, 0.069 moles) in dichloromethane (75 mL) under argon atmosphere were added triethylamine (21.0 g, 0.208 moles) and a solution of bromo lactone (12.0 g, 0.072 moles) in dichloromethane (75 mL) drop wise. The reaction mixture was allowed to stir for about 30 minutes at 0°C. After completion, reaction mixture was diluted by adding water and extracting in
15 dichloromethane. The organic layer was dried over anhydrous sodium sulphate and concentrated to get a crude product which was purified by silica gel column using 10% ethyl acetate in hexane as eluent.

Yield: 13.9 g

Step b: Preparation of methyl 2-[(4-chlorophenyl)sulfonyl]-4-hydroxybutanoate

20 To a solution of compound obtained from Step a (5.0 g, 0.0219 moles) in *N, N'*-dimethylformamide (20ml) and water (5ml) was added sodium hydroxide (1.05 g, 0.0263 moles). The reaction mixture was allowed to stir for about 30 minutes at room temperature. After 30 minutes, sodium bicarbonate (1.74 g, 0.0208 moles), 18 crown 6 (0.45 g, 0.0017 moles) and methyl iodide (3.68 g, 0.0259 moles) were added to reaction
25 mixture and again stirred for overnight at room temperature. After completion, reaction mixture was diluted by addition of water and extracting in ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to obtain a crude product which was purified by silica gel column using 8% ethyl acetate in hexane as eluent to get a title compound.

30 Yield: 3.5 g

Step c: Preparation of methyl 4-{[(4-chlorophenyl)carbamoyl]oxy}-2-[(4-chlorophenyl)sulfanyl]butanoate

- To a solution of compound obtained from Step *b* (0.425 g, 0.0016 moles) in tetrahydrofuran (10 mL) under argon atmosphere were added triethylamine (0.323 g, 0.0032 moles) and 1-chloro-4-isocyanatobenzene (0.293 g, 0.0019 moles) and stirred for about 2 hours at room temperature. After completion, reaction mixture was diluted by adding water and extracting in ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product which was purified by silica gel column using 15% ethyl acetate in hexane as eluent to get desired compound.
- Yield: 0.600 g

Step d: Preparation of 4-{[(4-chlorophenyl)carbamoyl]oxy}-2-[(4-chlorophenyl)sulfanyl]butanoic acid

- To a solution of compound obtained from Step *c* (0.600 g, 0.0014 moles) in tetrahydrofuran/methanol (5ml:5ml) was added a solution of lithium hydroxide (0.090 g, 0.0021 moles) in water (1 mL) and stirred for about one hour at room temperature. After completion, reaction mixture was acidify with sodium bisulphite solution and then extracted in ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product which was purified by preparative TLC using 10% methanol in dichloromethane as eluent to obtain the desired compound.
- Yield: 0.100 g
- LCMS: 401.23(M+1)
- NMR- (400 MHz, DMSO-*d*₆) δ : 9.73 (1H, s), 7.45 - 7.53 (6H, d, *J* = 8.4 Hz), 7.15 - 7.19 (2H, d, *J* = 8.4 Hz), 4.17 - 4.30 (2H, m), 3.91 - 3.95 (1H, t, *J* = 7.2 Hz), 2.15 - 2.24 (1H, m), 1.97 - 2.06 (1H, m).

- The following compounds can be prepared by following the above synthetic route.

2-[(4-Chlorophenyl)sulfanyl]-4-{[(4-fluorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 2);

LCMS: 384.22 (M⁺+1)

- Example 6: Synthesis of 4-{[(4-chlorophenyl)carbamoyl]oxy}-2-[(4-chlorophenyl)sulfonyl]butanoic acid (Compound no. 3) (Scheme I, Path C, Formula 20)**

To an ice-cooled solution of 4-[[[(4-chlorophenyl)carbamoyl]oxy]-2-[(4-chlorophenyl)sulfanyl]butanoic acid (0.100 g, 0.0002 moles) in chloroform (10 mL) was added meta-chloroperbenzoic acid (0.172 g, 0.001 moles) and stirred at room temperature for about one hour. After completion, reaction mixture was quenched by sodium metabisulphite solution and extracted in dichloromethane. The organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product which was purified by preparative TLC using 10% methanol in dichloromethane as eluent to get desired compound.

Yield: 0.090 g

LCMS: 432.12 (M), 434 (M+2), 449.17 (M+18)

NMR-(400 MHz, DMSO-*d*₆) δ : 9.79 (1H, s), 7.73 - 7.82 (2H, d, *J* = 8.8 Hz), 7.60 - 7.63 (2H, d, *J* = 8.8 Hz), 7.44 - 7.46 (2H, d, *J* = 8.8 Hz), 7.29 - 7.31 (2H, d, *J* = 8.8 Hz), 4.07 - 4.19 (1H, m), 3.97 - 4.03 (1H, m), 3.75 - 3.76 (1H, m), 2.03 - 2.10 (2H, m).

The following compounds can be prepared by following the above synthetic route.

2-[(4-Chlorophenyl)sulfonyl]-4-[[[(4-fluorophenyl)carbamoyl]oxy]butanoic acid (Compound no. 4);

LCMS: 416.13 (M+1)

Example 7: Synthesis of 4-(benzyloxy)-2-[(4-nitrophenyl)sulfonyl]butanoic acid (Compound no. 28 (Scheme II, Path D, Formula 27))

Step a: Synthesis of ethyl [(4-nitrophenyl)sulfanyl]acetate

To an ice-cooled solution of *p*-nitro thiophenol (5 g, 0.0322 moles) in dichloromethane (50 mL) under argon atmosphere were added triethylamine (9.7 g, 0.0967 moles) and a solution of ethyl bromoacetate (6.4 g, 0.0387 moles) drop wise. The reaction mixture was allowed to stir for about 5 hours at room temperature. After completion, reaction mixture was diluted with water and extracted in dichloromethane. The organic layer was dried over sodium sulphate and concentrated to get a crude product. The crude product obtained was purified by silica gel column using 10% ethyl acetate in hexane as eluent.

Yield: 6.5 g

LCMS: 242 (M+1)

Step b: Preparation of ethyl [(4-nitrophenyl)sulfonyl]acetate

To an ice-cooled solution of compound obtained from Step *a* (6.5 g, 0.0269 moles) in chloroform (70 mL) was added meta-chloroperbenzoic acid (18 g, 0.107 moles) and stirred at room temperature for about one hour. After completion, reaction mixture was
5 quenched with sodium metabisulphite solution and then extracted in dichloromethane. The organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product which was purified by preparative TLC using 10% methanol in dichloromethane as eluent to obtain a crude product.

Yield: 6.7 g

10 LCMS: 274 (M+1)

Step c: Preparation of ethyl 4-(benzyloxy)-2-[(4-nitrophenyl)sulfonyl]butanoate

To a solution of compound obtained from Step *b* (0.500 g, 0.0018 moles) in *N,N*-dimethylformamide (5 mL) under argon atmosphere were added potassium carbonate (0.745 g, 0.0054 moles), tetrabutylammonium iodide (0.067 g, 0.00018 moles) and *O*-
15 benzyl ethyl bromide (0.550 g, 0.0027 moles). The reaction mixture was heated to 50° C and stirred at same temperature for about 4 hours. After completion, reaction mixture was diluted by adding water and extracting in ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to get a crude product which was purified by silica gel column using 8% ethyl acetate in hexane as eluent to get title compound.

20 Yield: 0.450 g

LCMS: 408 (M+1)

Step d: Preparation of 4-(benzyloxy)-2-[(4-nitrophenyl)sulfonyl]butanoic acid

To a solution of compound obtained from Step *c* (0.100 g, 0.00024 moles) in tetrahydrofuran/methanol (5 mL:5 mL) was added a solution of lithium hydroxide (0.015
25 g, 0.00036 moles) in water (1 mL). The reaction mixture was allowed to stir at room temperature for about one hour. After completion, reaction mixture was acidify with sodium bisulphite solution and then extracted in ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and concentrated to get a crude product which was purified by preparative TLC using 10% methanol in dichloromethane as eluent
30 to get title compound.

Yield: 0.040 g

LCMS: 402.12 (M+23)

NMR-(400 MHz, DMSO-*d*₆) δ : 8.35 - 8.46 (2H, d, *J* = 8.8 Hz), 8.07 - 8.20 (2H, d, *J* = 8.8 Hz), 7.28 - 7.33 (5H, m, *J* = 5.6 Hz), 4.41 (2H, s), 3.80 - 3.84 (1H, m), 3.45 - 3.51 (4H, m), 2.05 - 2.09 (3H, m), 1.83 (1H, m).

Example 8: Synthesis of 4-(benzyloxy)-2-[(4-{[(4-methylphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 22) (Scheme II, Path E, Formula 30)

Step a: Preparation of ethyl 2-[(4-aminophenyl)sulfonyl]-4-(benzyloxy)butanoate

To a solution of ethyl 4-(benzyloxy)-2-[(4-nitrophenyl)sulfonyl]butanoate (0.500 g, 0.0012 moles) in ethyl acetate (10 mL) was added stannous chloride (0.829 g, 0.0036 moles) and stirred at 80°C for about 2 hours. After completion, reaction mixture was quenched by adding sodium bicarbonate solution and then extracted in ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to get desired compound.

Yield: 0.450 g

LCMS: 378 (M+1)

Step b: Preparation of ethyl 4-(benzyloxy)-2-[(4-{[(4-methylphenyl)carbonyl]amino}phenyl)sulfonyl]butanoate

To a solution of compound obtained from Step a (0.500 g, 0.0013 moles) in dichloromethane (10 mL) under argon atmosphere was added pyridine (0.314 g, 0.0039 moles) and cooled to 0°C. To this cooled solution was added 4-methylbenzoyl chloride (0.220 g, 0.0014 moles) slowly drop wise. After completion, reaction mixture was quenched by adding water and extracting in dichloromethane. The organic layer was washed with sodium bicarbonate, dried over anhydrous sodium sulphate and concentrated to get crude product which was purified by silica gel column using 10% ethyl acetate in hexane as eluent to get desired compound.

Yield: 0.400 g

LCMS: 348 (M+1)

Step c: Preparation of 4-(benzyloxy)-2-[(4-{[(4-methylphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid

To a solution of compound obtained from Step *b* (0.100 g, 0.00020 moles) in tetrahydrofuran/methanol (5 mL:5ml) was added a solution of lithium hydroxide (0.012 g, 0.00030 moles) in water (1 mL) and stirred at room temperature for about one hour. After completion, reaction mixture was acidify by adding sodium bisulphite solution and then extracted in ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product which was purified by preparative TLC using 10% methanol in dichloromethane as eluent to afford desired compound.

Yield: 0.050 g

LCMS: 467.93 (M), 484.95 (M+17)

¹H NMR(400 MHz, DMSO-*d*₆) δ: 10.6 (1H, s), 7.98 - 8.00 (2H, d, *J* = 8.8 Hz), 7.89 - 7.91 (2H, d, *J* = 8.0 Hz), 7.76 - 7.78 (2H, d, *J* = 8.4 Hz), 7.24 - 7.35 (7H, d, *J* = 8.0 Hz), 4.36 (2H, s), 3.77 (1H, m), 3.46 - 3.49 (1H, m), 2.38 (3H, s), 1.99 - 2.01 (2H, t, *J* = 6.8 Hz),

1.21-1.22 (3H, t, *J* = 4.0Hz).

The following compounds can be prepared by following the above synthetic route.

4-(Benzyloxy)-2-[(4-{[(3-fluorophenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 23);

LCMS: 470.07 (M-1)

4-(Benzyloxy)-2-[(4-{[(3-chlorophenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 24);

LCMS: 486.04 (M-1)

4-(Benzyloxy)-2-[(4-{[(4-ethylphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 25);

LCMS: 480.14 (M-1)

4-(Benzyloxy)-2-[(4-{[(3-methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 26);

LCMS: 483.98 (M), 500.97 (M+17)

4-(Benzyloxy)-2-[(4-{[(2-fluorophenyl)carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 27)

LCMS: 470.07 (M-1)

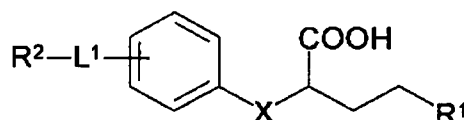
Assay for Matrix Metallo Proteinases (MMPs)

NCEs/standards were prepared (stock 10 mM) in 100% DMSO and subsequent dilutions were made in 50% DMSO-50% TCNB (50 mM Tris, 10 mM CaCl₂, 150 mM NaCl, 0.05% Brij-35, pH 7.5). 1 µl of the compound and 88 µl of TCNB was added to wells of 96 well plate to achieve the desired final concentration of NCE (final DMSO concentration should not exceed 0.5%). 1 µl of activated, recombinant MMPs was added to each well (20-100 ng/100 µl reaction mixture) except the “negative well”. (MMP-1, 9 & 14 enzymes require prior activation. For this, supplied enzyme was incubated with either APMA, final concentration 1 mM, for a time period of 1 hour at 37°C). Incubation was done at room temperature (~ 25°C) for 4 minutes to 5 minutes. Reaction was initiated with 10 µl of 100 µM substrate (ES001: Aliquots were freshly diluted in TCNB; stock: 2 mM) and increase in fluorescence was monitored at excitation wavelength 320 nm followed by emission at 405 nm for 25-30 cycles. Increase in fluorescence (RFU) was calculated for positive, negative and NCE/standard wells. The percent inhibition compared to controls was calculated and IC₅₀ values determined using Graph-prism software.

Activities for MMP-9 provided IC₅₀ values below 10 nanomolar-10 micromolar.

We claim:

- 1 1. A compound of Formula I:

**Formula I**

- 2
3
4 including racemates, enantiomers and diastereomers, thereof or a pharmaceutically
5 acceptable salts thereof, wherein,

6 X is S, SO or SO₂;

7 L¹ is selected from bond, -O-, -S-, -SO-, -SO₂-, -CH₂-, -NR⁴-, -NHCO(CH₂)_n-,
8 -(CH₂)_nCONH-, -NHCONH-, -SO₂NH-, -NHSO₂-, -NHCO(O)-, -O-(CH₂)_n-,
9 -(CH₂)_n-O-, -OC(O)NH-, -C(S)NH-, -NHC(S)-, -NHC(S)NH-, -COO- wherein n is
10 zero or an integer between 1 and 2;

11 R¹ is -OCONHR³, OCSNHR³, OCH₂R³;

12 When R¹ is OCONHR³ or OCSNHR³ then R² is hydrogen, C₁-C₆alkyl, hydroxyl,
13 C₁-C₆alkoxy, cyano, nitro, halogen, halogeno C₁-C₆alkyl, C₆-C₁₂ aryl, C₃-
14 C₈cycloalkyl, C₅-C₁₂ heteroaryl wherein C₆-C₁₂ aryl, C₃-C₈cycloalkyl, C₅-C₁₂
15 heteroaryl is optionally substituted with one or more times with R⁵;

16 When R¹ is OCH₂R³, then R² is C₆-C₁₂ aryl, C₃-C₈ cycloalkyl, C₆-C₁₂ heteroaryl;

17 R³ is alkyl, alkenyl, alkynyl, C₆-C₁₂ aryl, C₃-C₈ cycloalkyl, C₅-C₁₂ heteroaryl, C₃-
18 C₁₂ heterocyclyl which is optionally substituted one or more times with R⁵;

19 R⁴ is H, C₁₋₆alkyl, C₁₋₄alkylaryl;

20 R⁵ is selected from alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno-C₁-C₆
21 alkyl, halogeno-C₁-C₆ alkoxy, azido, thiol, alkylthiol, -(CH₂)_n-OR_f, -C(=O)-R_f,
22 -COOR_f, -NR_fR_q, -(CH₂)_n-C(=O)NR_fR_q, -(CH₂)_n-NHC(=O)-R_f, -(CH₂)_n-O-
23 C(=O)-NR_fR_q, (CH₂)_n NHC(=O)NR_fR_q, -(CH₂)_n-O-C(=O)-R_f, -(CH₂)_n-NH-C(=O)-
24 R_f or -(CH₂)_nS(=O)_m-NR_fR_q {wherein R_f and R_q are independently selected from
25 hydrogen, alkyl, alkenyl, cycloalkyl aryl, heteroaryl, heterocyclyl, alkylaryl,
26 alkylheteroaryl and alkylheterocyclyl, n is as define earlier and m is an integer 0-2}.

- 1 2. A compound of Formula I, which is:
- 2 4-{{(4-Chlorophenyl)carbamoyl}oxy}-2-[(4-chlorophenyl)sulfanyl]butanoic acid
3 (Compound no. 1);
- 4 2-[(4-Chlorophenyl)sulfanyl]-4-{{(4-fluorophenyl)carbamoyl}oxy}butanoic acid
5 (Compound no. 2);
- 6 4-{{(4-Chlorophenyl)carbamoyl}oxy}-2-[(4-chlorophenyl)sulfonyl]butanoic acid
7 (Compound no. 3);
- 8 2-[(4-Chlorophenyl)sulfonyl]-4-{{(4-fluorophenyl)carbamoyl}oxy}butanoic acid
9 (Compound no. 4);
- 10 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-{{(4-fluorophenyl
11 carbamoyl}oxy}butanoic acid (Compound no. 5);
- 12 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-{{[2-fluoro-5-
13 (trifluoromethyl)phenyl]carbamoyl}oxy}butanoic acid (Compound no. 6);
- 14 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-{{[3,5-
15 dimethoxyphenyl]carbamoyl}oxy}butanoic acid (Compound no. 7);
- 16 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-{{[5-fluoro-2-methyl
17 phenyl]carbamoyl}oxy}butanoic acid (Compound no. 8);
- 18 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-{{[2-fluoro phenyl]
19 carbamoyl}oxy}butanoic acid (Compound no. 9);
- 20 4-{{[3-Chloro-4-methoxyphenyl]carbamoyl}oxy}-2-[(4-{{(4-chlorophenyl)
21 carbonyl}amino}phenyl)sulfanyl]butanoic acid (Compound no. 10);
- 22 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-{{[3-
23 ethoxyphenyl]carbamoyl}oxy}butanoic acid (Compound no. 11);
- 24 4-{{[3-Chlorophenyl]carbamoyl}oxy}-2-[(4-{{(4-chlorophenyl)carbonyl]
25 amino}phenyl)sulfanyl]butanoic acid (Compound no. 12);
- 26 4-{{(4-Chlorophenyl)carbamothioyl}oxy}-2-[(4-{{(4-chlorophenyl)carbonyl]
27 amino}phenyl)sulfanyl]butanoic acid (Compound no. 13);
- 28 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-{{[3-cyanophenyl]
29 carbamothioyl}oxy}butanoic acid (Compound no. 14);
- 30 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfonyl]-4-{{(4-fluorophenyl)
31 carbamoyl}oxy}butanoic acid (Compound no. 15);
- 32 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfonyl]-4-{{[2-fluoro-5-
33 (trifluoromethyl)phenyl]carbamoyl}oxy}butanoic acid (Compound no. 16);
- 34 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfonyl]-4-{{[5-fluoro-2-methyl
35 phenyl]carbamoyl}oxy}butanoic acid (Compound no. 17);
- 36 4-{{[3-Chloro-4-methoxyphenyl]carbamoyl}oxy}-2-[(4-{{(4-
37 chlorophenyl)carbonyl}amino}phenyl)sulfonyl]butanoic acid (Compound no. 18);
- 38 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfonyl]-4-{{[2-
39 fluorophenyl]carbamoyl}oxy}butanoic acid (Compound no. 19);

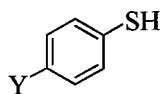
- 40 4-{[(3-Chlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-chlorophenyl)carbonyl]
41 amino}phenyl)sulfonyl]butanoic acid (Compound no. 20);
- 42 2-[(4-{[(4-Chlorophenyl)carbonyl]amino}phenyl)sulfonyl]-4-{[(3-
43 cyanophenyl)carbamothioyl]oxy}butanoic acid (Compound no. 21);
- 44 4-(Benzyloxy)-2-[(4-{[(4-methylphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic
45 acid (Compound no. 22);
- 46 4-(Benzyloxy)-2-[(4-{[(3-fluorophenyl)carbonyl]amino}phenyl)sulfonyl]butanoic
47 acid (Compound no. 23);
- 48 4-(Benzyloxy)-2-[(4-{[(3-chlorophenyl)carbonyl]amino}phenyl)sulfonyl]butanoic
49 acid (Compound no. 24);
- 50 4-(Benzyloxy)-2-[(4-{[(4-ethylphenyl)carbonyl]amino}phenyl)sulfonyl]butanoic
51 acid (Compound no. 25);
- 52 4-(Benzyloxy)-2-[(4-{[(3-methoxyphenyl)carbonyl]amino}phenyl)
53 sulfonyl]butanoic acid (Compound no. 26);
- 54 4-(Benzyloxy)-2-[(4-{[(2-fluorophenyl)carbonyl]amino}phenyl)sulfonyl]butanoic
55 acid (Compound no. 27)
- 56 4-(Benzyloxy)-2-[(4-nitrophenyl)sulfonyl]butanoic acid (Compound no. 28);
- 57 4-{[(2-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)carbonyl]amino}
58 phenyl)sulfanyl]butanoic acid (Compound no. 29);
- 59 4-{[(3-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)carbonyl]
60 amino}phenyl)sulfanyl]butanoic acid (Compound no. 30);
- 61 4-{[(3-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)carbonyl]
62 amino}phenyl)sulfonyl]butanoic acid (Compound no. 31);
- 63 4-{[(4-Chlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]
64 amino}phenyl)sulfanyl]butanoic acid (Compound no. 32);
- 65 4-{[(4-Ethylphenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]
66 amino}phenyl)sulfanyl]butanoic acid (Compound no. 33);
- 67 2-[(4-{[(4-Methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]-4-({[4-
68 (trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 34);
- 69 4-{[(2,6-Dichlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)
70 carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 35);
- 71 2-[(4-{[(4-Methoxyphenyl)carbonyl]amino}phenyl)sulfanyl]-4-{[(2-methylphenyl)
72 carbamoyl]oxy}butanoic acid (Compound no. 36);
- 73 4-{[(4-Methoxyphenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]
74 amino}phenyl)sulfanyl]butanoic acid (Compound no. 37);
- 75 4-[(*tert*-Butylcarbamoyl)oxy]-2-[(4-{[(4-methoxyphenyl)carbonyl]
76 amino}phenyl)sulfanyl]butanoic acid (Compound no. 38);
- 77 4-{[(2,4-Difluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)
78 carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 39);

- 79 4-{[(2-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]
80 amino}phenyl)sulfanyl]butanoic acid (Compound no. 40);
- 81 4-{[(3-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]
82 amino}phenyl)sulfanyl]butanoic acid (Compound no. 41);
- 83 4-{[(3,4-Dichlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)
84 carbonyl]amino}phenyl)sulfanyl]butanoic acid (Compound no. 42);
- 85 4-{[(3,4-Dichlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)carbonyl]
86 amino}phenyl)sulfanyl]butanoic acid (Compound no. 43);
- 87 4-{[(2,4-Difluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)carbonyl]
88 amino}phenyl)sulfanyl]butanoic acid (Compound no. 44);
- 89 4-{[(4-Chlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]
90 amino}phenyl)sulfonyl]butanoic acid (Compound no. 45);
- 91 4-{[(4-Ethylphenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]
92 amino}phenyl)sulfonyl]butanoic acid (Compound no. 46);
- 93 2-[(4-{[(4-Methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]-4-{[(4-
94 (trifluoromethyl)phenyl)carbamoyl]oxy}butanoic acid (Compound no. 47);
- 95 4-{[(2,6-Dichlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)
96 carbonyl]aminophenyl})sulfonyl]butanoic acid (Compound no. 48);
- 97 2-[(4-{[(4-Methoxyphenyl)carbonyl]amino}phenyl)sulfonyl]-4-{[(2-
98 methylphenyl)carbamoyl]oxy}butanoic acid (Compound no. 49);
- 99 4-[(*tert*-Butylcarbamoyl)oxy]-2-[(4-{[(4-methoxyphenyl)carbonyl]
100 amino}phenyl)sulfonyl]butanoic acid (Compound no. 50);
- 101 4-{[(2,4-Difluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)
102 carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 51);
- 103 4-{[(2-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]amino}
104 phenyl)sulfonyl]butanoic acid (Compound no. 52);
- 105 4-{[(3-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)carbonyl]
106 amino}phenyl)sulfonyl]butanoic acid (Compound no. 53);
- 107 4-{[(5-Chloro-2-methoxyphenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)
108 carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 54);
- 109 4-{[(3,4-Dichlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methoxyphenyl)
110 carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 55);
- 111 4-{[(3,4-Dichlorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)
112 carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 56);
- 113 4-{[(2,4-Difluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)
114 carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 57);
- 115 4-{[(2-Fluorophenyl)carbamoyl]oxy}-2-[(4-{[(4-methylphenyl)
116 carbonyl]amino}phenyl)sulfonyl]butanoic acid (Compound no. 58);
- 117 2-[(4-{[(4-Chlorophenyl)carbamoyl]phenyl})sulfanyl]-4-{[(2-
118 fluorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 59);

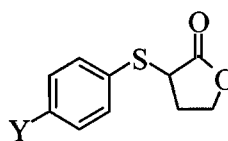
- 119 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-ethylphenyl)
120 carbamoyl]oxy}butanoic acid (Compound no. 60);
- 121 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{[4-(propan-2-yl)phenyl]
122 carbamoyl]oxy}butanoic acid (Compound no. 61);
- 123 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-methoxyphenyl)
124 carbamoyl]oxy}butanoic acid (Compound no. 62);
- 125 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(2-
126 methylphenyl)carbamoyl]oxy}butanoic acid (Compound no. 63);
- 127 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(3-fluorophenyl)
128 carbamoyl]oxy}butanoic acid (Compound no. 64);
- 129 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-methylphenyl)
130 carbamoyl]oxy}butanoic acid (Compound no. 65);
- 131 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{[4-(trifluoromethyl)
132 phenyl]carbamoyl]oxy}butanoic acid (Compound no. 66);
- 133 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(2,4-difluorophenyl)
134 carbamoyl]oxy}butanoic acid (Compound no. 67);
- 135 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(4-fluorophenyl)
136 carbamoyl]oxy}butanoic acid (Compound no. 68);
- 137 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(2,6-
138 dichlorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 69);
- 139 4-[(*tert*-Butylcarbamoyl)oxy]-2-({4-[(4-chlorophenyl)carbamoyl]
140 phenyl}sulfanyl)butanoic acid (Compound no. 70);
- 141 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-{{(3,4-
142 dichlorophenyl)carbamoyl]oxy}butanoic acid (Compound no. 71);
- 143 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfanyl)-4-[(pentylcarbamoyl)
144 oxy]butanoic acid (Compound no. 72);
- 145 4-{{(3-Chlorophenyl)carbamoyl]oxy}-2-({4-[(4-chlorophenyl)
146 carbamoyl]phenyl}sulfanyl)butanoic acid (Compound no. 73);
- 147 4-[(Butylcarbamoyl)oxy]-2-({4-[(4-chlorophenyl)carbamoyl]
148 phenyl}sulfanyl)butanoic acid (Compound no. 74);
- 149 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(2-fluorophenyl)
150 carbamoyl]oxy}butanoic acid (Compound no. 75);
- 151 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(4-ethylphenyl)
152 carbamoyl]oxy}butanoic acid (Compound no. 76);
- 153 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(2-methylphenyl)
154 carbamoyl]oxy}butanoic acid (Compound no. 77);
- 155 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(4-methylphenyl)
156 carbamoyl]oxy}butanoic acid (Compound no. 78);
- 157 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{[4-(trifluoromethyl)
158 phenyl]carbamoyl]oxy}butanoic acid (Compound no. 79);

- 159 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(2,4-
160 difluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 80);
- 161 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(4-
162 fluorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 81);
- 163 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(2,6-
164 dichlorophenyl)carbamoyl}oxy}butanoic acid (Compound no. 82);
- 165 4-[(*tert*-Butylcarbamoyl)oxy]-2-({4-[(4-chlorophenyl)carbamoyl]
166 phenyl}sulfonyl)butanoic acid (Compound no. 83);
- 167 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-{{(3,4-dichlorophenyl)
168 carbamoyl}oxy}butanoic acid (Compound no. 84);
- 169 2-({4-[(4-Chlorophenyl)carbamoyl]phenyl}sulfonyl)-4-[(pentylcarbamoyl)
170 oxy]butanoic acid (Compound no. 85);
- 171 4-{{(3-Chlorophenyl)carbamoyl}oxy}-2-({4-[(4-chlorophenyl)carbamoyl]
172 phenyl}sulfonyl)butanoic acid (Compound no. 86);
- 173 4-[(Butylcarbamoyl)oxy]-2-({4-[(4-chlorophenyl)carbamoyl]phenyl}
174 sulfonyl)butanoic acid (Compound no. 87);
- 175 2-[(4-{{(2-Fluorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-(trifluoromethyl)
176 phenyl]carbamoyl}oxy)butanoic acid (Compound no. 88);
- 177 2-[(4-{{(4-Chlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-
178 (trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 89);
- 179 2-[(4-{{(2,6-Dimethoxyphenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-
180 (trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 90);
- 181 2-({4-{{(Cyclopropylcarbonyl)amino}phenyl}sulfanyl)-4-({[4-
182 (trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 91);
- 183 2-[(4-{{(2-Methylphenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-
184 (trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 92);
- 185 2-[(4-{{(2-Ethoxyphenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-
186 (trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 93);
- 187 2-[(4-{{(2,3-Difluorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-
188 (trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 94);
- 189 2-[(4-{{(3,4-Dichlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-
190 (trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 95);
- 191 2-[(4-{{(4-Ethoxyphenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-
192 (trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 96);
- 193 2-({4-[(Cyclohexylcarbonyl)amino]phenyl}sulfanyl)-4-({[4-(trifluoromethyl)
194 phenyl]carbamoyl}oxy)butanoic acid (Compound no. 97);
- 195 2-[(4-{{(2,4-Dichlorophenyl)carbonyl}amino}phenyl)sulfanyl]-4-({[4-
196 (trifluoromethyl)phenyl]carbamoyl}oxy)butanoic acid (Compound no. 98).

- 1 3. A pharmaceutical composition comprising a therapeutically effective amount of
2 one or more of compound of Formula I according to claims 1 and 2, together with one or
3 more pharmaceutically acceptable carrier, excipient or diluents.
- 1 4. A compound according to any one of claims 1-2, for use in the treatment or
2 prophylaxis of an animal or a human suffering from an inflammatory or allergic disease.
- 1 5. A compound according to claim 4, wherein the inflammatory disease or allergic
2 disease is asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis,
3 psoriasis, pulmonary fibrosis, pulmonary inflammation, acute respiratory distress
4 syndrome, periodontitis, multiple sclerosis, gingivitis, atherosclerosis, dry eye, neointimal
5 proliferation associated with restenosis and ischemic heart failure, stroke, renal disease or
6 tumor metastasis.
- 1 6. A pharmaceutical composition according to claim 3, further comprising one or
2 more of additional active ingredients selected from:
- 3 a) anti-inflammatory agents, experimental or commercial, selected from (i) the
4 nonsteroidal anti-inflammatory agents piroxicam, diclofenac, propionic acids,
5 fenamates, pyrazolones, salicylates, PDE-4/p38 MAP Kinase/Cathepsin
6 inhibitors, (ii) leukotrienes LTC₄/LTD₄/LTE₄/LTB₄-Inhibitors, 5-
7 lipoxigenase inhibitor and PAF-receptor antagonists, (iii) Cox-2 inhibitors,
8 (iv) other MMP inhibitors, and (v) interleukin-I inhibitors;
- 9 b) antihypertensive agents, selected from (i) the ACE inhibitors, enalapril,
10 lisinopril, valsartan, telmisartan and quinapril, (ii) the angiotensin II receptor
11 antagonists and agonists, losartan, candesartan, irbesartan, valsartan, and
12 eprosartan, (iii) β -blockers, and (iv) calcium channel blockers.
- 13 c) immunosuppressive agents selected from, cyclosporine, azathioprine and
14 methotrexate, and anti inflammatory corticosteroids.
- 1 7. A process for preparing a compound of Formula 9 (Formula I when L¹ is -CONH-,
2 X is SO₂ and R¹ is OC(Z)NHR³) comprising:
- 3 a) reacting a compound of Formula 2 with alpha bromolactone to give a
4 compound of Formula 3;



Formula 2

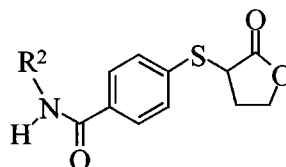


Formula 3

- b) reacting a compound of Formula 3 (where Y is COOH) with a compound of Formula 3' to give a compound of Formula 4;



Formula 3'

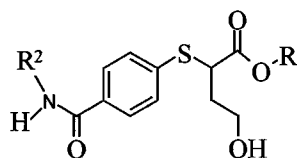


Formula 4

- c) coupling a compound of Formula 4 with a compound of Formula 4' to give a compound of Formula 5;

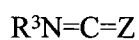


Formula 4'

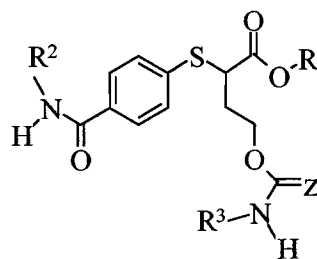


Formula 5

- d) reacting a compound of Formula 5 with a compound of Formula 6 to give a compound of Formula 7;

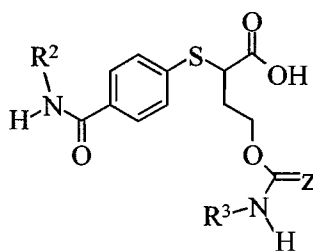


Formula 6



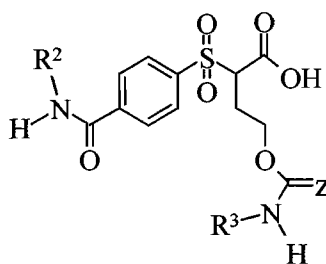
Formula 7

- e) hydrolyzing a compound of Formula 7 to give a compound of Formula 8;



Formula 8

f) oxidizing a compound of Formula 8 to give a compound of Formula 9;



Formula 9

wherein,

R^2 is hydrogen, C_1 - C_6 alkyl, hydroxyl, C_1 - C_6 alkoxy, cyano, nitro, halogen, halogeno C_1 - C_6 alkyl, C_6 - C_{12} aryl, C_3 - C_8 cycloalkyl, C_5 - C_{12} heteroaryl wherein C_6 - C_{12} aryl, C_3 - C_8 cycloalkyl, C_6 - C_{12} heteroaryl is optionally substituted with one or more times with R^5 ;

R^3 is alkyl, alkenyl, alkynyl, C_6 - C_{12} aryl, C_3 - C_8 cycloalkyl, C_5 - C_{12} heteroaryl, C_3 - C_{12} heterocyclyl optionally substituted one or more times with R^5 ;

R^5 is selected from alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno- 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 $-(CH_2)_n-S(=O)_m-NR_fR_q$ {wherein R_f and R_q are independently selected from hydrogen, alkyl, alkenyl, cycloalkyl aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and alkylheterocyclyl};

n is zero or an integer between 1 and 2;

m is an integer 0-2;

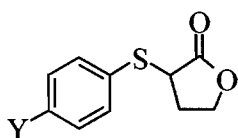
R' is alkyl, allyl, benzyl, *t*-butyl, silyl;

43 Hal is F, Cl, Br, I; and

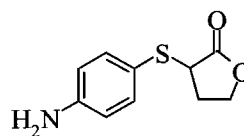
44 Z is O, S.

1 8. A process for preparing a compound of Formula 16 (Formula I when L^1 is –
 2 $\text{NHCO}-$, X is SO_2 and R^1 is $\text{OC}(\text{Z})\text{NHR}^3$), Formula 20 (Formula I when L^1 is bond, X is
 3 SO_2 and R^1 is $\text{OC}(\text{Z})\text{NHR}^3$) comprising:

4 a) reducing a compound of Formula 3 (where Y is NO_2) to give a compound of
 5 Formula 10;

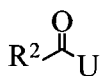


7 Formula 3

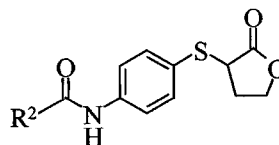


9 Formula 10

8 b) coupling a compound of Formula 10 with a compound of Formula 11 to give
 9 a compound of Formula 12;

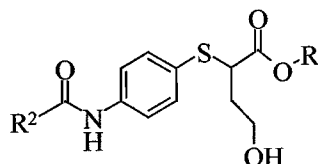


11 Formula 11



13 Formula 12

12 c) reacting a compound of Formula 12 with a compound of Formula 4' to give a
 13 compound of Formula 13;

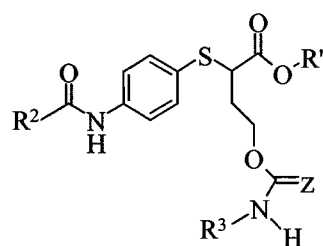


15 R'-Hal

16 Formula 4'

17 Formula 13

16 d) coupling a compound of Formula 13 with a compound of Formula 6 to give a
 17 compound of Formula 14;

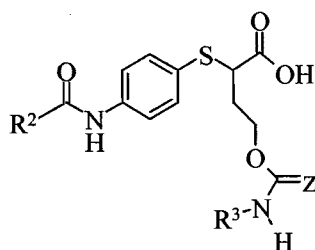


$$R^3N=C=Z$$

Formula 6

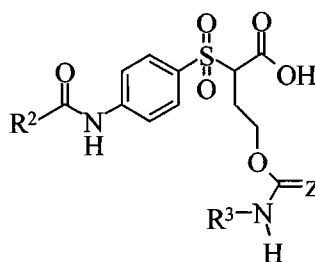
Formula 14

e) hydrolyzing a compound of Formula 14 to give a compound of Formula 15;



Formula 15

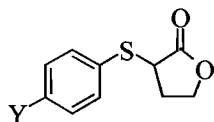
f) oxidizing a compound of Formula 15 to give a compound of Formula 16;



Formula 16

or

g) reacting a compound of Formula 3 (wherein Y is Hal) with a compound of Formula 4';

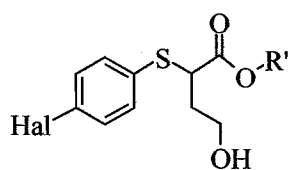


Formula 3

R'-Hal

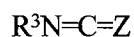
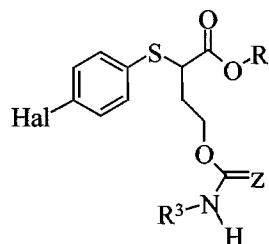
Formula 4'

to give a compound of Formula 17;



Formula 17

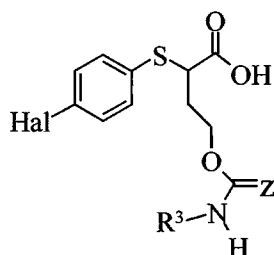
- h) coupling a compound of Formula 17 with a compound of Formula 6 to give a compound of Formula 18;



Formula 6

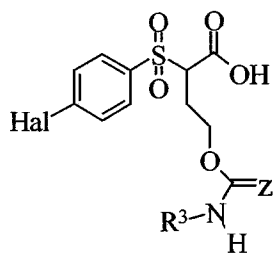
Formula 18

- i) hydrolyzing a compound of Formula 18 to give a compound of Formula 19;



Formula 19

- j) oxidizing a compound of Formula 19 to give a compound of Formula 20;



Formula 20

wherein,

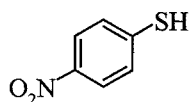
R^3 is alkyl, alkenyl, alkynyl, C_6 - C_{12} aryl, C_3 - C_8 cycloalkyl, C_5 - C_{12} heteroaryl, C_3 - C_{12} heterocyclyl optionally substituted one or more times with R^5 ;

R^2 is hydrogen, C_1 - C_6 alkyl, hydroxyl, C_1 - C_6 alkoxy, cyano, nitro, halogen, halogeno C_1 - C_6 alkyl, C_6 - C_{12} aryl, C_3 - C_8 cycloalkyl, C_5 - C_{12} heteroaryl,

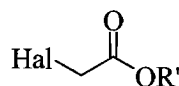
- 33 wherein C₆-C₁₂ aryl, C₃-C₈cycloalkyl, C₆-C₁₂ heteroaryl is optionally
 34 substituted with one or more times with R⁵;
 35 R⁵ is selected from alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno-
 36 C₁-C₆ alkyl, halogeno-C₁-C₆ alkoxy, azido, thiol, alkylthiol, -(CH₂)_n-OR_f -
 37 C(=O)-R_f -COOR_f -NR_fR_q, -(CH₂)_n-C(=O)NR_fR_q, -(CH₂)_n-NHC(=O)-R_f -
 38 -(CH₂)_n-O-C(=O)-NR_fR_q, (CH₂)_n NHC(=O)NR_fR_q, -(CH₂)_n-O-C(=O)-R_f -
 39 (CH₂)_n-NH-C(=O)-R_f or -(CH₂)_nS(=O)_m-NR_fR_q {wherein R_f and R_q each
 40 independently represent hydrogen, alkyl, alkenyl, cycloalkyl aryl, heteroaryl,
 41 heterocyclyl, alkylaryl, alkylheteroaryl and alkylheterocyclyl};
 42 n is zero or an integer between 1 and 2;
 43 m is an integer 0-2;
 44 Hal is F, Cl, Br, I;
 45 U is halide, alkyloxy, aryloxy;
 46 R' is alkyl, allyl, benzyl, *t*-butyl, silyl; and
 47 Z is O, S.

- 1 9. A process for preparing compounds of Formula 27 (Formula I when L¹ is bond, X
 2 is SO₂, R² is NO₂ and R¹ is -OBn) and 30 (Formula I when L¹ is -NHCO, X is SO₂ and R¹
 3 is -OBn) comprising:

- 4 a) reacting a compound of Formula 21 with a compound of Formula 22

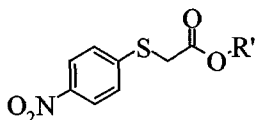


Formula 21



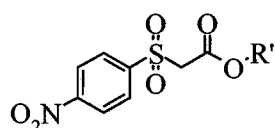
Formula 22

- 7 to give a compound of Formula 23;



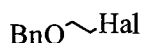
Formula 23

- 10 b) oxidizing a compound of Formula 23 to give a compound of Formula 24;

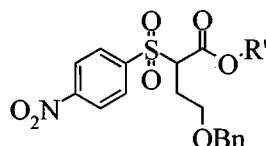


Formula 24

- c) coupling a compound of Formula 24 with a compound of Formula 25 to give a compound of Formula 26;

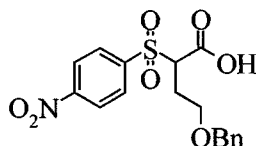


Formula 25



Formula 26

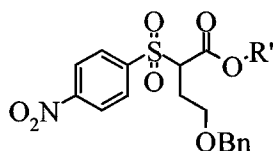
- d) hydrolyzing a compound of Formula 26 to give a compound of Formula 27;



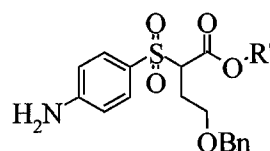
Formula 27

or

- e) reducing a compound of Formula 26 to give a compound of Formula 28;



Formula 26

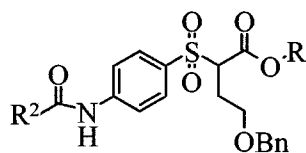


Formula 28

- f) reacting a compound of Formula 28 with a compound of Formula 11 to give a compound of Formula 29;

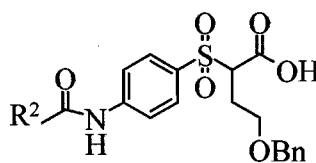


Formula 11



Formula 29

- g) hydrolyzing a compound of Formula 29 to give a compound of Formula 30;



Formula 30

wherein,

R² is hydrogen, C₁-C₆alkyl, hydroxyl, C₁-C₆alkoxy, cyano, nitro, halogen, halogeno C₁-C₆alkyl, C₆-C₁₂ aryl, C₃-C₈cycloalkyl, C₅-C₁₂ heteroaryl wherein C₆-C₁₂ aryl, C₃-C₈cycloalkyl, C₆-C₁₂ heteroaryl is optionally substituted with one or more times with R⁵;

R⁵ is selected from 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 each independently represent hydrogen, alkyl, alkenyl, cycloalkyl aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and alkylheterocyclyl};

n is zero or an integer between 1 and 2;

m is an integer 0-2;

Hal is F, Cl, Br, I;

U is halide, alkyloxy, aryloxy;

Bn is benzyl; and

R' is alkyl, allyl, benzyl, *t*-butyl, silyl.