

MATRIX METALLOPROTEINASE INHIBITORS

Field of the Invention

The present invention relates to methyl sulfonamides and *N*-formamides derivatives and to processes for their syntheses. The invention also relates to
5 pharmacological compositions containing these derivatives and methods of treating asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, psoriasis, pulmonary fibrosis, pulmonary inflammation, acute respiratory distress syndrome, periodontitis, multiple sclerosis, gingivitis, atherosclerosis, dry eye, neointimal proliferation which leads to restenosis and ischemic heart failure, stroke, renal 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 and sharing structural and functional features. Based on structural and functional considerations proteinases have been classified into different families and subfamilies (Vartak et al., *J. Drug Targeting*, 15, p. 1-20 (2007), and Hopper, *FEBS*, 354, p. 1-6 (1994)), such as collagenases (MMP-1, -8 and -13), gelatinases (MMP-2, and -9), metalloelastases (MMP-12), the MT-MMPs
20 (MMP-14, -15, -16, -17, -24 and -25), matrilysins (MMP-7 and -26), stromelysins (MMP-3, -10 and -11) and sheddases such as TNF-converting enzymes (TACE and ACE).

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

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

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

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

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

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

WO 95/35276 discloses N-substituted arylsulphonyl amino acid and their hydroxamic acid derivatives as matrix metallo-proteinase inhibitors. WO 00/06561 discloses tricyclic sulfonamides compounds as matrix metalloproteinases. U.S. Patent No. 6,366,675 discloses N-sulphonyl-diamino: carboxylic acid derivatives used as matrix metalloprotease inhibitors. WO 2004/113279 discloses substituted glycine derivatives, useful for treating inflammatory conditions or autoimmune disorders as matrix metalloproteinase inhibitors.

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

5 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 the present invention, which are single chiral isomers, have improved potency, improved pharmacokinetics and/or improved physicochemical properties as
10 compared to racemic compounds.

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

Summary of the Invention

The present invention provides the methyl sulfonamide and formamides derivatives as matrix metalloproteinase inhibitors, corresponding processes for the
15 synthesis of and pharmaceutical compositions containing the compounds of the present invention. The present invention relates to matrix metalloproteinase inhibitors useful as effective therapeutic or prophylactic agents in treatment of various inflammatory, autoimmune and allergic diseases and other inflammatory disorders characterized by the over expression and over activation of a matrix metalloproteinase using the compounds.

20 The present invention discloses a novel class of compounds that are dual MMP9/12 inhibitors and have desirable activity profiles. The compounds of this invention have beneficial potency and/or selectivity.

Pharmaceutical compositions containing such compounds are provided together with the pharmaceutically acceptable carriers or diluents, which can be used for the
25 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, specific enantiomers have been shown by way of examples, racemates,
30 diastereomers, and pharmaceutically acceptable salts are also provided. Pharmaceutical

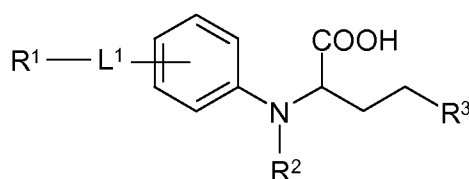
compositions comprising the compounds, their enantiomers, racemates, diastereomers and pharmaceutically acceptable salts are also included.

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, other anti-inflammatory agents, antihypertensive agents and immunosuppressive agents

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 compounds having structure of Formula I:



Formula 1

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

L^1 can be selected from bond, O, S, CH_2 , NR^4 , $NHCO(CH_2)_n$, $(CH_2)_nCONH$, $NHCONH$, SO_2NH , $NHSO_2$, $NHCO(O)$, $-O-(CH_2)_n$, $-(CH_2)_n-O-$, $-OC(O)NH-$, $C(S)NH$, $NHC(S)$, $NHC(S)NH$ or $-COO-$ wherein n can be zero or an integer between 1 and 2;

R^1 can be selected from hydrogen, C_1 - C_6 alkyl, hydroxyl, C_1 - C_6 alkoxy, cyano, nitro, halogen, halogeno C_1 - C_6 alkyl, C_5 - C_{12} aryl, C_6 - C_{12} heteroaryl, C_3 - C_6 cycloalkyl wherein aryl, heteroaryl, cycloalkyl is optionally substituted by one or more substituents independently selected from R^5 ;

R^2 can be CHO or SO_2C_{1-6} alkyl;

R^3 can be unsubstituted or substituted heteroaryl or $-OCONHR'$ where R' is C_6 - C_{12} aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl,

heterocyclylalkyl each of which is optionally substituted by one or more substituents independently selected from R⁵;

R⁴ can be H or C₁₋₆alkyl;

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

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

- 2-[Formyl(4'-methylbiphenyl-4-yl)amino]-4-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 1);
 4-(7-Chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)-2-[formyl(4'-methylbiphenyl-4-yl)amino]butanoic acid (Compound no. 2);
 15 2-[(4'-Ethylbiphenyl-4-yl)(formyl)amino]-4-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 3);
 O-[(4-Fluorophenyl)carbamoyl]-N-formyl-N-(4'-methylbiphenyl-4-yl)homoserine (Compound no. 4);
 20 N-Formyl-N-(4'-methylbiphenyl-4-yl)-O-[(4-methylphenyl)carbamoyl]homoserine (Compound no. 5);
 O-[(3,4-Dichlorophenyl)carbamoyl]-N-formyl-N-(4'-methylbiphenyl-4-yl)homoserine (Compound no. 6);
 N-(4'-Ethylbiphenyl-4-yl)-N-formyl-O- {[4-(propan-2-yl)phenyl]carbamoyl} homoserine (Compound no. 7);
 25 N-(4'-Ethylbiphenyl-4-yl)-O-[(3-fluorophenyl)carbamoyl]-N-formylhomoserine (Compound no. 8);
 O-[(2,4-Difluorophenyl)carbamoyl]-N-(4'-ethylbiphenyl-4-yl)-N-formylhomoserine (Compound no. 9);
 30 N-(4'-Ethylbiphenyl-4-yl)-O-[(2-fluorophenyl)carbamoyl]-N-formylhomoserine (Compound no. 10);
 N-(4'-Ethylbiphenyl-4-yl)-N-formyl-O- {[4-(trifluoromethyl)phenyl]carbamoyl} homoserine (Compound no. 11);
 N-(4'-Ethylbiphenyl-4-yl)-N-formyl-O-[(2-methylphenyl)carbamoyl]homoserine
 35 (Compound no. 12);

- N*-(4'-Ethylbiphenyl-4-yl)-*O*-[(4-ethylphenyl)carbamoyl]-*N*-formylhomoserine (Compound no. 13);
- N*-(4'-Ethylbiphenyl-4-yl)-*N*-formyl-*O*-[(4-methoxyphenyl)carbamoyl]homoserine (Compound no. 14);
- 5 *O*-[(2,6-Dichlorophenyl)carbamoyl]-*N*-(4'-ethylbiphenyl-4-yl)-*N*-formylhomoserine (Compound no. 15);
- 2-[Biphenyl-4-yl(methylsulfonyl)amino]-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoic acid (Compound no. 16);
- 10 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-{[4-(6-methoxypyridin-3-yl)phenyl](methylsulfonyl)amino} butanoic acid (Compound no. 17);
- 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]butanoic acid (Compound no. 18);
- 2-{[4-(6-Methoxypyridin-3-yl)phenyl](methylsulfonyl)amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 19);
- 15 4-(7-Methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-{[4-(6-methoxypyridin-3-yl)phenyl](methylsulfonyl)amino} butanoic acid (Compound no. 20);
- 2-{[4-(6-Methoxypyridin-3-yl)phenyl](methylsulfonyl)amino}-4-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]butanoic acid (Compound no. 21);
- 20 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-{[4-(6-methoxypyridin-3-yl)phenyl](methylsulfonyl)amino} butanoic acid (Compound no. 22);
- 4-(6-Methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-{[4-(4-methylphenoxy)phenyl](methylsulfonyl)amino} butanoic acid (Compound no. 23);
- 4-(7-Methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-{[4-(4-methylphenoxy)phenyl](methylsulfonyl)amino} butanoic acid (Compound no. 24);
- 25 2-{[4-(4-Methylphenoxy)phenyl](methylsulfonyl)amino}-4-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]butanoic acid (Compound no. 25);
- 2-{[4-(4-Methylphenoxy)phenyl](methylsulfonyl)amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 26);
- 30 2-[(3',4'-Difluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 27);
- 2-[(4'-Ethylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 28);
- 2-{[4-(2-Methoxypyrimidin-5-yl)phenyl](methylsulfonyl)amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 29);
- 35 2-[(3'-Fluoro-4'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 30);
- 2-[(2',4'-Dimethoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 31);

- 2-[(4-Methoxyphenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 32);
- 4-(7-Methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-[(4-methoxyphenyl)(methylsulfonyl)amino]butanoic acid (Compound no. 33);
- 5 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(4-methoxyphenyl)(methylsulfonyl)amino]butanoic acid (Compound no. 34);
- 2-[(4-Methoxyphenyl)(methylsulfonyl)amino]-4-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindo-2-yl)butanoic acid (Compound no. 35);
- 10 4-(7-Methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-{[4-(4-methylphenoxy)phenyl](methylsulfonyl)amino} butanoic acid (Compound no. 36);
- 4-(5-Methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-{[4-(4-methylphenoxy)phenyl](methylsulfonyl)amino} butanoic acid (Compound no. 37);
- 2-[(3'-Methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 38);
- 15 2-[(4'-Fluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 39);
- 2-{(Methylsulfonyl)[4'-(propan-2-yl)biphenyl-4-yl]amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 40);
- 2-[Biphenyl-4-yl(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 41);
- 20 2-{[4-(6-Methylpyridin-3-yl)phenyl](methylsulfonyl)amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 42);
- 2-{(Methylsulfonyl)[4-(pyrimidin-5-yl)phenyl]amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 43);
- 25 2-{(Methylsulfonyl)[4-(pyridin-3-yl)phenyl]amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 44);
- 2-{(Methylsulfonyl)[4'-(trifluoromethyl)biphenyl-4-yl]amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 45);
- 2-{(Methylsulfonyl)[4-(pyridin-4-yl)phenyl]amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 46);
- 30 2-[(3',4'-Dichlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 47);
- 2-[(4'-*tert*-Butylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 48);
- 35 2-[(2',3'-Difluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 49);
- 2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 50);

- 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(methylsulfonyl)[4-(propan-2-yl)phenyl]amino]butanoic acid (Compound no. 51);
- 4-(6-Methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-[(methylsulfonyl)[4-(propan-2-yl)phenyl]amino]butanoic acid (Compound no. 52);
- 5 4-(7-Methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-[(methylsulfonyl)[4-(propan-2-yl)phenyl]amino]butanoic acid (Compound no. 53);
- 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(4-ethylphenyl)(methylsulfonyl)amino]butanoic acid (Compound no. 54);
- 10 2-[(4-Ethylphenyl)(methylsulfonyl)amino]-4-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoic acid (Compound no. 55);
- 2-[(4-Ethylphenyl)(methylsulfonyl)amino]-4-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 56);
- 2-[(4-Ethylphenyl)(methylsulfonyl)amino]-4-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 57);
- 15 2-[(Methylsulfonyl)(phenyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 58);
- 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoic acid (Compound no. 59);
- 20 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 60);
- 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 61);
- 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 62);
- 25 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]butanoic acid (Compound no. 63);
- 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 64);
- 30 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 65);
- 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)butanoic acid (Compound no. 66);
- 4-[(Methylsulfonyl)[1-oxo-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-1-(prop-2-en-1-yloxy)butan-2-yl]amino]benzoic acid (Compound no. 67);
- 35 2-[(4-[(4-Methylphenyl)carbamoyl]phenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 68);
- 2-[(4-[(4-Chlorophenyl)carbamoyl]phenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 69);

- 2-[(Methylsulfonyl)[4-(phenylcarbamoyl)phenyl]amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 70);
- 2-[[4-[(3-Fluorophenyl)carbamoyl]phenyl](methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 71);
- 5 2-[(Methylsulfonyl)(4-[[4-(propan-2-yl)phenyl]carbamoyl]phenyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 72);
- 2-[[4-[(4-Methoxyphenyl)carbamoyl]phenyl](methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 73);
- 10 2-[[4-[(4-Fluorophenyl)carbamoyl]phenyl](methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 74);
- 2-[(Methylsulfonyl)(4-[[4-(trifluoromethyl)phenyl]carbamoyl]phenyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 75);
- (2*R*)-2-[(4'-Fluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 76);
- 15 (2*R*)-2-[(Methylsulfonyl)[4-(pyrimidin-5-yl)phenyl]amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 77);
- (2*R*)-2-[(Methylsulfonyl)[4'-(propan-2-yl)biphenyl-4-yl]amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 78);
- (2*R*)-2-[(3',4'-Dichlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 79);
- 20 (2*R*)-2-[(3',4'-Difluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 80);
- (2*R*)-2-[(3'-Fluoro-4'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 81);
- 25 (2*R*)-2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 82);
- (2*R*)-2-[(3'-Methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 83);
- (2*R*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 84);
- 30 (2*R*)-2-[Biphenyl-4-yl(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 85);
- (2*R*)-2-[[4-(6-Methoxypyridin-3-yl)phenyl](methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 86);
- 35 (2*S*)-2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 87);
- (2*S*)-2-[(3',4'-Dichlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 88);

- (2*S*)-2-[(3'-Fluoro-4'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 89);
- (2*S*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 90);
- 5 (2*R*)-2-[(3',4'-Dimethoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 91);
- (2*R*)-2-{[4-(2,3-Dihydro-1,4-benzodioxin-6-yl)phenyl](methylsulfonyl)amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 92);
- 10 (2*R*)-2-[(4'-Methoxy-3'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 93);
- (2*R*)-2-[(4'-Fluoro-3'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 94);
- (2*R*)-2-{(Methylsulfonyl)[4'-(trifluoromethoxy)biphenyl-4-yl]amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 95);
- 15 (2*R*)-2-{[4'-Chloro-3'-(trifluoromethyl)biphenyl-4-yl](methylsulfonyl)amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 96);
- (2*R*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]butanoic acid (Compound no. 97);
- 20 (2*R*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 98);
- (2*R*)-4-(7-Chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-[(3'-fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]butanoic acid (Compound no. 99);
- (2*R*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 100);
- 25 (2*R*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 101);
- (2*R*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 102);
- 30 (2*R*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 103);
- 4-(5-Chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-[(4-chlorophenyl)(methylsulfonyl)amino]butanoic acid (Compound no. 104);
- 2-[(4-Bromophenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 105);
- 35 2-[(4-Chlorophenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 106);
- 2-[(4-Chlorophenyl)(methylsulfonyl)amino]-4-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 107);

2-[(4-Chlorophenyl)(methylsulfonyl)amino]-4-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 108).

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

In another aspect, provided herein, are methods for treating or prophylaxis of an animal or a human suffering from various inflammatory or 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 one embodiment, the diseases or conditions of inflammation and associated pathologies are selected from asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, psoriasis, pulmonary fibrosis, pulmonary inflammation, acute respiratory distress syndrome, periodontitis, multiple sclerosis, gingivitis, atherosclerosis, dry eye, neointimal proliferation which leads to restenosis and ischemic heart failure,
15 stroke, renal disease, tumor metastasis, and other inflammatory disorders

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,

- 20 1) 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,
25 (iv) MMP inhibitors, and (v) interleukin-I inhibitors;
- 2) 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.
- 30 3) immunosuppressive agents such as cyclosporine, azathioprine and methotrexate, and anti inflammatory corticosteroids.

The following definitions apply to terms, as used herein.

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.

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, 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 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.

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 8 to 10 ring atoms, with one or more heteroatom(s) independently selected from N, O or S and optionally are benzofused or fused heteroaryl having 5-6 ring members.

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

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.

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

The term “amino” refers to —NH_2

The term “halogen” refers to fluorine, chlorine, bromine or iodine;

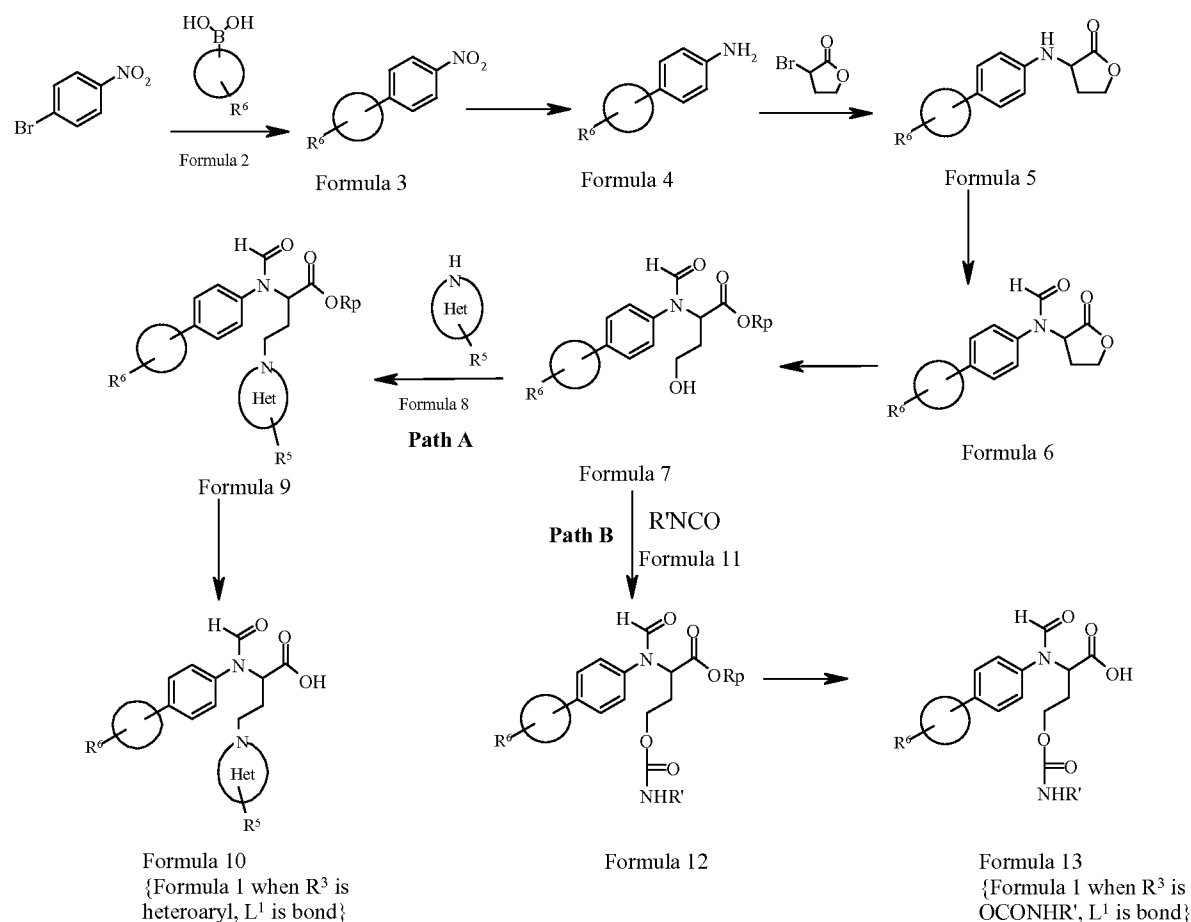
The term “leaving group” refers to groups that exhibit or potentially exhibit the properties of being labile under the synthetic conditions and also, of being readily separated from synthetic products under defined conditions. Examples of leaving groups include, but are not limited to, halogen (*e.g.*,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

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

The compounds of this invention can contain one or more 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* 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 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, 5 and lithium hydroxide; alkaline earth metal hydroxides such as magnesium hydroxide and calcium hydroxide. Further, the salts of organic bases, such as lysine, arginine, guanidine, ethanolamine, choline and the like, inorganic bases, *e.g.*, ammonium or substituted ammonium salts are also included. Wherever appropriate, compounds with pharmaceutically acceptable organic and inorganic acids, *e.g.*, hydro halides, such as 10 hydrochloride, hydrobromide, hydroiodide; other mineral acids and their corresponding salts, such as sulphate, nitrate, phosphate, etc.; and alkyl and mono-arylsulphonates, such as ethane sulphonate, toluene sulphonate and benzene sulphonate; and other organic acids and their corresponding salts, such as acetate, tartaratae, maleate, succinate, citrate, etc.

In another aspect, the compounds, disclosed herein, may be prepared by following 15 reaction sequences as depicted in Schemes I, II, III, IV, V and VI.

Scheme I

The compound of Formula 10 (Path A) and Formula 13 (Path B) can be prepared according to Scheme I. Thus, reacting 4-bromo-nitrobenzene with a compound of

5 Formula 2 (wherein $\bigcirc$ is aryl or heteroaryl ring and R^6 is hydrogen, alkyl, halogen, alkoxy or halogeno- C_1 - C_6 alkyl) gives a compound of Formula 3 which on reduction forms a compound of Formula 4. The reaction of a compound of Formula 4 with α -bromolactone gives a compound of Formula 5 which on upon formylation forms a compound of Formula 6. The compound of Formula 6 on ring opening forms a compound

10 of Formula 7 (wherein R_p is carboxy protecting group, such as methyl, ethyl, allyl, benzyl, t-butyl, silyl, BOC-anhydride) which on reaction with a compound of Formula 8 (wherein $\bigcirc_{\text{Het}}$ is a heteroaryl ring, R^5 is same as defined earlier) gives a compound of Formula 9 which finally on deprotection gives a compound of Formula 10. The reaction of a

compound of Formula 7 with a compound of Formula 11 (where R' is same as defined earlier) gives a compound of Formula 12 which on deprotection give a compound of Formula 13.

5 The coupling of 4-bromo-nitrobenzene with a compound of Formula 2 to give a compound of Formula 3 can be carried out in the presence of inorganic base selected from, for example, potassium carbonate, sodium carbonate, sodium acetate, potassium acetate in presence of a solvent selected from, tetrahydrofuran, *N,N'*-dimethylformamide, dimethylsulfoxide, toluene, or mixture(s) thereof.

10 The reduction of a compound of Formula 3 to give a compound of Formula 4 can be carried out using reducing agent selected from, for example, Raney Nickel in hydrazine hydrate or ammonium formate, zinc, tin or iron in the presence of hydrochloric acid or lithium aluminum hydride, Pd/C in H₂ in the presence of a solvent, for example, tetrahydrofuran, methanol, ethanol, diethyl ether, dioxane, or mixture(s) thereof.

15 The coupling of a compound of Formula 4 with alpha-bromolactone to give a compound of Formula 5 can be carried out using inorganic base selected from, for example, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium bicarbonate using solvent selected from, for example, acetonitrile, water, or mixture(s) thereof.

20 The formylation of a compound of Formula 5 to give a compound of Formula 6 can be carried out using formylating agent selected from, for example, formic acid, acetic formic anhydride, chloral, activated formic acid using *N, N'*-dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI), activated formic ester, ammonium formate in the presence of a solvent selected from, for example, toluene, dimethoxymethane, xylene, or mixture(s) thereof.

25 The ring opening of a compound of Formula 6 to give a compound of Formula 7 can be carried out with alkyl/aryl halide in the presence of 18-crown-6 using one or more inorganic base selected from sodium bicarbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide in the presence of a solvent, for example, *N, N'*-dimethylformamide, methanol, ethanol, propanol, butanol, tetrahydrofuran, acetonitrile, water, or mixture(s) thereof.

The coupling of a compound of Formula 7 with a compound of Formula 8 to give a compound of Formula 9 can be carried out in the presence of redox couple. The oxidizing part of the redox couple is selected from, for example, 1,1'-(azodicarbonyl)piperidine (ADDP), 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD), *N,N,N',N'*-tetramethylazodicarboxamide (TMAD), *N,N,N',N'*-tetraisopropylazodicarboxamide (TIPA), diethyl azodicarboxylate (DEAD), di-*t*-butylazodicarboxylate or diisopropylazodicarboxylate (DIAD). The reducing part of the redox couple is selected from, for example, tributylphosphine, triphenylphosphine, *p*-(dimethylaminophenyl) or triscyclohexylphosphine in the presence of a solvent, for example, tetrahydrofuran, dimethylsulfoxide, *N,N'*-dimethylformamide, acetonitrile, or mixture(s) thereof.

The deprotection of a compound of Formula 9 to give a compound of Formula 10 can be carried out in the presence of mineral acid, for example, hydrochloric, hydrobromic, hydroiodic acid in a solvent selected from dichloromethane, chloroform, carbon tetrachloride, dichloroethane, methanol, ethanol, acetonitrile, tetrahydrofuran, or mixture(s) thereof.

Or alternatively, the deprotection of a compound of Formula 9 to give a compound of Formula 10 can be carried out in the presence of one or more organic acid(s), for example, trifluoroacetic acid, *p*-toluenesulphonic acid or camphor sulphonic acid, in a solvent selected from dichloromethane, chloroform, carbon tetrachloride, dichloroethane, methanol, ethanol, acetonitrile, tetrahydrofuran, or mixture(s) thereof.

Or alternatively, the deprotection of a compound of Formula 9 to give a compound of Formula 10 can be carried out in the presence of inorganic base, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, cesium hydroxide, potassium carbonate in a solvent selected from dichloromethane, chloroform, carbon tetrachloride, dichloroethane, methanol, ethanol, acetonitrile, tetrahydrofuran, or mixture(s) thereof.

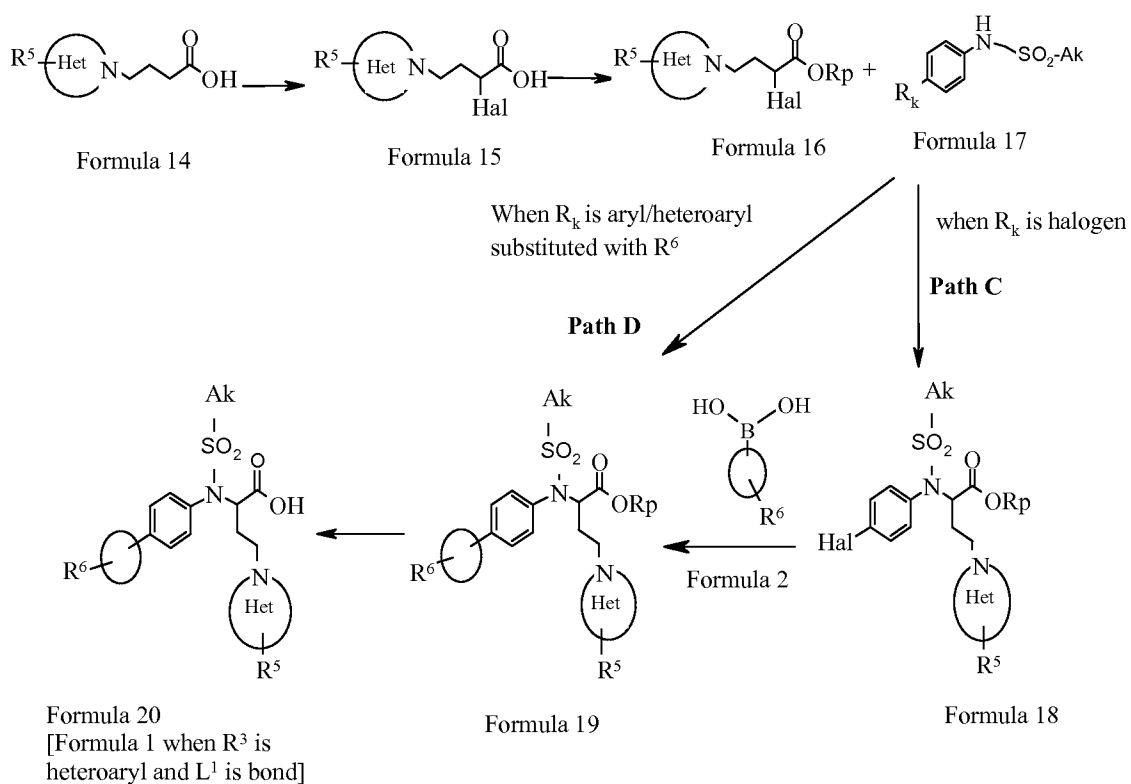
Or alternatively, the deprotection of a compound of Formula 9 to give a compound of Formula 10 can be carried out in the presence of deprotecting agent, for example, Pd/C in presence of H₂, Pd/C with ammonium formate, Pd/C in presence of triethylsilane, ozone, boron trichloride dimethylsulfide (BCl₃.SMe₂), 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), tetrakis triphenylphosphine in the presence of morpholine using solvent selected

from dichloromethane, chloroform, carbon tetrachloride, dichloroethane, methanol, ethanol, acetonitrile, tetrahydrofuran, or mixture(s) thereof.

The reaction of a compound of Formula 7 with a compound of Formula 11 to give a compound of Formula 12 can be carried out in the presence of base selected from, for example, triethylamine, *N,N'*-dimethylaminopyridine, 2,6-lutidine, 1-methylpiperidine, *N*-ethyl-diisopropylamine, *N,N'*-diisopropylethylamine or *N*-methylmorpholine in a solvent selected from, tetrahydrofuran, *N,N'*-dimethylformamide, dimethylsulfoxide, acetonitrile, or mixture(s) thereof.

The deprotection of a compound of Formula 12 to give a compound of Formula 13 can be carried out under similar conditions as described for the compound of Formula 9 to give a compound of Formula 10.

Scheme II



The compound of Formula 20 can be prepared according to Scheme II. Thus, the
 15 alpha halogenation of a compound of Formula 14 (wherein Het-N is a heteroaryl ring, R^5 is

same as defined earlier) to give a compound of Formula 15 (wherein Hal is F, Cl, Br, I) which upon protection gives a compound of Formula 16 (wherein R_p is the same as defined earlier). The reaction of a compound of Formula 16 with a compound of Formula 17 (wherein Ak is C₁₋₆alkyl and R_k is alkyl, halogen, aryl, heteroaryl) can take place in two ways.

Path C (when R_k is halogen): The compound of Formula 16 react with a compound of Formula 17 to form a compound of Formula 18 which upon coupling with a compound of Formula 2 (wherein  is aryl or heteroaryl ring and R⁶ is the same as defined earlier) gives a compound of Formula 19. The compound of Formula 19 on deprotection gives a compound of Formula 20.

Path D (when R_k is aryl/heteroaryl substituted with R⁶): The compound of Formula 16 on reaction with a compound of Formula 17 gives a compound of Formula 19 which upon deprotection gives a compound of Formula 20.

The alpha halogenation of a compound of Formula 14 to form a compound of Formula 15 can be carried out in the presence of red phosphorous/Br₂, in the presence of a solvent selected from, for example, carbon tetrachloride, chloroform, dichloromethane, dichloroethane, or mixture(s) thereof.

The *O*-protection of a compound of Formula 15 to give a compound of Formula 16 can be carried out with carboxy protecting group, for example, methyl, benzyl, allyl, *t*-butyl, silyl, BOC anhydride in the presence of organic base selected from, for example, triethylamine, *N,N'*-dimethylaminopyridine, 2,6-lutidine, 1-methylpiperidine, *N*-ethyl-diisopropylamine, *N,N'*-diisopropylethylamine or *N*-methylmorpholine using solvents selected from, tetrahydrofuran, *N,N'*-dimethylformamide, dimethylsulfoxide, acetonitrile, or mixture(s) thereof.

Or alternatively, the *O*-protection of a compound of Formula 15 to give a compound of Formula 16 can be carried out with carboxy protecting group, for example, methyl, benzyl, allyl, *t*-butyl, silyl, BOC anhydride in the presence of inorganic base selected from, sodium bicarbonate, lithium bicarbonate, potassium bicarbonate in one or more solvents selected from, for example, *N,N'*-dimethylformamide, acetonitrile, dimethylsulfoxide, tetrahydrofuran, methanol, ethanol, water, or mixture(s) thereof.

The reaction of a compound of Formula 16 with a compound of Formula 17 (Path C) to give a compound of Formula 18 can be carried out in the presence of inorganic base selected from, for example, lithium carbonate, sodium carbonate, potassium carbonate, magnesium carbonate, barium carbonate using solvent, for example, acetonitrile, tetrahydrofuran, dioxane, *N,N'*-dimethylformamide, dimethylsulfoxide, or mixture(s) thereof.

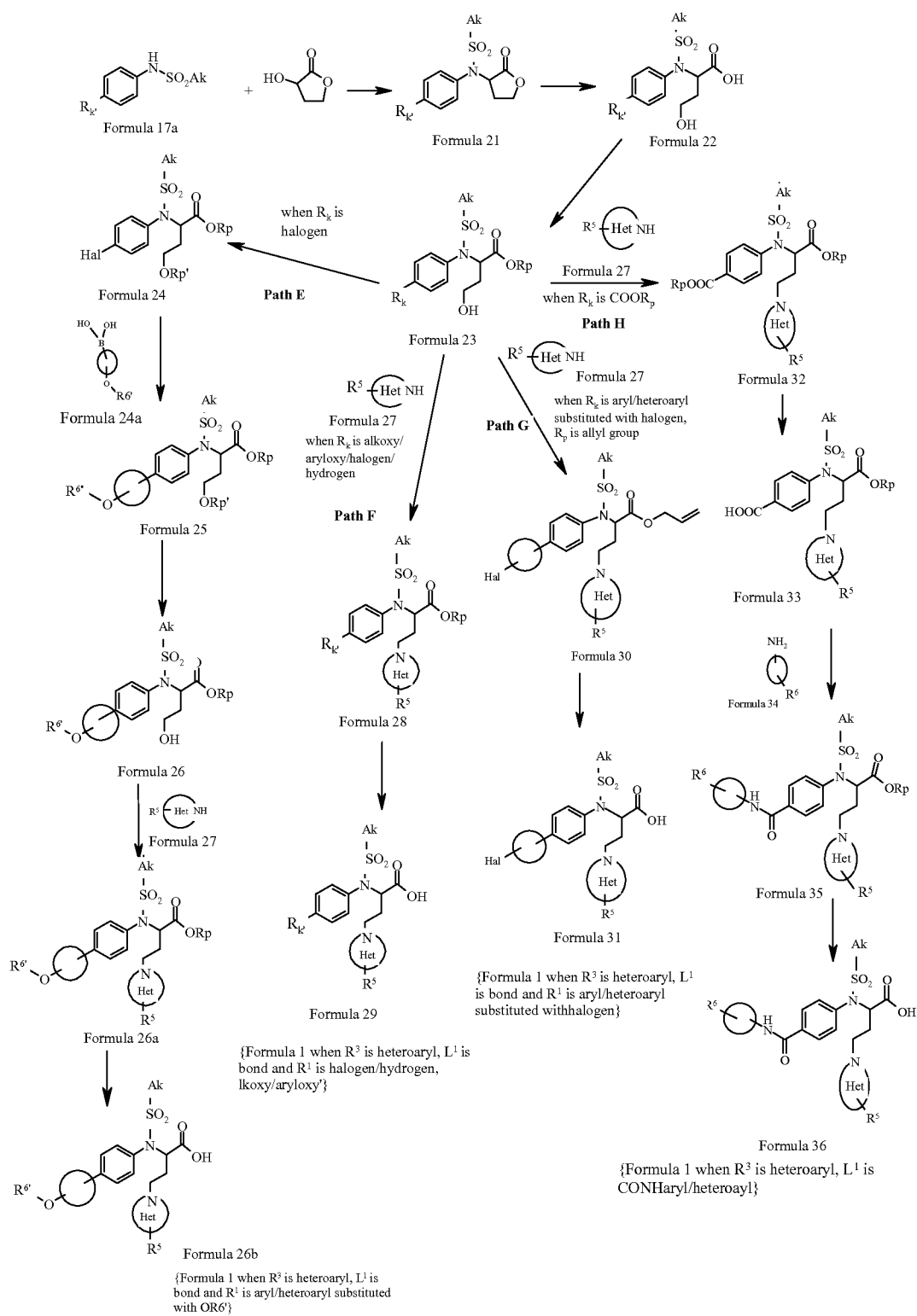
The coupling of a compound of Formula 18 with a compound of Formula 2 to give a compound of Formula 19 can be carried out in the presence of inorganic catalyst selected from, for example, *bis*-(diphenylphosphino)ferrocene palladium II dichloride (Pd(dppf)Cl₂), tetrakis(triphenylphosphine) palladium (0) [Pd(Ph₃P)₄], palladium acetate or dichlorotriphenylphosphine palladium (II), with suitable base selected from, for example, potassium carbonate, sodium acetate, potassium acetate in the presence of solvent selected from, tetrahydrofuran, *N,N'*-dimethylformamide, dimethylsulfoxide, toluene, or mixture(s) thereof.

The deprotection 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 9 to give a compound of Formula 10.

The reaction of a compound of Formula 16 with a compound of Formula 17 (Path D) to give a compound of Formula 19 can be carried out in the presence of inorganic base selected from, for example, potassium carbonate, sodium carbonate, lithium carbonate, barium carbonate in a solvent, for example, acetonitrile, tetrahydrofuran, *N,N'*-dimethylformamide, dimethylsulfoxide, or mixture(s) thereof.

Scheme III

22



The compound of Formula 26b (Path E), Formula 29 (Path F), Formula 31 (Path G), Formula 36 (Path H) can be prepared according to Scheme III. Thus reacting a compound of Formula 17a (wherein $R_{k'}$ is hydrogen, halogen, alkoxy, aryloxy, aryl, carboxy) with α -hydroxy lactone gives a compound of Formula 21 which upon ring opening gives a compound of Formula 22. The carboxy-protection of compound of Formula 22 gives a compound of Formula 23 (wherein R_p is same as defined earlier).

Path E (when $R_{k'}$ is halogen): the compound of Formula 23 upon hydroxy protection gives a compound of Formula 24 (wherein $R_{p'}$ is hydroxy protecting group). The coupling of a compound of Formula 24 with a compound of Formula 24a (wherein $R^{6'}$ is alkyl, aryl, heteroaryl) gives a compound of Formula 25 which upon deprotection gives a compound of Formula 26. The reaction of a compound of Formula 26 with a compound of Formula 27 gives a compound of Formula 26a. The deprotection of a compound of Formula 26a gives a compound of Formula 26b.

Path F (when $R_{k'}$ is alkoxy/aryloxy/halogen/hydrogen): the reaction of a compound of Formula 23 with a compound of Formula 27 gives a compound of Formula 28 which upon deprotection gives a compound of Formula 29.

Path G: (when $R_{k'}$ is aryl substituted with halogen and R_p is allyl): the reaction of a compound of Formula 23 with a compound of Formula 27 gives a compound of Formula 30 which upon deprotection gives a compound of Formula 31.

Path H: (when $R_{k'}$ is $COOR_p$): the coupling of a compound of Formula 23 with a compound of Formula 27 gives a compound of Formula 32 which upon deprotection gives a compound of Formula 33. The coupling of a compound of Formula 33 with a compound of Formula 34 gives a compound of Formula 35 which finally upon deprotection forms a compound of Formula 36.

The reaction of a compound of Formula 17a with α -hydroxy lactone to give a compound of Formula 21 can be carried out under similar conditions as described for the reaction of a compound of Formula 7 with a compound of Formula 8 to give a compound of Formula 9.

The ring-opening of a compound of Formula 21 to give a compound of Formula 22 can be carried out as described for the compound of Formula 6 to give a compound of Formula 7.

5 The carboxy-protection of a compound of Formula 22 to give a compound of Formula 23 can be carried out under similar conditions as described for the compound of Formula 15 to give a compound of Formula 16.

10 The hydroxy-protection of a compound of Formula 23 to give a compound of Formula 24 (Path E) can be carried out using protecting group selected from, for example, *tert*-butyldimethylsilylchloride (TBDMSCl), trimethylsilylchloride (TMSCl), *tert*-butyldimethylsilyloxymethylchloride (TOMCl), triisopropylsilylchloride (TIPSCl), benzoyl chloride in the presence of base, for example, imidazole, *N*-methylimidazole, triethylamine, pyridine, diisopropylethylamine, *N,N'*-dimethylaminopyridine in the presence of solvent, for example, *N,N'*-dimethylformamide, toluene, acetonitrile, dichloromethane, or mixture thereof.

15 The coupling of a compound of Formula 24 with a compound of Formula 24a to give a compound of Formula 25 can be carried out under similar conditions as for the reaction of a compound of Formula 18 with a compound of Formula 2 to give a compound of Formula 19.

20 The deprotection of a compound of Formula 25 to give a compound of Formula 26 can be carried out using deprotecting agent selected from, for example, boron trifluoride etherate (BF₃.OEt₂), HF-pyridine, boron trichloride, boron tribromide, cesium fluoride (CsF), potassium fluoride (KF), *n*-tetrabutylammonium fluoride, Pd/C in H₂, potassium carbonate in presence of solvent, for example, dichloromethane, *N,N'*-dimethylformamide, acetonitrile, methanol, ethanol, acetone, tetrahydrofuran, or mixture thereof.

25 The reaction of a compound of Formula 26 with a compound of Formula 27 to give a compound of Formula 26a can be carried out under similar conditions as described for the reaction of a compound of Formula 7 with a compound of Formula 8 to give a compound of Formula 9.

The deprotection of a compound of Formula 26a to give a compound of Formula 26b can be out under similar conditions as described for the deprotection of a compound of Formula 9 to give a compound of Formula 10.

5 The reaction of a compound of Formula 23 (Path F) with a compound of Formula 27 to give a compound of Formula 28 can be carried out under similar condition as described for the reaction of a compound of Formula 7 with a compound of Formula 8 to give a compound of Formula 9.

10 The deprotection of a compound of Formula 28 to give a compound of Formula 29 can be out under similar conditions as described for the deprotection of a compound of Formula 9 to give a compound of Formula 10.

The reaction of a compound of Formula 23 (Path G) with a compound of Formula 27 to give a compound of Formula 30 can be carried out under similar conditions as described for reaction of a compound of Formula 7 with a compound of Formula 8 to give a compound of Formula 9.

15 The deprotection of a compound of Formula 30 to give a compound of Formula 31 can be carried out under similar conditions as described for the deprotection of a compound of Formula 9 to give a compound of Formula 10.

20 The reaction of a compound of Formula 23 (Path H) with a compound of Formula 27 to give a compound of Formula 32 can be carried out under similar conditions as described for the compound of Formula 7 with a compound of Formula 8 to give a compound of Formula 9.

The deprotection of a compound of Formula 32 to give a compound of Formula 33 can be carried out as described for the compound of Formula 9 to give a compound of Formula 10.

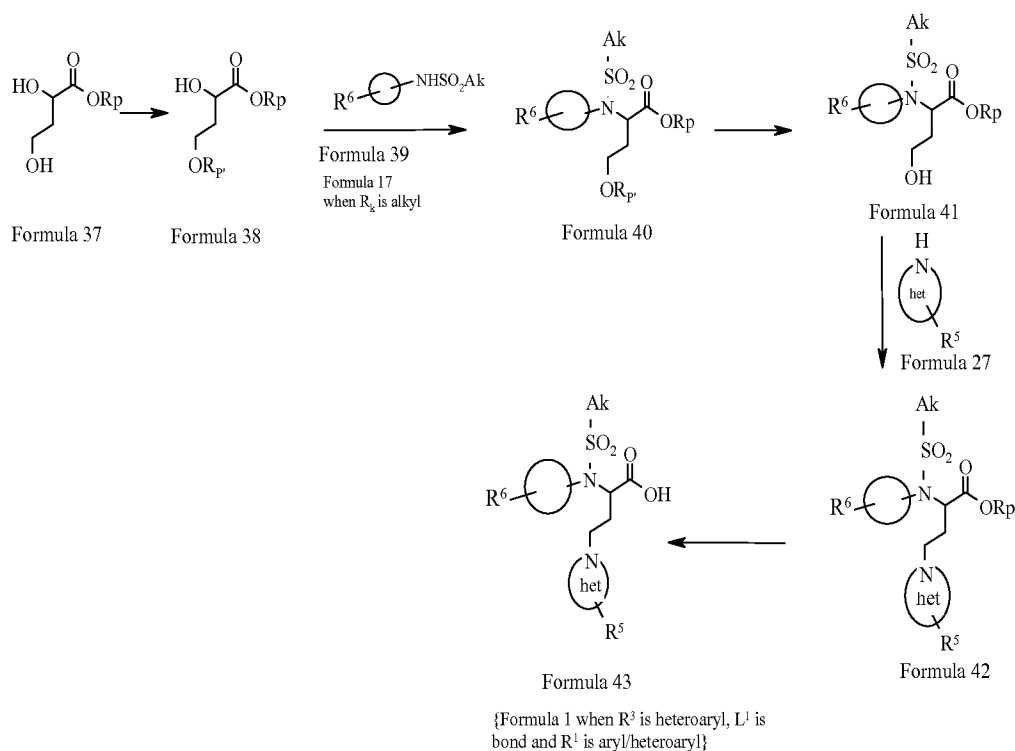
25 The coupling of a compound of Formula 33 with a compound of Formula 34 to give a compound of Formula 35 can be carried out using base selected from triethylamine, *N,N*-dimethylaminopyridine, 2,6-lutidine, 1-methylpiperidine, *N*-ethyl-diisopropylamine, *N,N*-diisopropylethylamine or *N*-methylmorpholine, 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
30

condensing agent, for example, dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, chlorotripyrrolidinophosphonium hexafluorophosphate or (benzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate in the presence of a solvent selected from, for example, *N,N'*dimethylformamide,

5 dimethylsulfoxide, acetonitrile, or mixture(s) thereof.

The deprotection of a compound of Formula 35 to give a compound of Formula 36 can be carried out under similar condition as described for the compound of Formula 9 to give a compound of Formula 10.

Scheme IV



10

The compound of Formula 43 can be prepared according to Scheme IV. Thus, protecting a compound of Formula 37 (wherein R_p is same as defined earlier) gives a compound of Formula 38 (wherein R_p is same as defined earlier) which on reaction with a compound of Formula 39 (Wherein R^6 is alkyl and Ak is same as defined earlier) gives a compound of Formula 40. The compound of Formula 40 on deprotection gives a compound of Formula 41 which on reaction with a compound of Formula 27 (wherein R^5

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is same as defined earlier) forms a compound of Formula 42. The deprotection of a compound of Formula 42 gives a compound of Formula 43.

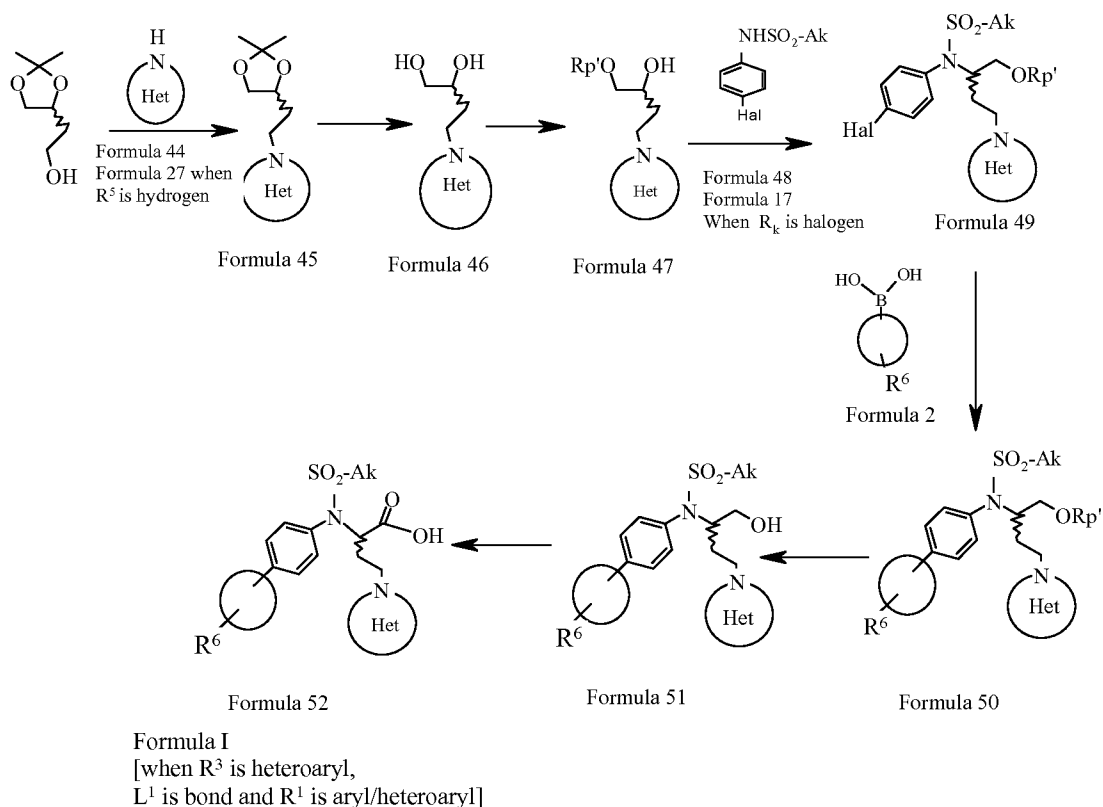
5 The protection of a compound of Formula 37 to give a compound of Formula 38 can be carried out under similar conditions as described for the compound of Formula 23 to give a compound of Formula 24.

The reaction of a compound of Formula 38 with a compound of Formula 39 to give a compound of Formula 40 can be carried out under similar conditions as described for the reaction of a compound of Formula 7 with a compound of Formula 8 to give a compound of Formula 9.

10 The deprotection of a compound of Formula 40 to give a compound of Formula 41 can be carried out under similar conditions as described for the compound of Formula 25 to give a compound of Formula 26.

15 The reaction of a compound of Formula 41 with a compound of Formula 27 to give a compound of Formula 42 can be carried out under similar conditions as described for the reaction of a compound of Formula 7 with a compound of Formula 8 to give a compound of Formula 9.

The deprotection of a compound of Formula 42 to give a compound of Formula 43 can be carried as described for the compound of Formula 9 to give a compound of Formula 10.

Scheme V

The compound of Formula 52 can be prepared according to Scheme V. Thus

5 reacting 4-(2-hydroxyethyl)-2,2-dimethyl 1,3-dioxolane with a compound of Formula 44 gives a compound of Formula 45 which upon ring opening gives a compound of Formula 46. The compound of Formula 46 on O-protection gives a compound of Formula 47 (wherein R_p' is same earlier) which upon reaction with a compound of Formula 48 (wherein Hal and Ak are same as defined earlier) gives a compound of Formula 49. The

10 coupling of a compound of Formula 49 with a compound of Formula 2 gives a compound of Formula 50. The compound of Formula 50 on deprotection forms a compound of Formula 51 which finally on oxidation gives a compound of Formula 52.

The reaction of 4-(2-hydroxyethyl)-2,2-dimethyl 1,3-dioxolane with a compound of Formula 44 form a compound of Formula 45 can be carried out under similar condition

15 as for the compound of Formula 7 with a compound of Formula 8 to give a compound of Formula 9.

The ring opening of a compound of Formula 45 to give a compound of Formula 46 can be carried out in the presence of mineral acids selected from, for example, hydrochloric acid, hydrobromic acid, hydroiodic acid, or in the presence of catalytic amount of cerium(IV) ammonium nitrate (CAN), cerium(III) trifluoromethane sulfonate
5 using solvent, for example, acetone, nitromethane, acetonitrile, water, or described thereof.

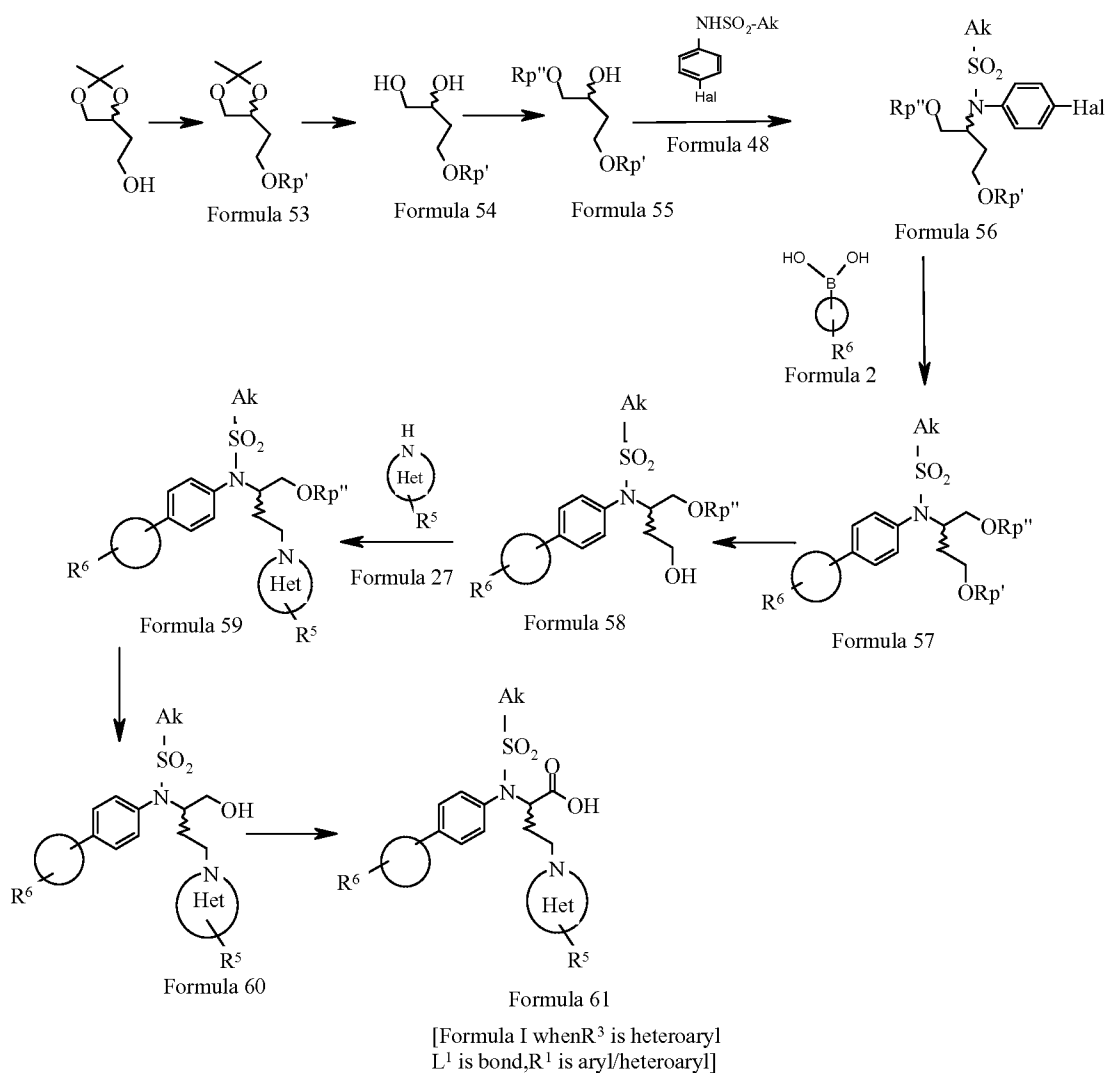
The protection of a compound of Formula 46 to give a compound of Formula 47 can be carried out under similar conditions as described for the compound of Formula 23 to give a compound of Formula 24.

The reaction of a compound of Formula 47 with a compound of Formula 48 to give
10 a compound of Formula 49 can be carried out under similar conditions as described for the reaction of a compound of Formula 7 with a compound of Formula 8 to give a compound of Formula 9.

The coupling of a compound of Formula 49 with a compound of Formula 2 to give a compound of Formula 50 can be carried out under similar conditions as described for
15 coupling of a compound of Formula 18 with a compound of Formula 2 to give a compound of Formula 19.

The deprotection of a compound of Formula 50 to give a compound of Formula 51 can be carried out under similar condition as described for the deprotection of a compound of Formula 25 to give a compound of Formula 26.

The oxidation of a compound of Formula 51 to give a compound of Formula 52 can be carried using oxidizing agent, for example, sodium chlorite and sodium hypochlorite in presence of 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO), sodium periodate in presence of ruthenium trichloride, potassium dichromate, potassium permanganate, using a solvent selected from, acetonitrile, carbon tetrachloride, water, or
25 mixture(s) thereof.

Scheme VI

- The compound of Formula 61 can be prepared according to Scheme VI. Thus,
- 5 protecting 4-(2-hydroxyethyl)-2,2-dimethyl 1,3-dioxolane gives a compound of Formula 53 (wherein R_p is same as defined earlier) which upon ring opening forms a compound of Formula 54. The compound of Formula 54 upon further protection gives a compound of Formula 55 (wherein R_p' is same as defined earlier) which on reaction with a compound of Formula 48 (wherein Hal is same as defined earlier) gives a compound of Formula 56.
 - 10 The coupling of a compound of Formula 56 with a compound of Formula 2 gives a compound of Formula 57 which on deprotection forms a compound of Formula 58. The

reaction of a compound of Formula 58 with a compound of Formula 27 (wherein R⁵ is same as defined earlier) gives a compound of Formula 59. The compound of Formula 59 on deprotection gives a compound of Formula 60 which on oxidation forms a compound of Formula 61.

5 The protection of 4-(2-hydroxyethyl)-2,2-dimethyl 1,3-dioxolane to give a compound of Formula 53 can be carried out using alkyl/aryl halides using inorganic base selected from lithium hydride, sodium hydride or organic base selected from pyridine, triethylamine, trimethylamine, tributylamine, *N*-ethyldiisopropylamine, 4-*N,N*-dimethylaminopyridine, *N*-methylmorpholine or 2,6-lutidine in the presence of a solvent,
10 for example, *N,N'*-dimethylformamide, dimethylsulfoxide, acetonitrile, or mixture(s) thereof.

 The ring opening of a compound of Formula 53 to give a compound of Formula 55 can be carried out under similar conditions as described for compound of Formula 45 to give a compound of Formula 46.

15 The protection of a compound 54 to give a compound of Formula 55 can be carried out under similar conditions as described for the protection of compound of Formula 23 to give a compound of Formula 24.

 The reaction of a compound of Formula 55 with a compound of Formula 48 to give a compound of Formula 56 can be carried out under similar conditions as described for the
20 compound of Formula 7 with a compound of Formula 8 to give a compound of Formula 9.

 The coupling of a compound of Formula 56 with a compound of Formula 2 to give a compound of Formula 57 can be carried out under similar conditions as described for coupling of a compound of Formula 18 with a compound of Formula 2 to give a compound of Formula 19.

25 The deprotection of a compound of Formula 57 to give a compound of Formula 58 can be carried out as described for the deprotection of a compound of Formula 9 to give a compound of Formula 10.

 The coupling of a compound of Formula 58 with a compound of Formula 27 to gives a compound 59 can be carried out under similar conditions as described for the
30 compound of Formula 7 with a compound of Formula 8 to give a compound of Formula 9.

The deprotection of a compound of Formula 59 to give a compound of Formula 60 can be carried out under similar conditions as described for the compound of Formula 25 to give a compound of Formula 26.

5 The oxidation of a compound of Formula 60 to give a compound of Formula 61 can be carried out under similar condition as described for the compound of Formula 51 to give a compound of Formula 52.

In the above schemes, where specific reagents, for example, bases, acids, solvents, condensing agents, reducing agent, deprotecting agent, hydrolyzing agents, catalysts, etc., as mentioned, is to be understood that other reagents, *e.g.*, other acids, bases, solvents, 10 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 15 orally, topically, rectally, intranasally 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, 20 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 25 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; antiadherents, for example, 30 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.

5 General Example

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

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 %
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 %

10 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, 15 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.

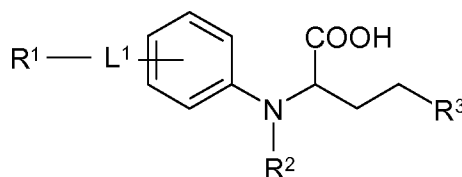
20 Injectable preparations, for example, sterile injections, and aqueous suspensions may be formulated according to methods known to one of ordinary skill in the art, and in particular, using one or more suitable dispersing or wetting and suspending agents. Acceptable vehicles and solvents that may be 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 cocoa butter and polyethylene glycols, which are solid at ordinary temperatures but liquid at body temperature and which therefore melt in the rectum and release the drug.

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.

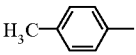
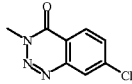
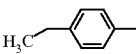
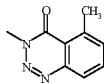
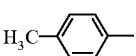
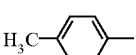
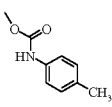
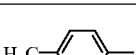
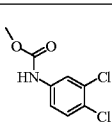
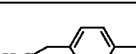
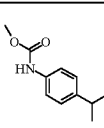
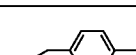
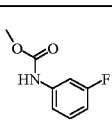
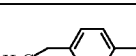
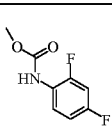
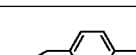
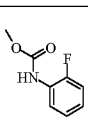
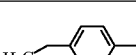
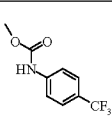
Pharmaceutical preparations may be in unit dosage form. In unit dosage form, the preparations can be subdivided into unit doses containing appropriate quantities of active components. Unit dosage forms can be packaged preparations containing discrete capsules, powders, in vials or ampoules, ointments,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

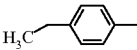
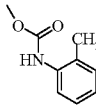
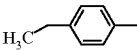
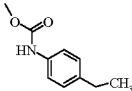
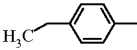
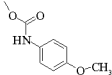
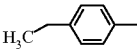
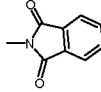
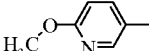
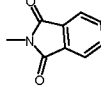
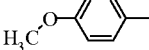
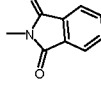
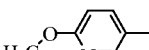
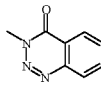
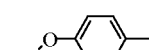
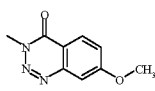
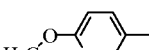
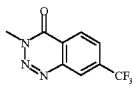
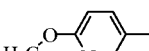
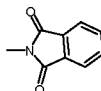
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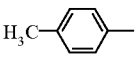
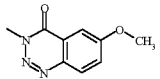
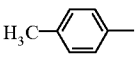
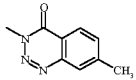
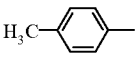
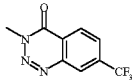
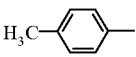
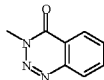
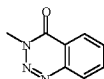
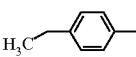
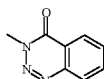
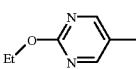
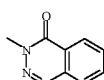
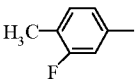
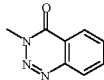
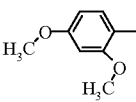
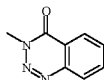
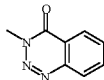
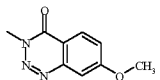


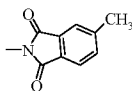
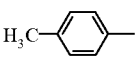
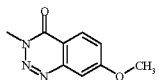
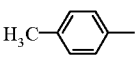
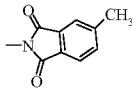
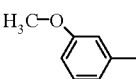
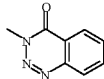
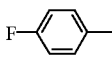
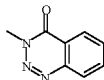
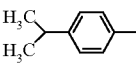
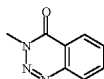
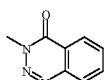
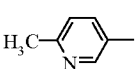
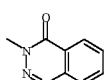
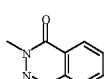
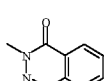
Formula 1

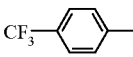
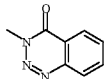
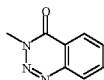
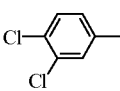
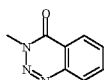
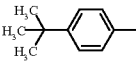
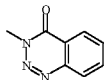
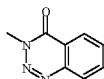
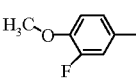
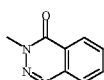
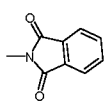
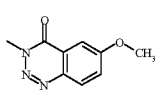
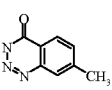
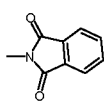
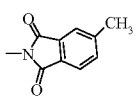
C No.	R ¹	L ¹	R ²	R ³
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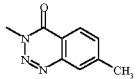
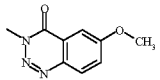
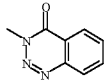
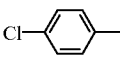
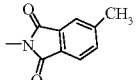
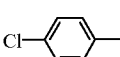
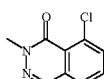
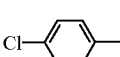
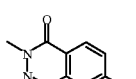
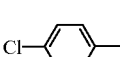
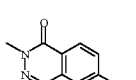
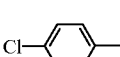
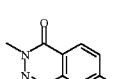
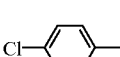
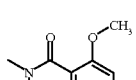
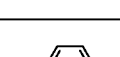
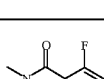
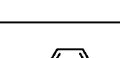
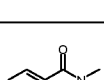
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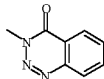
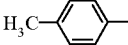
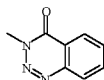
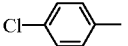
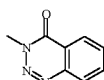
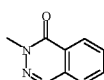
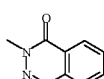
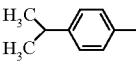
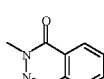
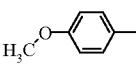
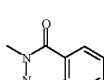
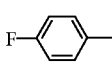
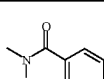
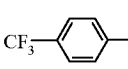
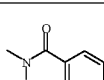
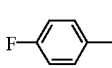
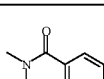
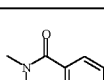
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16		bond	-SO ₂ CH ₃	
17		bond	-SO ₂ CH ₃	
18		bond	-SO ₂ CH ₃	
19		bond	-SO ₂ CH ₃	
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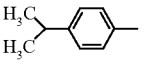
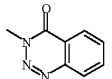
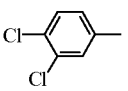
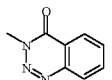
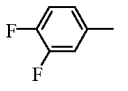
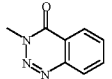
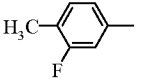
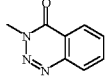
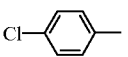
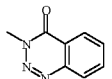
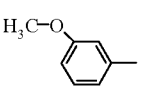
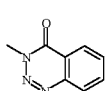
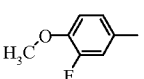
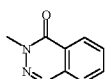
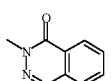
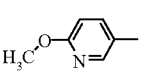
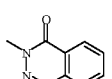
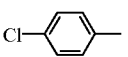
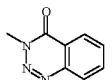
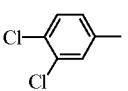
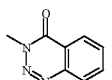
23		O	-SO ₂ CH ₃	
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28		bond	-SO ₂ CH ₃	
29		bond	-SO ₂ CH ₃	
30		bond	-SO ₂ CH ₃	
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33	CH ₃	O-	SO ₂ CH ₃	

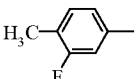
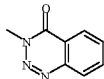
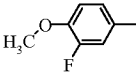
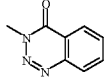
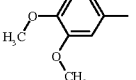
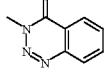
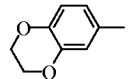
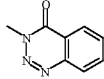
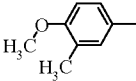
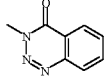
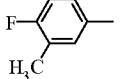
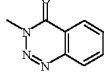
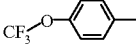
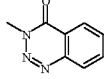
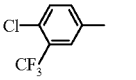
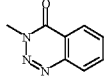
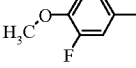
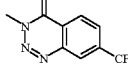
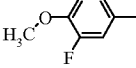
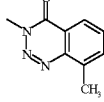
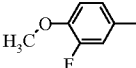
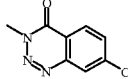
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38		bond	-SO ₂ CH ₃	
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40		bond	-SO ₂ CH ₃	
41		bond	-SO ₂ CH ₃	
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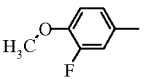
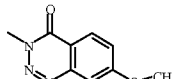
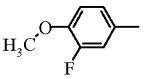
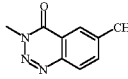
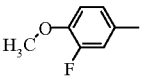
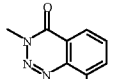
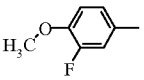
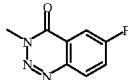
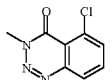
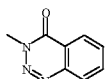
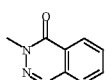
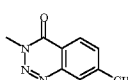
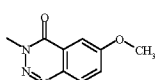
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49		bond	-SO ₂ CH ₃	
50		bond	-SO ₂ CH ₃	
51	-CH(CH ₃) ₂	bond	-SO ₂ CH ₃	
52	-CH(CH ₃) ₂	bond	-SO ₂ CH ₃	
53	-CH(CH ₃) ₂	bond	-SO ₂ CH ₃	
54	-CH ₂ CH ₃	bond	-SO ₂ CH ₃	
55	-CH ₂ CH ₃	bond	-SO ₂ CH ₃	

56	-CH ₂ CH ₃	bond	-SO ₂ CH ₃	
57	-CH ₂ CH ₃	bond	-SO ₂ CH ₃	
58	H	bond	-SO ₂ CH ₃	
59		bond	-SO ₂ CH ₃	
60		bond	-SO ₂ CH ₃	
61		bond	-SO ₂ CH ₃	
62		bond	-SO ₂ CH ₃	
63		bond	-SO ₂ CH ₃	
64		bond	-SO ₂ CH ₃	
65		bond	-SO ₂ CH ₃	
66		bond	-SO ₂ CH ₃	

67	H	COO	-SO ₂ CH ₃	
68		CONH	-SO ₂ CH ₃	
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71		CONH	-SO ₂ CH ₃	
72		CONH	-SO ₂ CH ₃	
73		CONH	-SO ₂ CH ₃	
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75		CONH	-SO ₂ CH ₃	
76		bond	-SO ₂ CH ₃	
77		bond	-SO ₂ CH ₃	

78		bond	-SO ₂ CH ₃	
79		bond	-SO ₂ CH ₃	
80		bond	-SO ₂ CH ₃	
81		bond	-SO ₂ CH ₃	
82		bond	-SO ₂ CH ₃	
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85		bond	-SO ₂ CH ₃	
86		bond	-SO ₂ CH ₃	
87		bond	-SO ₂ CH ₃	
88		bond	-SO ₂ CH ₃	

89		bond	-SO ₂ CH ₃	
90		bond	-SO ₂ CH ₃	
91		bond	-SO ₂ CH ₃	
92		bond	-SO ₂ CH ₃	
93		bond	-SO ₂ CH ₃	
94		bond	-SO ₂ CH ₃	
95		bond	-SO ₂ CH ₃	
96		bond	-SO ₂ CH ₃	
97		bond	-SO ₂ CH ₃	
98		bond	-SO ₂ CH ₃	
99		bond	-SO ₂ CH ₃	

100		bond	-SO ₂ CH ₃	
101		bond	-SO ₂ CH ₃	
102		bond	-SO ₂ CH ₃	
103		bond	-SO ₂ CH ₃	
104	Cl	bond	-SO ₂ CH ₃	
105	Br	bond	-SO ₂ CH ₃	
106	Cl	bond	-SO ₂ CH ₃	
107	Cl	bond	-SO ₂ CH ₃	
108	Cl	bond	-SO ₂ CH ₃	

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

Experimental

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

5 Synthesis of intermediate

Synthesis of 6-methyl-1,2,3-benzotriazin-4(3H)-one

The title compound was prepared following the procedure outlined in *J. Med. Chem.*, **35**(14), p. 2626-2630 (1992).

The following analogues of benzotriazin-4(3H)-one were prepared analogously:

- 10 7-Methoxy-1,2,3-benzotriazin-4(3H)-one
7-(Trifluoromethyl)-1,2,3-benzotriazin-4(3H)-one;
7-Methyl-1,2,3-benzotriazin-4(3H)-one;
6-Methoxy-1,2,3-benzotriazin-4(3H)-one;
5-Chloro-1,2,3-benzotriazin-4(3H)-one;
15 7-Chloro-1,2,3-benzotriazin-4(3H)-one;
5-Methoxy-1,2,3-benzotriazin-4(3H)-one;
5-Fluoro-1,2,3-benzotriazin-4(3H)-one;
8-Methoxy-1,2,3-benzotriazin-4(3H)-one;
6-Fluoro-1,2,3-benzotriazin-4(3H)-one.

20 Synthesis of 5-methyl-1H-isoindole-1,3(2H)-dione

The title compound was prepared following the procedure outline in *Chem. Ber.* **1877**, **10**, 1163.

Synthesis of 4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butanoic acid

- 25 To a solution of γ -aminobutyric acid (20.68 g, 0.199 moles) and phthalic anhydride (29.6 g, 0.199 moles) in toluene (300 mL) was added triethylamine (3 mL, 0.0215 moles) and heated at 110°C for about 18 hours. After completion, the reaction mixture was

allowed to cool to room temperature. The reaction mixture was washed with 1N HCl solution (20 mL) at 40°C and solid was crystallized out from organic layer. The residues was filtered, washed with water and dried under vacuum overnight to get desired product. Yield: 31.64 g

5 LCMS: 234.2 (M+1)

Synthesis of *N*-(4-bromophenyl)methane sulfonamide

To a solution of 4-bromoaniline (100 g, 581 mmoles) in dichloromethane (75 mL) and pyridine (75 mL) was slowly added methanesulphonyl chloride (99 g, 872 mmoles). The reaction mixture was allowed to stir for about one hour at the same temperature.

10 After one hour, dilute hydrochloric acid was added to the reaction mixture to remove pyridine. The organic layer was collected, dried over anhydrous sodium sulphate and evaporated under reduced pressure to obtain a crude product. The crude product was purified on a silica gel column using 60% ethyl acetate: hexane as eluent to afford a desired compound.

15 Yield: 110 g

LCMS: 267.03, 268.97 (M+Na)

Synthesis of *N*-[4-(4-methylphenoxy)phenyl]methane sulfonamide

To a solution of 4-(4-methylphenoxy)aniline (3.5 g, 17.6 mmoles) in pyridine (20 mL) and dichloromethane (20 mL) at 0°C was added methanesulfonyl chloride (2.2 mL, 26.4 mmoles). The reaction mixture was allowed to stir at room temperature for about 2 hours. After completion of reaction, pyridine was evaporated and the reaction mixture was extracted with ethyl acetate. The organic layer was collected, washed with water, dried over anhydrous sodium sulphate and evaporated to get a crude product. The crude product obtained was purified on silica gel column using 25% ethyl acetate: hexane as

25 eluent to get desired compound.

Yield: 3.1 g

The following compound can be prepared accordingly: *N*-(4-Methoxyphenyl) methanesulfonamide.

Synthesis of benzyl 2,4-dihydroxybutanoate

To a solution of α -hydroxylactone (10 g, 0.098 moles) in methanol (50 mL) was added sodium hydroxide (5.88 g, 0.147 moles) in water (10 mL) and allowed to stir at room temperature for about one hour. The reaction mixture was concentrated and taken in
5 *N,N'*-dimethylformamide (40 mL) and benzyl bromide (14 mL, 0.117 moles) was added drop wise. The reaction mixture was again allowed to stir for overnight at room temperature. After completion of reaction, solvent was evaporated under vacuum and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulphate and evaporated under vacuum to
10 obtain a crude product. The crude product was purified on silica gel column using 80% ethyl acetate: hexane as eluent to afford the title compound.

Yield: 10.4 g

LCMS: 211.47 (M+1), 233.5 (M+Na)

Synthesis of *N*-(biphenyl-4-yl)methanesulfonamide

15 To the solution of 4-biphenyl amine (1 g, 0.0059 moles) in dimethylformamide (10 mL) was added potassium carbonate (1.63 g, 0.0118 moles) and stirred for about 10 minutes and then methanesulfonyl chloride (3.64 mL, 0.0472 moles) was added slowly. The reaction mixture was allowed to stir at room temperature for about 30 minutes. After
20 completion, the reaction mixture was extracted with ethyl acetate while washing with water. The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get a crude product which was purified on silica gel column to get desired product.

Yield: 0.75 g

Synthesis of *tert*-butyl 4- {[4-hydroxy-1-oxo-1-(prop-2-en-1-yloxy)butan-2-yl](methylsulfonyl)amino} benzoate

Step a: Preparation of *tert*-butyl 4-nitrobenzoate

To a solution of *p*-nitrophenol (10 g, 59.88 mmol) in *tert*-butanol (100 mL) and tetrahydrofuran (100 mL) were added *N,N*-dimethylaminopyridine (1.4 g, 11.97 mmol) and Boc anhydride (38.4 mL, 179.64 mmol) at room temperature. The reaction mixture was allowed to stir for about 10 hours at room temperature. The temperature was increased slowly to 35°C and reaction mixture was stirred for about 6 hours. After completion, solvent was evaporated under reduced pressure and reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, brine and evaporated under vacuum to get a crude product. The crude product was purified on silica gel column using 20% ethyl acetate: hexane as eluent to get desired compound.

Yield 12 g

Step b: Preparation of *tert*-butyl 4-aminobenzoate

To a solution of compound obtained from Step a (11 g) in tetrahydrofuran (50 mL) and methanol (50 mL) was added 10% Pd/C (3 g) and H₂ was supplied at 60 psi in Parr apparatus for about 2 hours. After completion, reaction mixture was filtered through celite pad and residue was washed with ethyl acetate. The filtrate obtained was concentrated under vacuum to get the desired compound.

Yield: 10 g.

LCMS: 194.47 (M+1)

Step c: Preparation of *tert*-butyl 4-[(methylsulfonyl)amino]benzoate

To an ice cooled solution of compound obtained from Step b (10 g, 51.81 mmol) in pyridine (50 mL) and dichloromethane (50 mL) was added methanesulphonyl chloride (8.86 g, 77.72 mmol). The reaction mixture was allowed to stir for about one hour at same temperature. After one hour, HCl (11 N) solution was added to bring the pH of the reaction mixture to neutral and then extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated under vacuum

to get crude product. The crude product obtained was purified on silica gel column using 50% ethyl acetate: hexane as eluent to get desired product.

Yield: 10 g

LCMS: 293.76 (M+Na)

5 **Step d: Preparation of *tert*-butyl 4-[(methylsulfonyl)(2-oxotetrahydrofuran-3-yl)amino] benzoate**

To an ice cooled solution alpha-hydroxy lactone (1 g, 9.80 mmoles) in tetrahydrofuran (30 mL) were added compound obtained from Step c (2.6 g, 9.80 mmoles) and triphenylphosphine (13.6 g, 14.70 mmoles). The reaction mixture was stirred for
10 about 15 minutes and diisopropylazodicarboxylate (DIAD) (2.9 g, 14.70 mmoles) was added at same temperature. The reaction mixture was allowed to stir for about 2 hours at room temperature. After complete conversion of starting material, solvent was evaporated under vacuum to obtain a crude compound. The crude compound was purified on silica gel column using 30% ethyl acetate: hexane as eluent to get the desired product.

15 Yield: 6 g

LCMS: 354.82 (M).

Step e: Preparation of *N*-[4-(*tert*-butoxycarbonyl)phenyl]-*N*-(methylsulfonyl) homoserine

To an ice-cooled solution of compound obtained from Step d (4 g, 11.26 mmoles)
20 in ethanol (30 mL) and methanol (10 mL) was added sodium hydroxide (0.495 g, 12.39 mmoles) in water (5 mL). The reaction mixture was allowed to stir at same temperature for about 30 minutes. After 30 minutes, solvent was evaporated and reaction mixture was extracted with ethyl acetate while washing with water. The aqueous layer was acidified with aqueous solution of sodium bisulfate and extracted with ethyl acetate. The combined
25 organic layer was dried over anhydrous sodium sulphate and evaporated to get desired compound.

Yield: 3g

Step f: Preparation of *tert*-butyl 4-{{[4-hydroxy-1-oxo-1-(prop-2-en-1-yloxy)butan-2-yl]}(methylsulfonyl)amino}benzoate

To a solution of compound obtained from step e (3 g, 8.04 mmoles) in *N,N*-dimethylformamide (25 mL) were added sodium bicarbonate (1 g, 12.06 mmoles) and allyl bromide (1.07 g, 8.84 mmoles) at room temperature. The reaction mixture was allowed to stir at room temperature for about 12 hours. After completion of reaction, solvent was evaporated and reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated to get crude product. The crude product was purified on silica gel column using 40% ethyl acetate: hexane to get the desired compound.

Yield: 1.4 g.

LCMS: 413.87 (M+1).

Synthesis of prop-2-en-1-yl *N*-(4'-chlorobiphenyl-4-yl)-*N*-(methylsulfonyl)homoserinate**Step a: Preparation of *N*-(4'-chlorobiphenyl-4-yl)methanesulfonamide**

To a solution of *N*-(4-bromophenyl)methanesulfonamide (2 g, 0.008 moles) in *N,N*-dimethylformamide (15 mL) and water (15 mL) were added 4-chlorophenylboronic acid (2.49 g, 0.016 moles), potassium carbonate (3.3 g, 0.024 moles) and tetrakis triphenylphosphine (277 mg, 0.002 moles). The reaction mixture was heated upto 100°C for about 14 hours. After completion, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and evaporated under reduced pressure to obtain a crude product. The crude product was purified on silica gel column using 25% ethyl acetate: hexane as eluent to get title compound.

Yield: 1.8 g

Step b: Preparation of *N*-(4'-chlorobiphenyl-4-yl)-*N*-(2-oxotetrahydrofuran-3-yl)methane sulfonamide

To a compound obtained from step a (10 g, 0.035 moles) in tetrahydrofuran (70 mL) were added α -hydroxy lactone (8.8 g, 0.05 moles) and triphenylphosphine (13.9 g, 0.05 moles) at 0°C. The reaction mixture was allowed to stir for about 10 minutes and

diisopropylazodicarboxylate DIAD (10.7 mL, 0.05 moles) was added to it at 0°C. The reaction mixture was again stirred for about 2 hours at room temperature. After completion, solvent was evaporated to obtain a crude product which was purified on silica gel column using 20% ethyl acetate: hexane as eluent to get the desired product.

5 Yield: 10 g

LCMS: 365.71 (M+1)

Step c: Preparation of *N*-(4'-chlorobiphenyl-4-yl)-*N*-(methylsulfonyl)homoserine

To a solution of compound obtained from step b (10 g, 0.0273 moles) in ethanol: water mixture (10:1) (100ml: 10mL) at 0°C was added sodium hydroxide (1.2g, 0.037
10 moles) in water (2 mL). The reaction mixture was allowed to stir for about 2 hours at 0°C. After 2 hours, solvent was evaporated under reduced pressure and residues obtained were taken in water and extracted with ethyl acetate. The aqueous layer obtained was acidified by aqueous solution of sodium bisulphite and then extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over anhydrous sodium
15 sulphate and evaporated under reduced pressure to get title compound.

Yield:10g

Step d: Preparation of prop-2-en-1-yl *N*-(4'-chlorobiphenyl-4-yl)-*N*-(methylsulfonyl)homoserinate

To a compound obtained from step c (10 g, 0.026 moles) in ethanol: water: DMF
20 mixture (60 mL: 6 mL: 60 mL) at room temperature was added sodium bicarbonate (2.1 g, 0.026 moles). The reaction mixture was allowed to stir at room temperature for about 30 minutes. After 30 minutes, the reaction mixture was concentrated under reduced pressure and treated with toluene. The toluene was evaporated and residue so obtained was taken in dry *N,N*-dimethylformamide (20 mL) at room temperature. To this reaction mixture
25 was slowly added allyl bromide (3.4 g, 0.028 moles) and stirred for overnight at room temperature. After completion, water was added to the reaction mixture and extracted with ethyl acetate. The organic layer was collected, washed with water, brine, dried over anhydrous sodium sulphate solution and evaporated under reduced pressure to obtain a crude product. The crude product was purified on silica gel column using 30% ethyl
30 acetate: hexane as eluent to get title compound.

Yield: 5.2 g

Example 1: Synthesis of 2-[formyl(4'-methylbiphenyl-4-yl)amino]-4-(6-methyl-4-oxo-1,2,3-benzo triazin-3(4H)-yl)butanoic acid (Compound no. 1) (Scheme I, Path A)

Step a: Preparation of 4-methyl-4'-nitrobiphenyl

- 5 To a solution of 4-bromo-nitrobenzene (5 g, 0.0247 moles) in *N,N*-dimethylformamide (25 mL) were added potassium carbonate (10.2 g, 0.0741 moles) and 4-methylboronic acid (4 g, 0.0297 moles) under argon atmosphere and heated at 100°C for about 3 hours. After completion, reaction mixture was quenched by addition of water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous
- 10 sodium sulphate and concentrated under vacuum to get a crude product which was purified on silica gel column using 15% ethyl acetate: hexane as eluent to obtain desired compound. Yield: 5.3 g

LCMS: 236.07 (M+23)

Step b: Preparation of 4'-methylbiphenyl-4-amine

- 15 To a solution of compound obtained from Step a (5.2 g, 0.0244 moles) in tetrahydrofuran (25 mL) and methanol (25 mL) was added 10% Pd/C (5.2 g) under vacuum and then hydrogen gas was supplied by balloon. The reaction mixture was allowed to stir for about 2 hours at room temperature. After completion, reaction mixture was filtered through celite pad and filtrate was concentrated under vacuum to obtained title
- 20 compound. Yield: 5 g

LCMS: 184.01 (M+1)

Step c: Preparation of 3-[(4'-methylbiphenyl-4-yl)amino]dihydrofuran-2(3H)-one

- To alpha-bromo lactone (3 g, 0.018 moles) was added compound obtained from Step b (4.9 g, 0.027 moles) and heated to 100°C to 110°C for about 3 hours. After
- 25 completion consumption of starting material, reaction mixture was evaporated under reduced pressure and purified on silica gel column using 20% ethyl acetate: hexane as eluent to get desired compound.

Yield: 4 g

LCMS: 268.11 (M+1)

Step d: Preparation of *N*-(4'-methylbiphenyl-4-yl)-*N*-(2-oxotetrahydrofuran-3-yl)formamide

To a solution of compound obtained from Step c (2 g, 0.00749 moles) in toluene (30 mL) was added formic acid (0.4 g, 0.0089 moles) and reflux for about 9 hours. After
5 complete, reaction mixture was evaporated under reduced pressure to get a crude product which was purified over silica gel column using 15% ethyl acetate: hexane as eluent to obtain title compound.

Yield: 1.9 g

LCMS: 295.94 (M+1)

10 Step e: Preparation of methyl *N*-formyl-*N*-(4'-methylbiphenyl-4-yl)homoserinate

To a solution of compound obtained from Step d (1.9 g, 0.0064 moles) in *N,N*-dimethylformamide (4 mL) and water (1 mL) was added sodium hydroxide (0.309 g, 0.0077 moles) and stirred for about 30 minutes at room temperature. After 30 minutes sodium bicarbonate (0.624 g, 0.0074 moles), 18-crown-6 (0.168 g, 0.00064 moles) and
15 methyl iodide (1.3 g, 0.0914 moles) was added to the reaction mixture and again stirred for overnight at room temperature. After completion, reaction mixture was quenched by addition of water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to get crude product which was purified on silica gel column using 8% ethyl acetate: hexane as eluent.

20 Yield: 2.1 g

Step f: Preparation of methyl 2-[formyl(4'-methylbiphenyl-4-yl)amino]-4-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoate

To a compound obtained from step e (0.3 g, 0.0009 moles) in tetrahydrofuran (5 mL) were added 6-methylbenzotriazinone (0.177 g, 0.0011 moles) and triphenyl
25 phosphine (0.353 g, 0.0013 moles) under argon atmosphere. The reaction mixture was allowed to cool to 0°C and to it was added diisopropylazodicarboxylate (0.272 g, 0.0013 moles) and stirred for about 30 minutes at room temperature. After completion, reaction mixture was quenched by addition of water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and evaporated under reduced

pressure to get crude compound which was purified on silica gel column using 7% ethyl acetate: hexane as eluent to get desired product.

Yield: 0.15 g

LCMS: 470 (M+1)

5 **Step g: Preparation of 2-[formyl(4'-methylbiphenyl-4-yl)amino]-4-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid**

To a compound obtained from Step f (0.15 g, 0.0003 moles) in tetrahydrofuran (5 mL) and methanol (5 mL) was added solution of lithium hydroxide (0.018 g, 0.0004 moles) in water (1 mL). The reaction mixture was allowed to stir for about one hour at room temperature. After completion, the reaction mixture was acidified with sodium bisulphate solution (pH~2) and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated under vacuum to get crude compound which was purified by preparative TLC using 10% methanol: dichloromethane as mobile phase. Yield: 0.030 g

15 LCMS-455.35 (M-1)

¹H NMR (400 MHz) δ 8.40 (1H, s), 8.03-8.05 (1H, m), 7.87 (2H, m), 7.61-7.63 (2H, m), 7.52-7.54 (2H, m), 7.40-7.42 (2H, m), 7.24-7.26 (2H, m), 4.84 (1H, m), 4.39 (2H, m), 2.51 (2H, m), 2.28-2.33 (6H, m).

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

20 4-(7-Chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)-2-[formyl(4'-methylbiphenyl-4-yl)amino]butanoic acid (Compound no. 2);

LCMS-447.23 (M-28)

2-[(4'-Ethylbiphenyl-4-yl)(formyl)amino]-4-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 3).

25 LCMS-469.34 (M-1)

Example 2: Synthesis of O-[(4-fluorophenyl)carbamoyl]-N-formyl-N-(4'-methylbiphenyl-4-yl)homoserine (Compound no. 4) (Scheme I, Path B)

Step a: Preparation of methyl O-[(4-fluorophenyl)carbamoyl]-N-formyl-N-(4'-methylbiphenyl-4-yl)homoserinate

To a solution of methyl *N*-formyl-*N*-(4'-methylbiphenyl-4-yl)homoserinate (0.3 g, 0.0009 moles) in tetrahydrofuran (5 mL) was added triethylamine (0.272 g, 0.0027 moles) and 1-fluoro-4-isocyanatobenzene (0.147 g, 0.0010 moles) under argon atmosphere at room temperature. The reaction mixture was allowed to stir for about 2 hours at room temperature. After completion, the reaction mixture was quenched by addition of water and extracted with ethyl acetate. The organic layer obtained was dried over anhydrous sodium sulphate and concentrated under reduced pressure to get crude compound. The crude compound was purified on silica gel column using 15% ethyl acetate: hexane as eluent to obtain desired product.

Yield: 0.15 g

LCMS: 464.93 (M+1)

Step b: Preparation of *O*-(4-fluorophenyl)carbamoyl-*N*-formyl-*N*-(4'-methylbiphenyl-4-yl)homoserine

To a compound obtained from Step a (0.15 g, 0.0003 moles) in tetrahydrofuran (5 mL) and methanol (5 mL) was added solution of lithium hydroxide (0.018 g, 0.0004 moles) in water and stirred for about one hour at room temperature. After completion, the reaction mixture was acidified with sodium bisulfite (pH~2) and extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulphate and concentrated under vacuum to get crude compound which was purified by preparative TLC using 10% methanol: dichloromethane as mobile phase to obtain a desired product.

Yield: 0.03 g

LCMS-449.28 (M-1)

¹H NMR (400 MHz)-δ 9.63 (1H, s), 8.45(1H, s), 7.67-7.69 (2H, m), 7.53-7.55 (4H, m), 7.26-7.28 (2H, m), 7.12-7.14 (4H, m), 4.89-4.93 (1H, m), 4.06-4.10 (2H, s), 2.45 (2H, m), 2.41-2.43 (3H, m).

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

N-Formyl-*N*-(4'-methylbiphenyl-4-yl)-*O*-(4-methylphenyl)carbamoyl]homoserine (Compound no. 5);

LCMS-417.27 (M-28)

- O*-[(3,4-Dichlorophenyl)carbamoyl]-*N*-formyl-*N*-(4'-methylbiphenyl-4-yl)homoserine (Compound no. 6);
LCMS-501.15 (M)
- 5 *N*-(4'-Ethylbiphenyl-4-yl)-*N*-formyl-*O*-{[4-(propan-2-yl)phenyl]carbamoyl}homoserine (Compound no. 7);
LCMS-487.35 (M-1)
- N*-(4'-Ethylbiphenyl-4-yl)-*O*-[(3-fluorophenyl)carbamoyl]-*N*-formylhomoserine (Compound no. 8);
LCMS-463.33 (M-1)
- 10 *O*-[(2,4-Difluorophenyl)carbamoyl]-*N*-(4'-ethylbiphenyl-4-yl)-*N*-formylhomoserine (Compound no. 9);
LCMS-481.32 (M-1)
- N*-(4'-Ethylbiphenyl-4-yl)-*O*-[(2-fluorophenyl)carbamoyl]-*N*-formylhomoserine (Compound no. 10);
15 LCMS-463.33 (M-1)
- N*-(4'-Ethylbiphenyl-4-yl)-*N*-formyl-*O*-{[4-(trifluoromethyl)phenyl]carbamoyl}homoserine (Compound no. 11);
LCMS-513.32 (M-1)
- N*-(4'-Ethylbiphenyl-4-yl)-*N*-formyl-*O*-[(2-methylphenyl)carbamoyl]homoserine (Compound no. 12);
20 LCMS-459.33 (M-1)
- N*-(4'-Ethylbiphenyl-4-yl)-*O*-[(4-ethylphenyl)carbamoyl]-*N*-formylhomoserine (Compound no. 13);
LCMS-473.30 (M-1)
- N*-(4'-Ethylbiphenyl-4-yl)-*N*-formyl-*O*-[(4-methoxyphenyl)carbamoyl]homoserine (Compound no. 14);
25 LCMS-475.35 (M-1)
- O*-[(2,6-Dichlorophenyl)carbamoyl]-*N*-(4'-ethylbiphenyl-4-yl)-*N*-formylhomoserine (Compound no. 15);
30 LCMS-515.29 (M-1)

Example 3: Synthesis of 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(4'-methoxybiphenyl-4-yl) (methyl) amino]butanoic acid (Compound no. 18); (Scheme II, Path C)

Step a: Preparation of 2-bromo-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoic acid
35 **acid**

To a solution of 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoic acid (11.7 g, 0.050 moles) in carbon tetrachloride (60 mL) was added red phosphorous (5.2 g, 0.167 mole) and heated at about 60°C. To this reaction mixture, bromine (40 mL, 0.792 mole) was added slowly over a period of about one hour and again heated up to 60°C for about 8 hours then cooled to 0°C. After that, water (50 mL) was added to the reaction mixture. The reaction mixture was solidified and extracted with ethyl acetate. The organic layer was washed with aqueous solution of sodium bicarbonate. The obtained aqueous layer was acidified (pH~2) using aqueous solution of hydrochloric acid and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulphate and evaporated to get desired product.

Yield: 10.8 g

LCMS: 313.4 (M+1)

Step b: Preparation of *tert*-butyl 2-bromo-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoate

To a solution of compound obtained from Step a (180 mg, 0.576 mmoles) in tetrahydrofuran (5 mL) was added Boc anhydride (1 mL, 0.461 mmoles) and *N,N'*-dimethylaminopyridine (7 mg, 0.057 mmoles). The reaction mixture was allowed to stir at room temperature for about 18 hours. After completion of reaction, solvent was azeotropically distilled using toluene and ethyl acetate to obtain a crude product. The crude product was purified on silica gel column using 20% ethyl acetate: hexane as eluent to get the desired product.

Yield: 180 mg

Step c: Preparation of *tert*-butyl 2-[(4-bromophenyl)(methylsulfonyl)amino]-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoate

To a solution of *N*-(4-bromophenyl)methanesulfonamide (1 g, 0.04 moles) in acetonitrile (20 mL) was added potassium carbonate (0.276 g, 0.002 moles) at room temperature. The reaction mixture was allowed to stir for about 15 minutes and then compound obtained from Step b (1.472 g, 0.004 moles) was added. The reaction mixture was heated at about 80°C for about 56 hours. After completion, the reaction mixture was concentrated and residue obtained was taken in ethyl acetate. The organic layer was

washed with water, brine, dried over anhydrous sodium sulphate and evaporated under reduced pressure to get a crude product. The crude product was purified by preparative TLC using 30% ethyl acetate: hexane as mobile phase to get the desired product.

Yield: 1.7 g

5 **LCMS: 555.9 (M+NH₄⁺)**

Step d: Preparation of *tert*-butyl 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(4'-methoxy biphenyl-4-yl)(methylsulfonyl)amino]butanoate

To a solution of a compound obtained from Step c (0.205 g, 0.381 moles) in dry *N,N*-dimethylformamide (5 mL) were added tetrakis(triphenyl)phosphine (8 mg, 0.007
10 moles), potassium carbonate (0.21g, 1.527 moles) and 4-methoxyphenylboronic acid (0.191 g, 1.259 moles) at room temperature. The reaction mixture was heated to 105°C for about 4.5 hours. After 4.5 hours, it was allowed to cool to room temperature and *N,N*-dimethylformamide was evaporated and residues obtained were taken in ethyl acetate. The organic layer was washed with water, brine and evaporated under vacuum to get crude
15 product which was purified by preparative TLC using 30% ethyl acetate: hexane as mobile phase to get desired product.

Yield: 0.161 g

LCMS: 587.1 (M+Na)

20 **Step e: Preparation of 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]butanoic acid**

To a solution of compound obtained from step d (0.144 g, 0.00025 moles) in dichloromethane (5 mL) was added trifluoroacetic acid (1.2 mL) at 0°C. The reaction mixture was allowed to stir for about 3 hours at 0°C and then at room temperature for about 4 hours. After completion, the reaction mixture was extracted with dichloromethane,
25 washed with water and brine. The organic layer was evaporated under reduced pressure to get a crude product which was purified on silica gel column using 50% ethyl acetate: hexane as eluent to get desired product.

Yield: 0.113 g

LCMS: 509.1 (M+1)

¹H NMR (CDCl₃, 400 MHz) δ : 7.84 (2H, m), 7.71 (2H, m), 7.62 (4H, m), 7.51 (2H, d, J = 8 Hz), 6.97 (2H, d, J = 8 Hz), 5.04 (1H, m), 4.12 (2H, m), 3.85 (3H, s), 3.13 (3H, s), 2.36 (1H, m), 1.95 (1H, m).

5 Example 4: Synthesis of 2-[biphenyl-4-yl(methylsulfonyl)amino]-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butanoic acid (Compound no. 16) (Scheme II, Path D)

Step a: Preparation of *tert*-butyl 2-[biphenyl-4-yl(methylsulfonyl)amino]-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butanoate

To a solution of *tert*-butyl 2-bromo-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butanoate (300 mg, 0.815 mmol) in *N,N'*-dimethylformamide (5 mL) were added *N*-(biphenyl-4-yl)methanesulfonamide (161 mg, 0.652 mmol) and potassium carbonate (112 mg, 0.815 mmol). The reaction mixture was heated at 80°C for about 7.5 hours. After completion, reaction mixture was allowed to cool to room temperature and water was added to it. The reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulphate and
10 evaporated under reduced pressure to obtain a crude product. The crude product was purified on silica gel column using 40% ethyl acetate: hexane as eluent to get desired product.
15

Yield: 152 mg

LCMS: 552.1 (M+NH₄⁺)

20 **Step b: Preparation of 2-[biphenyl-4-yl(methylsulfonyl)amino]-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butanoic acid**

To an ice-cooled solution of compound obtained from Step a (152 mg, 0.0002 mol) in dichloromethane (10 mL) was added trifluoroacetic acid (0.7 mL) and stirred for about 2.5 hrs at room temperature. After completion of reaction, the solvent was
25 evaporated and the reaction mixture was taken in dichloromethane and washed with water. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated to get crude product. The crude product was purified on silica gel column using 40% ethyl acetate: hexane as eluent to get desired product.

Yield: 41.6 mg

LCMS: 479.0 (M+1)

¹H NMR (MeOH-d₆, 400 MHz): δ 7.85 (4H, m), 7.78 (4H, m), 7.63 (2H, m), 7.45 (2H, m), 7.36 (1H, m), 4.88 (1H, m), 3.86 (2H, m), 3.15 (3H, s), 2.36 (1H, m), 1.89 (1H, m).

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

- 5 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-{[4-(6-methoxypyridin-3-yl)phenyl](methylsulfonyl)amino} butanoic acid (Compound no. 17);

LCMS: 510.1(M+1)

Example 5: Synthesis of 2-{[4-(6-methoxypyridin-3-yl)phenyl](methylsulfonyl)amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 19) (when R_k is

- 10 halogen) (Scheme III, Path E)

Step a: Preparation of *N*-(4-bromophenyl)-*N*-(2-oxotetrahydrofuran-3-yl)methanesulfonamide

- To a solution of α-hydroxy lactone (673 mg, 0.0072 moles) at 0°C were added *N*-(4-bromophenyl)methanesulfonamide (1.5 g, 0.006 moles) and triphenylphosphine (2.35 g, 15 0.009 moles). The reaction mixture was allowed to stir for about 15 minutes at 0°C and diisopropylazodicarboxylate (1.8 g, 0.0009 moles) was added. The reaction mixture was again stirred for about 30 minutes at 0°C. After completion, the reaction mixture was concentrated to get a crude product which was purified on silica gel column using 40% ethyl acetate: hexane as eluent to get the desired compound.

- 20 Yield: 920 mg

LCMS: 351.18 and 353.12 (M+NH₄⁺)

Step b: Preparation of sodium 2-[(4-bromophenyl)(methylsulfonyl)amino]-4-hydroxy butanoate

- To a solution of compound obtained from Step a (1.5g, 0.0044 moles) in methanol 25 (10 mL) was added sodium hydroxide (79 mg, 0.0044 moles) and stirred for about one hour at room temperature. After completion, the reaction mixture was concentrated and ethyl acetate was added and decanted to get the desired product.

Yield: 850 mg.

Step c: Preparation of benzyl *N*-(4-bromophenyl)-*N*-(methylsulfonyl)homoserinate

To a solution of compound obtained from Step b (800 mg, 0.0022 moles) in *N,N*-dimethylformamide (5 mL) at 0°C was added benzyl bromide (388 mg, 0.0022 moles).

The reaction mixture was allowed to stir for overnight at room temperature. After

- 5 completion, reaction mixture was extracted with ethyl acetate while washing with water. The combined organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product. The crude product so obtain was purified on silica gel column using 70% ethyl acetate: hexane to get desired product.

Yield: 850 mg.

10 **Step d: Preparation of benzyl *N*-(4-bromophenyl)-*O*-[*tert*-butyl(dimethyl)silyl]-*N*-(methylsulfonyl)homoserinate**

To a solution of compound obtained from Step c (800 mg, 0.0018 moles) in *N,N*-dimethylformamide (8 mL) were added *tert*-butyldimethylsilylchloride (325 mg, 0.0021 moles) and imidazole (369 mg, 0.0054 moles). The reaction mixture was allowed to stir

15 for about one hour at room temperature. After completion, reaction mixture was quenched by addition of water and extracted with ethyl acetate. The organic layer was collected, dried over anhydrous sodium sulphate and evaporated under reduced pressure to afford the desired product.

Yield: 1.2 g

- 20 LCMS: 556.77 and 558.78 (M+1)

Step e: Preparation of benzyl *O*-[*tert*-butyl(dimethyl)silyl]-*N*-[4-(6-methoxypyridin-3-yl)phenyl]-*N*-(methylsulfonyl)homoserinate

To a solution of compound obtained from Step d (1.7 g, 0.0045 moles) in *N,N*-dimethylformamide (20 mL) were added 5-methoxypyridineboronic acid (929 mg, 0.0061 moles), tetrakis triphenylphosphine palladium (0) (176 mg, 0.0008 moles) and potassium carbonate (1.26 g, 0.0091 moles). After completion of addition, reaction mixture was

25 heated up to 110°C for about 3 hours. After 3 hours, solvent was evaporated and reaction mixture was extracted with ethyl acetate while washing with water. The combined organic layer was collected, dried over anhydrous sodium sulphate and evaporated under

reduced pressure to get a crude product. The crude product obtained was purified on silica gel column using 40% ethyl acetate to get desired product.

Yield: 1.3 g

Step f: Preparation of benzyl *N*-[4-(6-methoxypyridin-3-yl)phenyl]-*N*-(methylsulfonyl) homo serinate

To a solution of compound obtained from Step e (1.1 g, 0.0019 moles) in dichloromethane (20 mL) was added boron trifluoride etherate BF₃.OEt (1.1 g, 0.0095 moles) slowly at room temperature. The reaction mixture was allowed to stir at room temperature for about one hour. After completion, reaction mixture was quenched with saturated solution of sodium bicarbonate and extracted with dichloromethane. The organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated to get crude product. The crude product was purified on silica gel column using 40% ethyl acetate: hexane as eluent to get desired product.

Yield: 750 mg

LCMS: 471.30 (M+1)

Step g: Preparation of benzyl 2-{[4-(6-methoxypyridin-3-yl)phenyl](methylsulfonyl)amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoate

To a solution of compound obtained from Step f (250 mg, 0.531 mmoles) in tetrahydrofuran (15 mL) at 0°C were added benzotriazinone (78 mg, 0.531 mmoles) and triphenylphosphine (278 mg, 1.063 mmoles). The reaction mixture was allowed to stir for about 15 minutes at 0°C and diisopropylazodicarboxylate (161 mg, 0.797 mmoles) was added at same temperature. The reaction mixture was again stirred for about one hour at same temperature. After completion of reaction, solvent was evaporated under reduced pressure to obtain a crude product. The crude product was purified on silica gel column using 40% ethyl acetate: hexane to get desired product.

Yield: 200 mg.

LCMS: 600.88 (M+1)

Step h: Preparation of 2-[[4-(6-methoxypyridin-3-yl)phenyl](methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid

To a solution compound obtained from Step g (200 mg) in tetrahydrofuran (10 mL) was added 10% Pd/C (200 mg) and hydrogen was supplied at 55 psi in Parr apparatus for about 8 hours at room temperature. After completion, reaction mixture was filtered through celite pad and residue was washed with 20% methanol: dichloromethane. The filtrate was concentrated to get solid material which was treated with ethyl acetate. The ethyl acetate layer was decanted to get desired product.

Yield: 18 mg

LCMS: 510.70 (M+1)

¹H NMR (DMSO-d₆, 400 MHz) δ: 8.52 (1H, s), 8.25 (1H, d, *J* = 8 Hz), 8.18 (1H, d, *J* = 8 Hz), 8.05 (2H, m), 7.92 (1H, m), 7.76 (2H, d, *J* = 8 Hz), 7.66 (2H, d, *J* = 8 Hz), 6.92 (1H, d, *J* = 8 Hz), 4.48 (3H, m), 3.90 (3H, s), 3.29 (3H, s), 2.3 (1H, m), 1.90 (1H, m).

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

4-(7-Methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)-2-[[4-(6-methoxypyridin-3-yl)phenyl](methylsulfonyl)amino]butanoic acid (Compound no. 20);

LCMS: 540.71 (M+1)

2-[[4-(6-Methoxypyridin-3-yl)phenyl](methylsulfonyl)amino]-4-[4-oxo-7-(trifluoro methyl)-1,2,3-benzotriazin-3(4H)-yl]butanoic acid (Compound no. 21);

LCMS: 578.74 (M+1)

Example 6: Synthesis of 2-[(4-methoxyphenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 32) (Scheme III, Path F)

Step a: Preparation of benzyl 2-[(4-methoxyphenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoate

To a solution of benzyl *N*-(4-methoxyphenyl)-*N*-(methylsulfonyl)homoserinate (200 mg, 0.508 moles) in tetrahydrofuran (15 mL) were added triphenylphosphine (200 mg, 0.763 moles) and benzotriazinone (82 mg, 0.550 moles) at 0°C. The reaction mixture was stirred for about 15 minutes and diisopropylazodicarboxylate (154 mg, 0.763 moles) was added to it at 0°C. The reaction mixture was again stirred for about 2 hours at room temperature. After completion, solvent was evaporated to get a crude product which was

purified on silica gel column using 30% ethyl acetate: hexane as eluent to get desired compound.

Yield: 180 mg

Step b: Preparation of 2-[(4-methoxyphenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid

To a compound obtained from Step a (180 mg) in tetrahydrofuran (10 mL) and methanol (10 mL) was added 10% Pd/C (60 mg) and hydrogen gas was supplied on Parr apparatus at 50 psi for about one hour at room temperature. After one hour, the reaction mixture was filtered through celite pad and residue obtained was washed with 10% methanol: dichloromethane. The filtrate was concentrated under reduced pressure to get desired compound.

Yield: 24 mg

LCMS: 433.69 (M+1)

¹H NMR (MeOD, 400 MHz): δ 8.31 (1H, d, J = 8 Hz), 8.14 (1H, d, J = 8 Hz), 8.03 (1H, m), 7.88 (1H, m), 7.58 (2H, d, J = 8 Hz), 6.92 (2H, d, J = 8 Hz), 4.92 (1H, m), 4.57-4.67 (2H, m), 3.79 (3H, s), 3.14 (3H, s), 2.48 (1H, m), 2.02 (1H, m).

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

- 4-(6-Methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)-2-{[4-(4-methylphenoxy)phenyl](methylsulfonyl)amino}butanoic acid (Compound no. 23);
LCMS: 539.84 (M+1)
- 4-(7-Methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)-2-{[4-(4-methylphenoxy)phenyl](methylsulfonyl)amino}butanoic acid (Compound no. 24);
LCMS: 523.78 (M+1)
- 2-{[4-(4-Methylphenoxy)phenyl](methylsulfonyl)amino}-4-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4H)-yl]butanoic acid (Compound no. 25);
LCMS: 572.86 (M+1)
- 2-{[4-(4-Methylphenoxy)phenyl](methylsulfonyl)amino}-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 26);
LCMS: 509.74 (M+1)
- 4-(7-Methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)-2-[(4-methoxyphenyl)(methylsulfonyl)amino]butanoic acid (Compound no. 33);
LCMS: 463.79 (M+1)

- 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(4-methoxyphenyl)(methylsulfonyl)amino]butanoic acid (Compound no. 34);
LCMS: 433.63 (M+1)
- 5 2-[(4-Methoxyphenyl)(methylsulfonyl)amino]-4-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoic acid(Compound no. 35);
LCMS: 469.70 (M+1)
- 4-(7-Methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-{[4-(4-methylphenoxy)phenyl] (methylsulfonyl)amino} butanoic acid (Compound no. 36);
LCMS: 539.84 (M+1)
- 10 4-(5-Methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-{[4-(4-methylphenoxy)phenyl](methylsulfonyl)amino} butanoic acid (Compound no. 37);
LCMS: 523.85 (M+1)
- 2-[(Methylsulfonyl)(phenyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 58);
- 15 LCMS: 402.85 (M+1)
- 4-(5-Chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-[(4-chlorophenyl)(methylsulfonyl)amino]butanoic acid (Compound no. 104);
LCMS: 473.67 (M+1)
- 2-[(4-Bromophenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 105);
- 20 LCMS: 481.54 and 483.51 (M+1)
- 2-[(4-Chlorophenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 106);
LCMS: 437.33 (M+1)
- 25 2-[(4-Chlorophenyl)(methylsulfonyl)amino]-4-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 107);
LCMS: 451.70 (M+1)
- 2-[(4-Chlorophenyl)(methylsulfonyl)amino]-4-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 108);
- 30 LCMS: 467.75 (M+1)

Example 7: Synthesis of 2-[(4'-chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoic acid (Compound no. 59) (Scheme III, Path G)

- Step a: Preparation of prop-2-en-1-yl 2-[(4'-chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoate**
- 35

To a solution of hydroxyl derivative (0.250 g, 0.591 moles) in tetrahydrofuran (10 mL) were added triphenylphosphine (0.232 g, 0.88 moles) and 4-methyl phthalimide (0.104 g, 0.65 moles) at 0°C. The reaction mixture was stirred for about 15 minutes and diisopropylazodicarboxylate (0.179 g, 0.0.88moles) was added to it at 0°C. The reaction mixture was again stirred for about 2 hours at room temperature. After completion, solvent was evaporated to get a crude product which was purified on silica gel column using 30% ethyl acetate: hexane as eluent to get desired compound.

Yield: 0.25 g.

Step b: Preparation of 2-[(4'-chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoic acid

To a compound obtained from Step a (250 mg, 0.441 moles) in acetonitrile (10 mL) at 0°C was added tetrakis triphenylphosphine (51 mg, 0.044 moles) and morpholine (384 mg, 4.4 moles). The reaction mixture was allowed to stir for about 3 hours at 0°C. After 3 hours, the reaction mixture was diluted by addition of water and extracted with ethyl acetate. The aqueous layer obtained was acidified with sodium bisulphite and extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and evaporated under reduced pressure to get a crude product. The crude product was purified on preparative TLC using 10% methanol: dichloromethane as mobile phase to get desired product.

Yield: 35 mg

LCMS: 526.84 (M+1)

¹H NMR (MeOH-d₆, 400 MHz) δ: 7.78 (2H, d, *J* = 8 Hz), 7.70 (1H, d, *J* = 4Hz), 7.61 (6H, m), 7.43 (2H, m), 4.73 (1H, m), 3.72-3.90 (2H, m), 3.20 (3H, s), 2.48 (3H, s), 2.31 (1H, m), 1.77 (1H, m).

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

2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 60);

LCMS: 546.66 (M)

2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(7-chloro-4-oxo-1,2,3-benzotriazin-3 (4*H*)-yl)butanoic acid (Compound no. 61);

LCMS: 546.73 and 548.68 (M+1)

2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 62);

LCMS: 526.70 and 528.72 (M+1)

- 5 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]butanoic acid (Compound no. 63);

LCMS: 580.74 (M+1)

2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 64);

- 10 LCMS: 542.76 (M+1)

2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 65);

LCMS: 530.73 (M+1)

- 15 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(1-methyl-2,4-dioxo-1,4-dihydro quinazolin-3(2*H*)-yl)butanoic acid (Compound no. 66);

LCMS: 543.6 (M+1)

Example 8: Synthesis of 2-[(4-[(4-methylphenyl)carbamoyl]phenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 68) Scheme III, Path H)

- 20 **Step a: Preparation of *tert*-butyl 4-[(methylsulfonyl)[1-oxo-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-1-(prop-2-en-1-yloxy)butan-2-yl]amino]benzoate**

To a solution of hydroxyl derivative (1.4 g, 3.389 mmoles) in tetrahydrofuran (20 mL) at 0°C were added triphenylphosphine (1.77g, 6.779 mmole) and 1,2,3-benzotriazin-4(3*H*)-one (0.498 g, 3.389 mmole) after 5 minutes at the same temperature

- 25 diisopropylazodicarboxylate (1.027 g, 5.084 mmole) was added. Then, the reaction mixture was stirred for 30 minutes at the same temperature. Solvent was evaporated and purification was performed on silica gel 60-120 mesh column using 40% EtOAc:Hexane as eluent to get 3 gm of product.

LCMS: 542.83 (M+1)

- 30 **Step b: Preparation of 4-[(methylsulfonyl)[1-oxo-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-1-(prop-2-en-1-yloxy)butan-2-yl]amino]benzoic acid**

To a solution of compound obtained from Step a (3 g, 5.535 mmoles) in dichloromethane (30 mL) was added trifluoroacetic acid (6 mL, 28.782 mmol) at room

temperature. The reaction mixture was allowed to stir for about 2 hours at the same temperature. After 2 hours, the solvent was evaporated and the reaction mixture was neutralized by aqueous solution of sodium bicarbonate. The reaction mixture was extracted with ethyl acetate, dried over anhydrous sodium sulphate and evaporated under vacuum to get desired product.

Yield: 1 g

LCMS: 486.78 (M+1)

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

4- {(Methylsulfonyl)[1-oxo-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-1-(prop-2-en-1-yloxy)butan-2-yl]amino} benzoic acid (Compound no. 67);

LCMS: 486.78 (M+1)

Step c: Preparation of prop-2-en-1-yl 2-[[4-[(4-methylphenyl)carbamoyl]phenyl](methyl sulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoate

To an ice-cooled solution of compound obtained from Step b (400 mg, 0.823 mmols) in *N, N'*-dimethylformamide (20 mL) were added *p*-toluidine (88 mg, 0.823 mmols), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (236 mg, 1.234 mmols), *N, N'*-dimethylaminopyridine (20 mg, 0.164 mmols) and hydroxybenzotriazole (111 mg, 0.823 mmols). The reaction mixture was allowed to stir at room temperature for 12 hours. After completion, the solvent was evaporated and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated under vacuum to get crude product. The crude product obtained was purified on silica gel column using 80% ethyl acetate: hexane as eluent to get the desired compound.

Yield: 520 mg

Step d: Preparation of 2-[[4-[(4-methylphenyl)carbamoyl]phenyl](methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid

To an ice-cooled solution of compound obtained from Step c (520 mg, 0.904 mmols) in acetonitrile (25 mL) were added tetrakis triphenylphosphine palladium (0) (208 mg, 0.180 mmols) and morpholine (786 mg, 9.043 mmols). The reaction mixture was allowed to stir at same temperature for about 30 minutes. After 30 minutes, the

solvent was evaporated and the reaction mixture was acidified using aqueous solution of sodium bisulphate and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated to get crude product. The crude product was purified on preparative TLC using 10% methanol: dichloromethane as mobile phase to get desired compound.

Yield: 250 mg.

LCMS: 535.84 (M+1), 557.82 (M+Na)

¹H NMR (DMSO-d₆, 400 MHz): δ 10.3 (1H, s), 8.25 (2H, m), 8.20 (1H, m), 8.06-8.10 (3H, m), 7.96 (4H, m), 7.15 (2H, d, *J* = 8 Hz), 4.78 (1H, m), 4.51 (2H, m), 3.16 (3H, s), 2.42 (1H, m), 2.20 (3H, s), 1.95 (1H, m).

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

2-[{4-[(4-Chlorophenyl)carbamoyl]phenyl}(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 69);

LCMS: 555.74 and 557.72 (M+1)

15 2-[(Methylsulfonyl)[4-(phenylcarbamoyl)phenyl]amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 70);

LCMS: 521.80 (M+1)

2-[{4-[(3-Fluorophenyl)carbamoyl]phenyl}(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 71);

20 LCMS: 539.74 (M+1)

2-[(Methylsulfonyl)(4-{{4-(propan-2-yl)phenyl}carbamoyl}phenyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 72);

LCMS: 563.80 (M+1)

25 2-[{4-[(4-Methoxyphenyl)carbamoyl]phenyl}(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 73);

LCMS: 551.77 (M+1)

2-[{4-[(4-Fluorophenyl)carbamoyl]phenyl}(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 74);

LCMS: 539.74 (M+1)

30 2-[(Methylsulfonyl)(4-{{4-(trifluoromethyl)phenyl}carbamoyl}phenyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 75).

LCMS: 589.75 (M+1)

Example 9: Synthesis of 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-
{(methylsulfonyl)[4-(propan-2-yl)phenyl]amino} butanoic acid (Compound no. 51)
(Scheme IV)

Step a: Preparation of benzyl 4-{{*tert*-butyl(dimethyl)silyl}oxy}-2-hydroxybutanoate

5 To an ice-cooled solution of benzyl 2,4-dihydroxybutanoate (10.4 g, 49.52
mmoles) in dichloromethane (100 mL) were added triethylamine (8.3 mL, 59.42 mmoles)
followed by *tert*-butyldimethylsilyl chloride (8.20 g, 54.47 mmoles) and *N, N'*-
dimethylaminopyridine (241 mg, 1.98 mmoles). The reaction mixture was allowed to stir
at room temperature for about one hour. After completion, reaction mixture was quenched
10 by addition of water and extracted with ethyl acetate. The organic layer was washed with
brine, dried over anhydrous sodium sulphate and concentrated under vacuum to afford the
crude compound. The crude compound obtained was purified on column chromatography
using silica gel and eluting with 10% ethyl acetate: hexane as eluent to get the desired
compound. Yield: 9.6 g

15 LCMS: 325.67 (M+1), 347.64 (M+Na)

Step b: Preparation of benzyl *O*-[*tert*-butyl(dimethyl)silyl]-*N*-(methylsulfonyl)-*N*-[4-(propan-2-yl)phenyl]homoserinate

To an ice-cooled solution of compound obtained from Step a (1 g, 3.08 mmoles) in
tetrahydrofuran (5 mL) were added *N*-[4-(propan-2-yl)phenyl]methanesulfonamide (722
20 mg, 3.39 mmoles) and triphenylphosphine (1.21 g, 4.62 mmoles) under argon atmosphere.
Diisopropylazodicarboxylate (0.67 mL, 3.39 mmoles) was added dropwise and the
reaction mixture was allowed to stir at the same temperature for about 30 minutes. After
completion, solvent was evaporated under vacuum and crude compound obtained was
purified on silica gel using 20% ethyl acetate: hexane as eluent to get desired compound.
25 Yield: 1.7 g.

Step c: Preparation of benzyl *N*-(methylsulfonyl)-*N*-[4-(propan-2-yl)phenyl]homoserinate

To a solution of compound obtained from Step b (1.7 g, 3.27 mmoles) in
dichloromethane (10 mL) was added borane trifluoride etherate BF₃.OEt₂ (2 mL, 16.35
30 mmoles) slowly at room temperature. The reaction mixture was allowed to stir at room

temperature for about one hour. After completion, reaction mixture was quenched with saturated solution of sodium bicarbonate and extracted with dichloromethane. The organic layer was washed with water, brine and dried over anhydrous sodium sulphate and concentrated under vacuum to get a crude compound. The crude compound obtained was
5 purified on silica gel column and eluting with 40% ethyl acetate: hexane as eluent to get the desired product.

Yield: 510 mg

Step d: Preparation of benzyl 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(methylsulfonyl)[4-(propan-2-yl)phenyl]amino]butanoate

10 To an ice-cooled solution of compound obtained from Step c (170 mg, 0.41 mmoles) in tetrahydrofuran (10 mL) were added phthalimide (67 mg, 0.46 mmoles) and triphenylphosphine (161 mg, 0.61 mmoles). Diisopropylazodicarboxylate (0.09 mL, 0.46 mmoles) was added to the reaction mixture and stirred for about 30 minutes at the same temperature. After completion, solvent was evaporated and crude product obtained was
15 purified on silica gel column chromatography using 50% ethyl acetate: hexane as eluent to get desired product.

Yield: 150 mg

Step e: Preparation of 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(methylsulfonyl)[4-(propan-2-yl)phenyl]amino]butanoic acid

20 To a solution of compound obtained from Step d (150 mg, 0.280 mmoles) in tetrahydrofuran (10 mL) at room temperature was added 10% Pd/C (100 mg) and hydrogen gas was supplied by balloon. The reaction mixture was allowed to stir for about 30 minutes at the same temperature. After completion, the reaction mixture was filtered using celite pad and residue obtained was washed with 10% methanol: dichloromethane
25 solution. The filtrate was concentrated and purification was performed on preparative TLC using 10% methanol: dichloromethane as mobile phase to afford desired product.

Yield: 30 mg.

LCMS: 445.79 (M+1), 467.75 (M+Na)

¹H NMR (MeOD-*d*₆, 400 MHz) δ : 7.78-7.85 (2H, m), 7.52 (1H, d, *J* = 8 Hz), 7.29 (1H, d, *J* = 8 Hz), 4.90 (1H, m), 3.74-3.91 (2H, m), 3.29 (3H, s), 2.93 (1H, m), 2.20 (1H, m), 1.79 (1H, m), 1.25 (6H, dd, *J* = 8 Hz).

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

- 5 4-(6-Methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-[(methanesulfonyl)[4-(propan-2-yl) phenyl]amino]butanoic acid (Compound no. 52);
 LCMS: 475.82 (M+1)
- 4-(7-Methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-[(methanesulfonyl)[4-(propan-2-yl) phenyl]amino]butanoic acid (Compound no. 53);
- 10 LCMS: 459.83 (M+1)
- 4-(1, 3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(4-ethylphenyl)(methanesulfonyl)amino] butanoic acid (Compound no. 54);
 LCMS: 431.75 (M+1)
- 2-[(4-Ethylphenyl)(methanesulfonyl)amino]-4-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butanoic acid (Compound no. 55);
- 15 LCMS: 445.79 (M+1)
- 2-[(4-Ethylphenyl)(methanesulfonyl)amino]-4-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl) butanoic acid (Compound no. 56);
 LCMS: 445.79 (M+1)
- 20 2-[(4-Ethylphenyl)(methanesulfonyl)amino]-4-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl) butanoic acid (Compound no. 57);
 LCMS: 461.79 (M+1)

Example 10: Synthesis of 2-[(3',4'-difluorobiphenyl-4-yl)(methanesulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 27) (Scheme V)

25 **Step a: Preparation of 3-[2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl]-1,2,3-benzotriazin-4(3*H*)-one**

 To an ice-cooled solution of 4-(2-hydroxyethyl)-2,2-dimethyl 1,3-dioxolane (3.8 g, 0.025 moles) in tetrahydrofuran (50 mL) were added benzotriazinone (4.2 g, 0.028 moles) and triphenylphosphine (13.6 g, 0.051 moles). The reaction mixture was allowed to stir

30 for about 15 minutes at 0°C and diisopropylazodicarboxylate (7.3 mL, 0.038 moles) was added to it. The reaction mixture was again stirred for about 2 hours at room temperature. After completion of reaction, solvent was evaporated under vacuum to obtain a crude

product which was purified on silica gel column using 30% ethyl acetate: hexane as eluent to get desired product.

Yield: 11g

LCMS: 294.99 (M+Na)

5 **Step b: Preparation of 3-(3,4-dihydroxybutyl)-1,2,3-benzotriazin-4(3H)-one**

To a solution of compound obtained from Step a (11 g, 39.954 mmols) in acetone (60 mL) was added concentrated HCl (12 mL) and reaction mixture was allowed to stir at room temperature for about one hour. After one hour, the solvent was evaporated under reduced pressure and reaction mixture was extracted with ethyl acetate. The organic layer
10 was washed with water, dried over anhydrous sodium sulphate and evaporated under vacuum to get crude compound. The crude compound obtained was purified on silica gel column using 70% ethyl acetate: hexane as eluent to get desired product.

Yield: 4.5 g

LCMS: 236.49 (M+1)

15 **Step c: Preparation of 2-hydroxy-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butyl benzoate**

To an ice-cooled solution of compound obtained from Step b (1 g, 0.0042 moles) in dichloromethane (150 mL) were added triethylamine (1.1 mL, 0.0085 moles) and benzoyl chloride (0.5 mL, 0.0042 moles) and stirred at same temperature for about 2 hours and at room temperature for about 3 hours. After completion, reaction mixture was
20 diluted with water and extracted with dichloromethane. The organic layer was collected, dried over anhydrous sodium sulphate and evaporated under vacuum to get crude product. The crude product was purified on silica gel column using 70% ethyl acetate: hexane as eluent to get desired product.

Yield: 1.8 g

25 LCMS: 340.59 (M+1)

Step d: Preparation of 2-[(4-bromophenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butyl benzoate

To an ice-cooled solution of compound obtained from Step c (1.8 g, 0.0053 moles) in tetrahydrofuran (20 mL) were added triphenylphosphine (2.78 g, 0.0161 moles) and *N*-(4-bromophenyl)methanesulfonamide (1.46 g, 0.00584 moles). The reaction mixture was allowed to stir for about 15 minutes and then diisopropylazodicarboxylate (1.5 mL, 0.00796 moles) was added at same temperature. The reaction mixture was again stirred at room temperature for about one hour. After one hour, solvent was evaporated under reduced pressure to obtain a crude product. The crude product obtained was purified on silica gel column using 30% ethyl acetate: hexane as eluent to get desired product.

Yield: 1.3 g.

Step e: Preparation of 2-[(3',4'-difluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butyl benzoate

To a solution of compound obtained from Step d (400 mg, 0.0007 moles) in *N,N*-dimethylformamide (15 mL) were added tetrakis triphenylphosphine palladium (0) (40 mg, 0.00035 moles), potassium carbonate (290 mg, 0.0021 moles) and 3, 4-difluorobenzene boronic acid (221 mg, 0.0014 moles). The reaction was heated upto 110°C for about 3 hours. After 3 hours, solvent was evaporated and reaction mixture was taken in ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get a crude product. The crude product was purified on silica gel column using 50% ethyl acetate: hexane to get desired product.

Yield: 300 mg

LCMS: 606.27 (M+2).

Step f: Preparation of *N*-(3',4'-difluorobiphenyl-4-yl)-*N*-[1-hydroxy-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butan-2-yl]methanesulfonamide

To a solution of compound obtained from Step e (300 mg, 0.496 moles) in methanol (10 mL) and tetrahydrofuran (10 mL) was added potassium carbonate (102 mg, 0.745 moles) and stirred for about one hour at room temperature. After one hour, solvent was evaporated and reaction mixture was taken in ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated under reduced

pressure to obtain a crude product. The crude product obtained was purified on silica gel column using 60% ethyl acetate: hexane as eluent to get the desired product.

Yield: 200 mg

LCMS: 501.81 (M+1)

5 **Step g: Preparation of 2-[(3',4'-difluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid**

To a solution of compound obtained from Step f (200 mg, 0.4 moles) in acetonitrile (10 mL) were added 2,2,6,6-tetramethylpiperidine-N-oxyl (6 mg, 0.04 moles), sodium chlorite (72 mg, 0.8 moles) and 5% aqueous solution of sodium hypochlorite (59 mg, 0.8 moles). The reaction was heated up to 35°C for about 6 hours. After 6 hrs, the solvent was evaporated and reaction mixture was taken in ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated under reduced pressure to get a crude product. The crude product was purified on preparative TLC using 10% methanol: dichloromethane as mobile phase to get desired product.

15 Yield: 30 mg.

LCMS: 515.72 (M+1)

¹H NMR (DMSO-d₆, 400 MHz): δ 8.28 (2H, d, *J* = 4 Hz), 8.22 (1H, d, *J* = 8 Hz), 8.12 (1H, dd, *J* = 8 and 4 Hz), 7.96 (1H, m), 7.85 (4H, m), 7.58 (2H, m), 4.74 (1H, d, *J* = 8 Hz), 4.56 (2H, m, -NCH₂), 3.21 (3H, s), 2.48 (2H, m).

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

4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-{[4-(6-methoxypyridin-3-yl)phenyl](methylsulfonyl)amino} butanoic acid (Compound no. 22);

LCMS: 510.69 (M+1)

25 2-[(4'-Ethylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 28);

LCMS: 507.79 (M+1)

2-{[4-(2-Methoxypyrimidin-5-yl)phenyl](methylsulfonyl)amino}-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 29);

LCMS: 511.76 (M+1)

30 2-[(3'-Fluoro-4'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 30);

- LCMS: 511.76 (M+1)
2-[(2',4'-Dimethoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 31);
LCMS: 539.84 (M+1)
- 5 2-[(3'-Methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 38);
LCMS: 509.81 (M+1)
2-[(4'-Fluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 39);
- 10 LCMS: 497.78 (M+1)
2-[(Methylsulfonyl)[4'-(propan-2-yl)biphenyl-4-yl]amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 40);
LCMS: 521.82 (M+1)
- 15 2-[Biphenyl-4-yl(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 41);
LCMS: 479.78 (M+1)
2-[(4-(6-Methylpyridin-3-yl)phenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 42);
LCMS: 494.83 (M+1)
- 20 2-[(Methylsulfonyl)[4-(pyrimidin-5-yl)phenyl]amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 43);
LCMS: 481.79 (M+1)
2-[(Methylsulfonyl)[4-(pyridin-3-yl)phenyl]amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 44);
- 25 LCMS: 480.79 (M+1)
2-[(Methylsulfonyl)[4'-(trifluoromethyl)biphenyl-4-yl]amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 45);
LCMS: 547.83 (M+1)
- 30 2-[(Methylsulfonyl)[4-(pyridin-4-yl)phenyl]amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 46);
LCMS: 480.7969 (M+1)
2-[(3',4'-Dichlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 47);
LCMS: 547.76 and 549.71 (M+1)
- 35 2-[(4'-*tert*-Butylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 48);
LCMS: 535.87 (M+1)

2-[(2',3'-Difluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 49);

LCMS: 515.79 (M+1)

5 2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 50).

LCMS: 527.81 (M+1)

Example 11: Synthesis of (2*R*)-2-[(3',4'-Dichlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 79); Scheme V

10 **Step a: Preparation of 3-[2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl]-1,2,3-benzotriazin-4(3*H*)-one**

To an ice-cooled solution of 4-(2-hydroxyethyl)-2,2-dimethyl 1,3-dioxolane (20 g, 0.136 mole) in tetrahydrofuran (200 mL) were added benzotriazinone (22 g, 0.150 mole) and triphenylphosphine (71 g, 0.273 mole). The reaction mixture was allowed to stir for about 15 minutes at 0°C and diisopropylazodicarboxylate (41.5 g, 0.205 mole) was added to it. The reaction mixture was again stirred for 2 hours at room temperature. After completion of reaction, solvent was evaporated under vacuum to obtain a crude product which was purified on silica gel column using 30% ethyl acetate: hexane as eluent to get desired product.

Yield: 69 g

20 **Step b: Preparation of 3-(3,4-dihydroxybutyl)-1,2,3-benzotriazin-4(3*H*)-one**

To a solution of compound obtained from Step a (69 g, 0.250 moles) in acetone (200 mL) was added concentrated HCl (70 mL) and reaction mixture was allowed to stir at room temperature for about one hour. After one hour, the solvent was evaporated under reduced pressure and reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated under vacuum to get crude compound. The crude compound obtained was purified on silica gel column using 70% ethyl acetate: hexane as eluent to get desired product.

Yield: 21 g

Step c: Preparation of 2-hydroxy-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butyl benzoate

To an ice-cooled solution of compound obtained from Step b (21 g, 0.089 mole) in dichloromethane (100 mL) were added triethylamine (27 g, 0.268 mole) and benzoyl chloride (15.5 mL, 0.134 mole) and stirred at same temperature for about 3 hours. After completion, the reaction mixture was diluted with water and extracted with
5 dichloromethane. The organic layer was collected, dried over anhydrous sodium sulphate and evaporated under vacuum to get crude product. The crude product was purified on silica gel column using 70% ethyl acetate: hexane as eluent to get desired product.

Yield: 16 g

10 Step d: Preparation of 2-[(4-bromophenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butyl benzoate

To an ice-cooled solution of compound obtained from Step c (11 g, 0.032 mole) in tetrahydrofuran (100 mL) were added triphenylphosphine (17 g, 0.064 mole) and *N*-(4-bromophenyl)methane sulfonamide (8.95 g, 0.035 mole). The reaction mixture was
15 allowed to stir for about 15 minutes and then diisopropylazodicarboxylate (9.8 g, 0.048 mole) was added at the same temperature. The reaction mixture was again stirred at room temperature for about one hour. After one hour, solvent was evaporated under reduced pressure to obtain a crude product. The crude product obtained was purified on silica gel column using 30% ethyl acetate: hexane as eluent to get desired product.

20 Yield: 1.3 g.

Step e: Preparation of 2-[(3',4'-dichlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butyl benzoate

To a solution of compound obtained from Step d (0.8g, 0.0014 mole) in *N,N*-dimethylformamide (20 mL) were added tetrakis triphenylphosphine palladium (0) (0.08 g, 0.00007 mole), potassium carbonate (.58 g, 0.0042 mole) and 3,4-dichlorobenzene boronic acid (0.535 g, 0.0028 mole). The reaction was heated up to 110°C for about 3 hours. After 3 hours, the solvent was evaporated and the reaction mixture was taken in ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get a crude product. The crude product
30 was purified on silica gel column using 50% ethyl acetate: hexane to get desired product.

Yield: 850 mg

Step f: Preparation of *N*-(3',4'-dichlorobiphenyl-4-yl)-*N*-[1-hydroxy-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butan-2-yl]methanesulfonamide

To a solution of compound obtained from Step e (0.85 g, 0.00133 mole) in
5 methanol (15 mL) was added potassium carbonate (0.276 g, 0.0020 mole) and stirred for about one hour at room temperature. After one hour, the solvent was evaporated and the reaction mixture was taken in ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated under reduced pressure to obtain a crude product. The crude product obtained was purified on silica gel column using 60%
10 ethyl acetate: hexane as eluent to get the desired product.

Yield: 0.430 g.

LCMS: 533.13 (M⁺)

Step g: Preparation of 2-[(3',4'-dichlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid

To a solution of compound obtained from Step f (0.43 g 0.0008 mole) in
15 acetonitrile (15 mL) were added 2,2,6,6-tetramethylpiperidine-N-oxyl (0.012 g, 0.000007 mole), sodium chlorite (0.145 g, 0.0016 mole) and 5% aqueous solution of sodium hypochlorite (0.12 g, 0.0016 moles). The reaction was heated up to 35°C for about 6 hours. After 6 hours, the solvent was evaporated and the reaction mixture was taken in
20 ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated under reduced pressure to get a crude product. The crude product was purified on preparative TLC using 10% methanol: dichloromethane as mobile phase to get desired product.

Yield: 0.15 g.

25 ¹HNMR (DMSO-*d*₆, 400 MHz): 8.22 (2H, m), 8.16 (1H, m), 8.03 - 8.05 (2H, m), 7.67 - 7.71 (6H, m), 4.63 (1H, m), 4.55 (2H, m), 3.15 (3H,s), 2.14 (1H, m), 1.99 (1H, m)

LCMS: 547.11 (M+1)

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

- (2*R*)-2-[(4'-Fluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 76);
LCMS: 497.19 (M+1)
- 5 (2*R*)-2-[(Methylsulfonyl)[4-(pyrimidin-5-yl)phenyl]amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 77);
LCMS: 481.21 (M+1)
- (2*R*)-2-[(Methylsulfonyl)[4'-(propan-2-yl)biphenyl-4-yl]amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 78);
LCMS: 521.29 (M+1)
- 10 (2*R*)-2-[(3',4'-Difluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 80);
LCMS: 515.22 (M+1)
- (2*R*)-2-[(3'-Fluoro-4'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 81);
15 LCMS: 511.32 (M+1)
- (2*R*)-2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 82);
LCMS: 513.71 (M+1)
- (2*R*)-2-[(3'-Methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 83);
20 LCMS: 509.25 (M+1)
- (2*R*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 84);
LCMS: 527.22 (M+1)
- 25 (2*R*)-2-[Biphenyl-4-yl(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 85);
LCMS: 479.25 (M+1)
- (2*R*)-2-[[4-(6-Methoxypyridin-3-yl)phenyl](methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 86);
30 LCMS: 510.169 (M+1)
- (2*S*)-2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 87);
LCMS: 513.23 (M+1)
- 35 (2*S*)-2-[(3',4'-Dichlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 88);
LCMS: 547.22 and 549.11 (M+1)

- (2*S*)-2-[(3'-Fluoro-4'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 89);
LCMS: 511.27 (M+1)
- 5 (2*S*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 90);
LCMS: 527.28 (M+1)
- (2*R*)-2-[(3',4'-Dimethoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 91);
LCMS: 537.5 (M-1)
- 10 (2*R*)-2-{[4-(2,3-Dihydro-1,4-benzodioxin-6-yl)phenyl](methylsulfonyl)amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 92);
LCMS: 537.30 (M+1)
- (2*R*)-2-[(4'-Methoxy-3'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 93);
15 LCMS: 545.22 (M+1)
- (2*R*)-2-[(4'-Fluoro-3'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 94);
LCMS: 533.27 (M+1)
- (2*R*)-2-{(Methylsulfonyl)[4'-(trifluoromethoxy)biphenyl-4-yl]amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 95);
20 LCMS: 563.16 (M+1)
- (2*R*)-2-{[4'-Chloro-3'-(trifluoromethyl)biphenyl-4-yl](methylsulfonyl)amino}-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 96);
LCMS: 581.9 (M+1)
- 25 Example 12: Synthesis of (2*R*)-2-[(3'-fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]butanoic acid (Compound no. 97) (Scheme VI)

Step a: Preparation of (4*S*)-4-[2-(benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxolane

- To an ice-cooled solution of 2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanol (5 g,
30 34.24 mmol) in *N,N'*-dimethylformamide (50 mL) was added sodium hydride (1.06 g,
44.52 mmol) and stirred for about 15 minutes. After 15 minutes, benzyl bromide (7.02 g,
41.09 mmol) was added and again stirred for about one hour at the same temperature.
After completion of reaction, aqueous solution of ammonium chloride was added and the
solvent was evaporated under vacuum. The reaction mixture was taken in ethyl acetate
35 and washed with water. The organic layer was collected, dried over anhydrous sodium

sulphate and evaporated under reduced pressure to obtain a crude product. The crude product was purified on silica gel column using 20% ethyl acetate: hexane as eluent to get the desired product.

Yield: 8 g

5 LCMS: 237.30 (M+1)

Step b: Preparation of (2*S*)-4-(benzyloxy)butane-1,2-diol

To a solution of compound obtained from Step a (8 g) in acetone (50 mL) was added hydrochloric acid (12 mL, 11 N) at room temperature and stirred for about 3 hours at room temperature. After completion of reaction, the solvent was evaporated under reduced
10 pressure and pH was adjusted to neutral by addition of aqueous solution of sodium bicarbonate. The reaction mixture was extracted with ethyl acetate while washing with water. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get a crude product. The crude product was purified on silica gel column using 20% ethyl acetate: hexane as eluent to get desired compound.

15 Yield: 5g

LCMS: 197.24 (M+1)

Step c: Preparation of (2*S*)-4-(benzyloxy)-2-hydroxybutyl benzoate

To an ice-cooled solution of compound obtained from Step b (5 g, 31.05 mmoles) in dichloromethane (100 mL) were added triethylamine (9.4 g, 93.16 mmoles) and benzoyl
20 chloride (3.9 g, 27.95 mmoles). The reaction mixture was allowed to stir for about 45 minutes at the same temperature. After 45 minutes, the reaction mixture was extracted with dichloromethane while washing with water. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get a crude product. The crude product was purified on silica gel column using 60% ethyl acetate:
25 hexane as eluent to get desired compound.

Yield: 5g

LCMS: 301.25 (M+1)

Step d: Preparation of (2*R*)-4-(benzyloxy)-2-[(4-bromophenyl)(methylsulfonyl)amino]butyl benzoate

To a solution of compound obtained from Step c (5 g, 16.66 mmole) in tetrahydrofuran (100 mL) at 0°C were added triphenyl phosphine (8.7 g, 33.33 moles), *N*-(4-bromophenyl)methanesulfonamide (4.58 g, 18.33 mmole) and diisopropylazodicarboxylate (5 g, 25 mmole). The reaction mixture was allowed to stir for about one hour at same temperature. After that the reaction mixture was concentrated to obtain a crude product which was purified on column chromatography on silica gel column using 60% ethyl acetate: hexane as eluent to get desired product.

Yield: 14 g

LCMS: 534.04 (M+2)

Step e: Preparation of (2*R*)-4-(benzyloxy)-2-[(3'-fluoro-4'-methoxybiphenyl-4-yl)(methyl sulfonyl)amino]butyl benzoate

To a solution of compound obtained from Step d (5 g, 9.398 mmole) in *N,N*-dimethylformamide (50 mL) were added 3-fluoro-4-methoxyphenylboronic acid (3.19 g, 18.796 mmole), potassium carbonate (3.89 g, 28.195 mmole) and tetrakis(triphenyl)phosphine palladium (0) (542 mg, 0.469 mmole). The reaction mixture was heated upto 110°C for about 3 hours. After 3 hours, the solvent was evaporated and the reaction mixture was extracted with ethyl acetate while washing with water. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to obtain a crude product. The crude product was purified on silica gel column using 30% ethyl acetate hexane as eluent to get desired product.

Yield: 4.3 g

Step f: Preparation of (2*R*)-2-[(3'-fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-hydroxybutyl benzoate

To a solution of compound obtained from Step e (4.39 g, 0.008 moles) in tetrahydrofuran (60 mL) and methanol (40 mL) was added Pd/C (2.5 g) in the presence of hydrogen gas supplied using balloon. The reaction mixture was allowed to stir for overnight at room temperature. After completion, reaction mixture was filtered through

celite and residue so obtained was washed with 10% methanol: dichloromethane (200 mL). The filtrate was collected and dried to get desired compound.

Yield: 2.5 g

LCMS: 488.16

5 **Step g: Preparation of (2*R*)-2-[(3'-fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]butyl benzoate**

To a solution of compound obtained from Step f (2.5 g, 0.0051 moles) in tetrahydrofuran (30 mL) were added 7-trifluoromethoxy benzotriazinone (1.21 g, 0.00564 moles) and triphenyl phosphine (2.68 g, 0.010 moles) at room temperature under nitrogen atmosphere. After 5 minutes, diisopropylazodicarboxylate (1.55 g, 0.0077 moles) was added under nitrogen atmosphere and the reaction mixture was stirred at the same temperature for about one hour. After completion, the reaction mixture was extracted with ethyl acetate and washed with water. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get crude product.

15 The crude product was purified on silica gel column using 30% ethyl acetate: hexane as eluent to get desired product.

Yield: 4.2 g

LCMS: 685.15 (M+1)

20 **Step h: Preparation of *N*-(3'-fluoro-4'-methoxybiphenyl-4-yl)-*N*-{(2*R*)-1-hydroxy-4-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]butan-2-yl}methanesulfonamide**

To a solution of compound obtained from Step g (4.2 g, 0.00614 moles) in methanol (40 mL) at room temperature was added potassium carbonate (1.27 g, 0.00921 moles) under argon atmosphere. The reaction mixture was allowed to stir for about one hour at same temperature. After completion, solvent was evaporated and the reaction mixture was extracted with ethyl acetate while washing with water. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get crude product. The crude product was purified on silica gel column using 40% ethyl acetate: hexane as eluent to obtain a desired compound.

25

Yield: 3.1 g

LCMS: 581.04

Step i: Preparation of (2R)-2-[(3'-fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4H)-yl]butanoic acid

- 5 To a solution of compound obtained from Step h (900 mg, 1.552 mmoles) in acetonitrile:carbon tetrachloride:water (12ml:12ml:16ml) at room temperature were added ruthenium trichloride (13 mg, 0.062 mmoles) and sodium periodate (996 mg, 4.66 mmoles). The reaction mixture was allowed to stir for about 30 minutes at same the temperature. After completion, solvent was evaporated and the reaction mixture was
- 10 extracted with ethyl acetate while washing with water. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get a crude product. The crude product was purified on preparative TLC using 10% methanol: dichloromethane as mobile phase to get the desired product.

Yield: 107 mg.

- 15 LCMS: 595 (M+1)

¹H NMR (DMSO-d₆, 400 MHz): δ 8.59 (1H, s), 8.44 (1H, d, *J* = 8 Hz), 8.22 (1H, d, *J* = 8 Hz), 7.71 (2H, d, *J* = 8 Hz), 7.59 (3H, m), 7.50 (1H, d, *J* = 8 Hz), 7.25 (1H, t, *J* = 8 Hz), 4.82 (1H, m), 4.55 (2H, m), 3.88 (3H, s, -OCH₃), 3.17 (3H, s, S-CH₃), 2.4 (1H, m), 1.90 (1H, m).

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

(2R)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 98);

LCMS: 541.11 (M+1)

- 25 (2R)-4-(7-Chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)-2-[(3'-fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]butanoic acid (Compound no. 99);

LCMS: 561.00 (M+1)

(2R)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 100);

LCMS: 557.10 (M+1)

- 30 (2R)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 101);

LCMS: 541.05 (M+1)

(2*R*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 102);

LCMS: 557.10 (M+1)

- 5 (2*R*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 103).

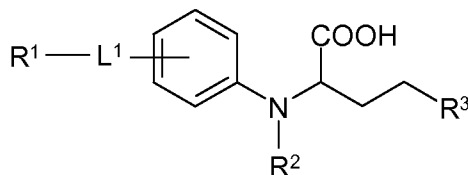
Assay for Matrix Metallo Proteinases (MMPs)

- New chemical entities (NCEs) of the present invention and corresponding standards used in the present invention were prepared (stock 10 mM) in 100% DMSO and
- 10 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”.
- 15 (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. The Reaction was initiated with 10 µl of 100 µM substrate (ES001: Aliquots were freshly diluted in TCNB; stock: 2 mM) and increase in florescence was monitored at excitation
- 20 wave length 320 nm followed by emission at 405 nm for 25-30 cycles. Increase in florescence (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 MMP9 provided IC₅₀ values below 10 micromolar. Activities for
- 25 MMP12 provided IC₅₀ values 35 nanomolar to 10 micromolar.

We Claim:

- 1 1. A compound of Formula I:

**Formula 1**

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

6 L^1 is selected from bond, O, S, CH_2 , NR^4 , $NHCO(CH_2)_n$, $(CH_2)_nCONH$, $NHCONH$,
7 SO_2NH , $NHSO_2$, $NHCO(O)$, $-O-(CH_2)_n$, $-(CH_2)_n-O-$, $-OC(O)NH-$, $C(S)NH$,
8 $NHC(S)$, $NHC(S)NH$ or $-COO-$ wherein n is zero or an integer between 1 and 2;

9 R^1 is selected from hydrogen, C_1 - C_6 alkyl, hydroxyl, C_1 - C_6 alkoxy, cyano, nitro,
10 halogen, halogeno C_1 - C_6 alkyl, C_5 - C_{12} aryl, C_6 - C_{12} heteroaryl, C_3 - C_6 cycloalkyl
11 wherein aryl, heteroaryl, cycloalkyl is optionally substituted by one or more
12 substituents independently selected from R^5 ;

13 R^2 is CHO or SO_2C_{1-6} alkyl;

14 R^3 is unsubstituted or substituted heteroaryl or $-OCONHR'$ where R' is C_6 - C_{12} aryl,
15 heteroaryl, cycloalkyl, heterocyclyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl,
16 heterocyclylalkyl each of which is optionally substituted by one or more
17 substituents independently selected from R^5 ;

18 R^4 is H or C_{1-6} alkyl;

19 R^5 is selected from alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno- C_1 - C_6
20 alkyl, halogeno- C_1 - C_6 alkoxy, azido, thiol, alkylthiol, $-(CH_2)_n-OR_f$, $-C(=O)-R_f$,
21 $COOR_f$, $-NR_fR_q$, $-(CH_2)_n-C(=O)NR_fR_q$, $-(CH_2)_n-NHC(=O)-R_f$, $-(CH_2)_n-O-$
22 $C(=O)-NR_fR_q$, $(CH_2)_n-NHC(=O)NR_fR_q$, $-(CH_2)_n-O-C(=O)-R_f$, $-(CH_2)_n-NH-C(=O)-$
23 R_f or $-(CH_2)_nS(=O)_m-NR_fR_q$ {wherein R_f and R_q are independently selected from
24 hydrogen, alkyl, alkenyl, cycloalkyl aryl, heteroaryl, heterocyclyl, alkylaryl,
25 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 2-[Formyl(4'-methylbiphenyl-4-yl)amino]-4-(6-methyl-4-oxo-1,2,3-benzotriazin-
3 3(4*H*)-yl)butanoic acid (Compound no. 1);
- 4 4-(7-Chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-[formyl(4'-methylbiphenyl-4-
5 yl)amino]butanoic acid (Compound no. 2);
- 6 2-[(4'-Ethylbiphenyl-4-yl)(formyl)amino]-4-(5-methyl-4-oxo-1,2,3-benzotriazin-
7 3(4*H*)-yl)butanoic acid (Compound no. 3);
- 8 *O*-[(4-Fluorophenyl)carbamoyl]-*N*-formyl-*N*-(4'-methylbiphenyl-4-yl)homoserine
9 (Compound no. 4);
- 10 *N*-Formyl-*N*-(4'-methylbiphenyl-4-yl)-*O*-[(4-methylphenyl)carbamoyl]homoserine
11 (Compound no. 5);
- 12 *O*-[(3,4-Dichlorophenyl)carbamoyl]-*N*-formyl-*N*-(4'-methylbiphenyl-4-
13 yl)homoserine (Compound no. 6);
- 14 *N*-(4'-Ethylbiphenyl-4-yl)-*N*-formyl-*O*-{[4-(propan-2-yl)phenyl]carbamoyl}
15 homoserine (Compound no. 7);
- 16 *N*-(4'-Ethylbiphenyl-4-yl)-*O*-[(3-fluorophenyl)carbamoyl]-*N*-formylhomoserine
17 (Compound no. 8);
- 18 *O*-[(2,4-Difluorophenyl)carbamoyl]-*N*-(4'-ethylbiphenyl-4-yl)-*N*-
19 formylhomoserine (Compound no. 9);
- 20 *N*-(4'-Ethylbiphenyl-4-yl)-*O*-[(2-fluorophenyl)carbamoyl]-*N*-formylhomoserine
21 (Compound no. 10);
- 22 *N*-(4'-Ethylbiphenyl-4-yl)-*N*-formyl-*O*-{[4-(trifluoromethyl)phenyl]carbamoyl}
23 homoserine (Compound no. 11);
- 24 *N*-(4'-Ethylbiphenyl-4-yl)-*N*-formyl-*O*-[(2-methylphenyl)carbamoyl]homoserine
25 (Compound no. 12);
- 26 *N*-(4'-Ethylbiphenyl-4-yl)-*O*-[(4-ethylphenyl)carbamoyl]-*N*-formylhomoserine
27 (Compound no. 13);
- 28 *N*-(4'-Ethylbiphenyl-4-yl)-*N*-formyl-*O*-[(4-methoxyphenyl)carbamoyl]homoserine
29 (Compound no. 14);
- 30 *O*-[(2,6-Dichlorophenyl)carbamoyl]-*N*-(4'-ethylbiphenyl-4-yl)-*N*-
31 formylhomoserine (Compound no. 15);
- 32 2-[Biphenyl-4-yl(methylsulfonyl)amino]-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-
33 yl)butanoic acid (Compound no. 16);
- 34 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-{[4-(6-methoxypyridin-3-yl)phenyl]
35 (methyl sulfonyl)amino}butanoic acid (Compound no. 17);
- 36 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(4'-methoxybiphenyl-4-yl)
37 (methylsulfonyl) amino]butanoic acid (Compound no. 18);

- 38 2- {[4-(6-Methoxypyridin-3-yl)phenyl](methylsulfonyl)amino} -4-(4-oxo-1,2,3-
39 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 19);
- 40 4-(7-Methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2- {[4-(6-methoxypyridin-3-
41 yl)phenyl](methylsulfonyl)amino} butanoic acid (Compound no. 20);
- 42 2- {[4-(6-Methoxypyridin-3-yl)phenyl](methylsulfonyl)amino} -4-[4-oxo-7-
43 (trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]butanoic acid (Compound no. 21);
- 44 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2- {[4-(6-methoxypyridin-3-
45 yl)phenyl](methyl sulfonyl)amino} butanoic acid (Compound no. 22);
- 46 4-(6-Methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2- {[4-(4-
47 methylphenoxy)phenyl](methyl sulfonyl)amino} butanoic acid (Compound no. 23);
- 48 4-(7-Methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2- {[4-(4-methylphenoxy)
49 phenyl](methyl sulfonyl) amino} butanoic acid (Compound no. 24);
- 50 2- {[4-(4-Methylphenoxy)phenyl](methylsulfonyl)amino} -4-[4-oxo-7-
51 (trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]butanoic acid (Compound no. 25);
- 52 2- {[4-(4-Methylphenoxy)phenyl](methylsulfonyl)amino} -4-(4-oxo-1,2,3-
53 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 26);
- 54 2-[(3',4'-Difluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
55 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 27);
- 56 2-[(4'-Ethylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-
57 3(4*H*)-yl)butanoic acid (Compound no. 28);
- 58 2- {[4-(2-Methoxypyrimidin-5-yl)phenyl](methylsulfonyl)amino} -4-(4-oxo-1,2,3-
59 benzotriazin -3(4*H*)-yl)butanoic acid (Compound no. 29);
- 60 2-[(3'-Fluoro-4'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
61 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 30);
- 62 2-[(2',4'-Dimethoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
63 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 31);
- 64 2-[(4-Methoxyphenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-
65 yl)butanoic acid (Compound no. 32);
- 66 4-(7-Methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-[(4-methoxyphenyl)
67 (methylsulfonyl)amino]butanoic acid (Compound no. 33);
- 68 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(4-
69 methoxyphenyl)methylsulfonyl]amino]butanoic acid (Compound no. 34);
- 70 2-[(4-Methoxyphenyl)(methylsulfonyl)amino]-4-(5-methyl-1,3-dioxo-1,3-dihydro-
71 2*H*-isoindo-2-yl)butanoic acid (Compound no. 35);
- 72 4-(7-Methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2- {[4-(4-
73 methylphenoxy)phenyl](methyl sulfonyl)amino} butanoic acid (Compound no. 36);
- 74 4-(5-Methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2- {[4-(4-methylphenoxy)
75 phenyl](methylsulfonyl)amino} butanoic acid (Compound no. 37);

- 76 2-[(3'-Methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-
77 3(4*H*)-yl)butanoic acid (Compound no. 38);
- 78 2-[(4'-Fluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-
79 3(4*H*)-yl)butanoic acid (Compound no. 39);
- 80 2-[(Methylsulfonyl)[4'-(propan-2-yl)biphenyl-4-yl]amino]-4-(4-oxo-1,2,3-
81 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 40);
- 82 2-[Biphenyl-4-yl(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-
83 yl)butanoic acid (Compound no. 41);
- 84 2-[[4-(6-Methylpyridin-3-yl)phenyl](methylsulfonyl)amino]-4-(4-oxo-1,2,3-
85 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 42);
- 86 2-[(Methylsulfonyl)[4-(pyrimidin-5-yl)phenyl]amino]-4-(4-oxo-1,2,3-
87 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 43);
- 88 2-[(Methylsulfonyl)[4-(pyridin-3-yl)phenyl]amino]-4-(4-oxo-1,2,3-benzotriazin-
89 3(4*H*)-yl)butanoic acid (Compound no. 44);
- 90 2-[(Methylsulfonyl)[4'-(trifluoromethyl)biphenyl-4-yl]amino]-4-(4-oxo-1,2,3-
91 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 45);
- 92 2-[(Methylsulfonyl)[4-(pyridin-4-yl)phenyl]amino]-4-(4-oxo-1,2,3-benzotriazin-
93 3(4*H*)-yl)butanoic acid (Compound no. 46);
- 94 2-[(3',4'-Dichlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
95 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 47);
- 96 2-[(4'-*tert*-Butylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
97 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 48);
- 98 2-[(2',3'-Difluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
99 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 49);
- 100 2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
101 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 50);
- 102 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(methylsulfonyl)[4-(propan-2-
103 yl)phenyl]amino]butanoic acid (Compound no. 51);
- 104 4-(6-Methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-[(methylsulfonyl)[4-(propan-
105 2-yl)phenyl]amino]butanoic acid (Compound no. 52);
- 106 4-(7-Methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-2-[(methylsulfonyl)[4-(propan-2-
107 yl)phenyl]amino]butanoic acid (Compound no. 53);
- 108 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-[(4-
109 ethylphenyl)(methylsulfonyl)amino]butanoic acid (Compound no. 54);
- 110 2-[(4-Ethylphenyl)(methylsulfonyl)amino]-4-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-
111 isoindol-2-yl)butanoic acid (Compound no. 55);
- 112 2-[(4-Ethylphenyl)(methylsulfonyl)amino]-4-(7-methyl-4-oxo-1,2,3-benzotriazin-
113 3(4*H*)-yl)butanoic acid (Compound no. 56);

- 114 2-[(4-Ethylphenyl)(methylsulfonyl)amino]-4-(6-methoxy-4-oxo-1,2,3-
115 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 57);
- 116 2-[(Methylsulfonyl)(phenyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic
117 acid (Compound no. 58);
- 118 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-methyl-1,3-dioxo-1,3-
119 dihydro-2*H*-isoindol-2-yl)butanoic acid (Compound no. 59);
- 120 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-chloro-4-oxo-1,2,3-
121 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 60);
- 122 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(7-chloro-4-oxo-1,2,3-
123 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 61);
- 124 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(7-methyl-4-oxo-1,2,3-
125 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 62);
- 126 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-[4-oxo-7-(trifluoromethyl)-
127 1,2,3-benzotriazin-3(4*H*)-yl]butanoic acid (Compound no. 63);
- 128 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-methoxy-4-oxo-1,2,3-
129 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 64);
- 130 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(5-fluoro-4-oxo-1,2,3-
131 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 65);
- 132 2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(1-methyl-2,4-dioxo-1,4-
133 dihydroquinazolin-3(2*H*)-yl)butanoic acid (Compound no. 66);
- 134 4-[(Methylsulfonyl)[1-oxo-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)-1-(prop-2-en-1-
135 yloxy)butan-2-yl]amino]benzoic acid (Compound no. 67);
- 136 2-[(4-[(4-Methylphenyl)carbamoyl]phenyl)(methylsulfonyl)amino]-4-(4-oxo-
137 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 68);
- 138 2-[(4-[(4-Chlorophenyl)carbamoyl]phenyl)(methylsulfonyl)amino]-4-(4-oxo-
139 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 69);
- 140 2-[(Methylsulfonyl)[4-(phenylcarbamoyl)phenyl]amino]-4-(4-oxo-1,2,3-
141 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 70);
- 142 2-[(4-[(3-Fluorophenyl)carbamoyl]phenyl)(methylsulfonyl)amino]-4-(4-oxo-
143 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 71);
- 144 2-[(Methylsulfonyl)(4-[(4-(propan-2-yl)phenyl)carbamoyl]phenyl)amino]-4-(4-
145 oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 72);
- 146 2-[(4-[(4-Methoxyphenyl)carbamoyl]phenyl)(methylsulfonyl)amino]-4-(4-oxo-
147 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 73);
- 148 2-[(4-[(4-Fluorophenyl)carbamoyl]phenyl)(methylsulfonyl)amino]-4-(4-oxo-
149 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 74);
- 150 2-[(Methylsulfonyl)(4-[(4-(trifluoromethyl)phenyl)carbamoyl]phenyl)amino]-4-
151 (4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 75);

- 152 (2*R*)-2-[(4'-Fluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
153 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 76);
- 154 (2*R*)-2-[(Methylsulfonyl)[4-(pyrimidin-5-yl)phenyl]amino]-4-(4-oxo-1,2,3-
155 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 77);
- 156 (2*R*)-2-[(Methylsulfonyl)[4'-(propan-2-yl)biphenyl-4-yl]amino]-4-(4-oxo-1,2,3-
157 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 78);
- 158 (2*R*)-2-[(3',4'-Dichlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
159 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 79);
- 160 (2*R*)-2-[(3',4'-Difluorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
161 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 80);
- 162 (2*R*)-2-[(3'-Fluoro-4'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
163 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 81);
- 164 (2*R*)-2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
165 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 82);
- 166 (2*R*)-2-[(3'-Methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
167 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 83);
- 168 (2*R*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-
169 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 84);
- 170 (2*R*)-2-[Biphenyl-4-yl(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-
171 yl)butanoic acid (Compound no. 85);
- 172 (2*R*)-2-[[4-(6-Methoxypyridin-3-yl)phenyl](methylsulfonyl)amino]-4-(4-oxo-
173 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 86);
- 174 (2*S*)-2-[(4'-Chlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
175 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 87);
- 176 (2*S*)-2-[(3',4'-Dichlorobiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
177 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 88);
- 178 (2*S*)-2-[(3'-Fluoro-4'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
179 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 89);
- 180 (2*S*)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-
181 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 90);
- 182 (2*R*)-2-[(3',4'-Dimethoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
183 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 91);
- 184 (2*R*)-2-[[4-(2,3-Dihydro-1,4-benzodioxin-6-yl)phenyl](methylsulfonyl)amino]-4-
185 (4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 92);
- 186 (2*R*)-2-[(4'-Methoxy-3'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-
187 1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 93);
- 188 (2*R*)-2-[(4'-Fluoro-3'-methylbiphenyl-4-yl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-
189 benzotriazin-3(4*H*)-yl)butanoic acid (Compound no. 94);

- 190 (2R)-2-[(Methylsulfonyl)[4'-(trifluoromethoxy)biphenyl-4-yl]amino]-4-(4-oxo-
191 1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 95);
- 192 (2R)-2-[(4'-Chloro-3'-(trifluoromethyl)biphenyl-4-yl](methylsulfonyl)amino]-4-
193 (4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 96);
- 194 (2R)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-[4-oxo-7-
195 (trifluoro methyl)-1,2,3-benzotriazin-3(4H)-yl]butanoic acid (Compound no. 97);
- 196 (2R)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(8-methyl-
197 4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 98);
- 198 (2R)-4-(7-Chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)-2-[(3'-fluoro-4'-
199 methoxybiphenyl-4-yl)(methylsulfonyl)amino]butanoic acid (Compound no. 99);
- 200 (2R)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(7-
201 methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 100);
- 202 (2R)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(6-methyl-
203 4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 101);
- 204 (2R)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(8-
205 methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 102);
- 206 (2R)-2-[(3'-Fluoro-4'-methoxybiphenyl-4-yl)(methylsulfonyl)amino]-4-(6-fluoro-4-
207 oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid (Compound no. 103);
- 208 4-(5-Chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)-2-[(4-
209 chlorophenyl)(methylsulfonyl)amino]butanoic acid (Compound no. 104);
- 210 2-[(4-Bromophenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-
211 yl)butanoic acid (Compound no. 105);
- 212 2-[(4-Chlorophenyl)(methylsulfonyl)amino]-4-(4-oxo-1,2,3-benzotriazin-3(4H)-
213 yl)butanoic acid (Compound no. 106);
- 214 2-[(4-Chlorophenyl)(methylsulfonyl)amino]-4-(7-methyl-4-oxo-1,2,3-
215 benzotriazin-3(4H)-yl)butanoic acid (Compound no. 107);
- 216 2-[(4-Chlorophenyl)(methylsulfonyl)amino]-4-(6-methoxy-4-oxo-1,2,3-
217 benzotriazin-3(4H)-yl)butanoic acid (Compound no. 108)
- 218 including racemates or diastereomers thereof; or a pharmaceutically acceptable salt thereof.

1 3. A pharmaceutical composition comprising a therapeutically effective amount of a
2 compound according to claims 1 and 2, together with one or more pharmaceutically
3 acceptable carriers, excipients or diluents.

1 4. A compound according to claims 1 and 2, for use in the treatment or prophylaxis of
2 an animal or a human suffering from an inflammatory or allergic disease.

1 5. A compound according to claim 4, wherein the inflammatory or allergic disease is
2 asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, psoriasis,

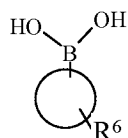
3 pulmonary fibrosis, pulmonary inflammation, acute respiratory distress syndrome,
 4 perodontitis, multiple sclerosis, gingivitis, atherosclerosis, dry eye, neointimal
 5 proliferation associated with restenosis and ischemic heart failure, stroke, renal disease,
 6 tumor metastasis.

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, selected from (i) the nonsteroidal anti-
 4 inflammatory agents piroxicam, diclofenac, propionic acids, fenamates,
 5 pyrazolones, salicylates, PDE-4 inhibitors, p38 MAP Kinase/Cathepsin
 6 inhibitors, (ii) leukotrienes LTC₄/LTD₄/LTE₄/LTB₄-Inhibitors, 5-
 7 lipoxygenase 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, like 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 10 (Formula 1 when R³ is
 2 heteroaryl, L¹ is bond, R² is CHO and R¹ is substituted aryl or heteroaryl) and Formula 13
 3 (Formula 1 when R³ is -OCONHR', L¹ is bond R² is CHO and R¹ is substituted aryl or
 4 heteroaryl) comprising:

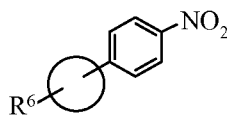
- 5 a) reacting 4-bromo-4-nitrobenzene with a compound of Formula 2



7 Formula 2

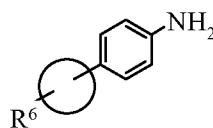
8 to give a compound of Formula 3;

95



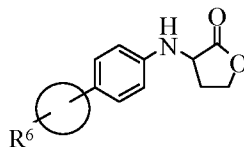
Formula 3

- b) reducing a compound of Formula 3 to give a compound of Formula 4



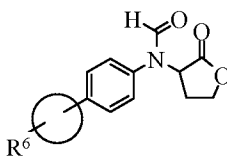
Formula 4

- c) reacting a compound of Formula 4 with alpha-bromolactone, to give a compound of Formula 5



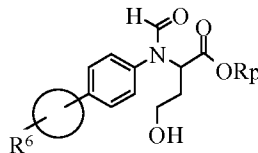
Formula 5

- d) formylating a compound of Formula 5 to give a compound of Formula 6



Formula 6

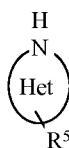
- e) ring opening of a compound of Formula 6 to give a compound of Formula 7



Formula 7

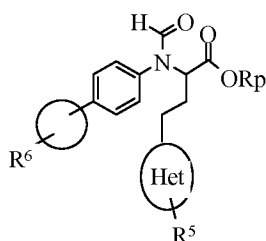
- f) reacting a compound of Formula 7 with a compound of Formula 8

96



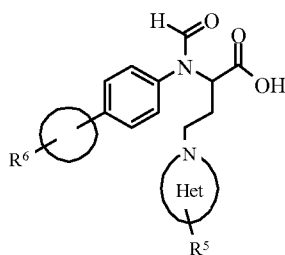
Formula 8

to give a compound of Formula 9



Formula 9

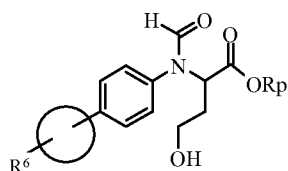
g) deprotecting a compound of Formula 9 to give a compound of Formula 10



Formula 10

or

h) reacting a compound of Formula 7 with a compound of Formula 11



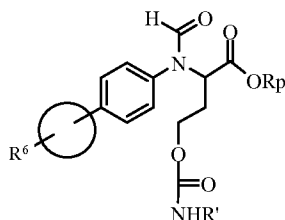
Formula 7



Formula 11

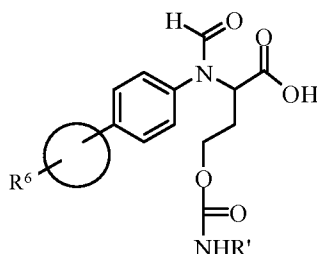
to give a compound of Formula 12

97



Formula 12

i) deprotecting a compound of Formula 12 to give a compound of Formula 13



Formula 13

wherein,

 is aryl or heteroaryl ring;

R^6 is hydrogen, alkyl, halogen, alkoxy or halogeno- C_1 - C_6 alkyl;

R_p is carboxy protecting group, such as methyl, ethyl, allyl, benzyl, t-butyl, silyl, BOC anhydride;

 is a heteroaryl ring;

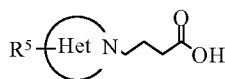
R' is C_6 - C_{12} aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclalkyl each of which is optionally substituted by one or more substituents independently selected from R^5 ;

R^5 is alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno- C_1 - C_6 alkyl, halogeno- C_1 - C_6 alkoxy, azido, thiol, alkylthiol, $-(CH_2)_n-OR_f$, $-C(=O)-R_f$, $-COOR_f$, $-NR_fR_q$, $-(CH_2)_n-C(=O)NR_fR_q$, $-(CH_2)_n-NHC(=O)-R_f$, $-(CH_2)_n-O-C(=O)-NR_fR_q$, $(CH_2)_n-NHC(=O)NR_fR_q$, $-(CH_2)_n-O-C(=O)-R_f$, $-(CH_2)_n-NH-$

50 C(=O)-R_f or -(CH₂)_nS(=O)_m-NR_fR_q {wherein R_f and R_q are independently
 51 selected from hydrogen, alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclyl,
 52 alkylaryl, alkylheteroaryl and alkylheterocyclyl; n can be zero or an integer
 53 between 1 and 2 and m is an integer 0-2}.

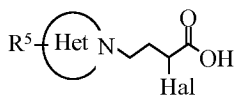
1 8. A process for preparing a compound of Formula 20 (Formula 1 when R³ is
 2 heteroaryl, L¹ is bond, R² is SO₂-C₁₋₆-alkyl and R¹ is substituted aryl or heteroaryl)
 3 comprising:

4 a) halogenating a compound of Formula 14 at alpha position



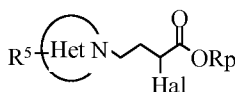
6 Formula 14

7 to give a compound of Formula 15



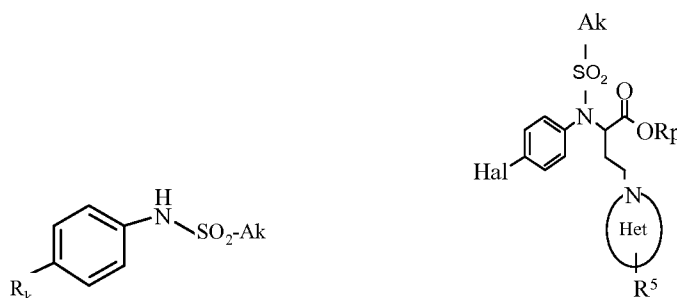
9 Formula 15

10 b) protecting a compound of Formula 15 to give a compound of Formula 16



12 Formula 16

13 c) reacting a compound of Formula 16 with a compound of Formula 17 (where
 14 R_k is halogen) to give a compound of Formula 18



16

Formula 17

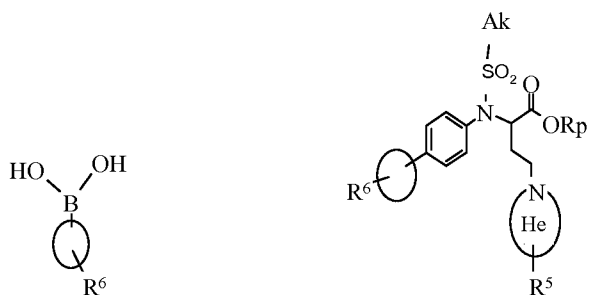
Formula 18

17

d) coupling of a compound of Formula 18 with a compound of Formula 2 to

18

give a compound of Formula 19



19

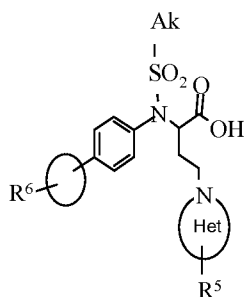
20

Formula 2

Formula 19

21

e) deprotecting a compound of Formula 19 to give a compound of Formula 20



22

23

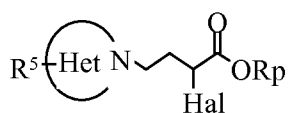
Formula 20

24 or

25

f) reacting a compound of Formula 16, with a compound of Formula 17 (where

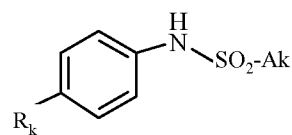
26

 R_k is aryl/heteroaryl substituted with R^6)

27

28

Formula 16

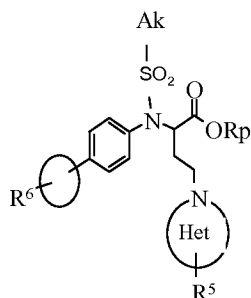


Formula 17

29

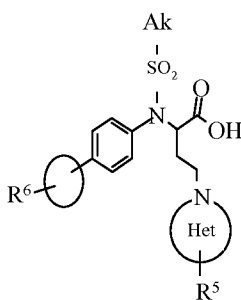
to give a compound of Formula 19

100



Formula 19

g) deprotecting a compound of Formula 19 to give a compound of Formula 20



Formula 20

wherein,



is a heteroaryl ring;

R_p is carboxy protecting group such as methyl, ethyl, allyl, benzyl, t-butyl, silyl, BOC anhydride;

R^5 is 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 $-(CH_2)_nS(=O)_m-NR_fR_q$ {wherein R_f and R_q are independently selected from hydrogen, alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and alkylheterocyclyl; n can be zero or an integer between 1 and 2 and m is an integer 0-2};

Hal is F, Cl, Br, I;

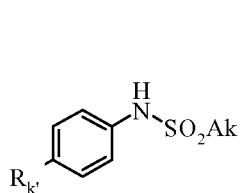
48 Ak is C₁₋₆alkyl;

49  is aryl or heteroaryl ring;

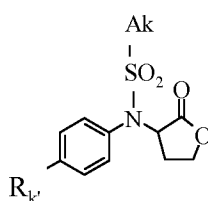
50 R⁶ is hydrogen, alkyl, halogen, alkoxy or halogeno-C₁-C₆ alkyl.

1 9. A process for preparing a compound of Formula 26b (Formula 1 when R³ is
 2 heteroaryl, L¹ is bond, R² is SO₂-C₁₋₆-alkyl and R¹ is aryl/heteroaryl substituted with
 3 OR⁶) and Formula 29 (Formula 1 when R³ is heteroaryl, L¹ is bond, R² is SO₂-C₁₋₆-alkyl
 4 and R¹ is halogen/hydrogen, alkoxy/aryloxy) comprising:

5 a) reacting a compound of Formula 17a with alpha hydroxy lactone, to give a
 6 compound of Formula 21

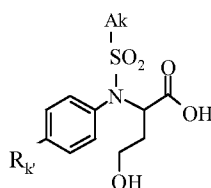


8 Formula 17a



Formula 21

9 b) ring opening of a compound of Formula 21 to give a compound of Formula
 10 22

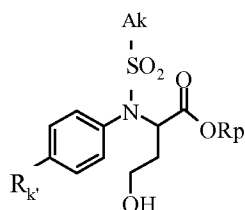


12 Formula 22

13 c) protecting a compound of Formula 22 at carboxyl group to give a compound
 14 of Formula 23

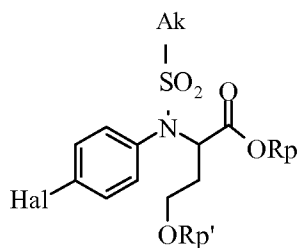
15

102



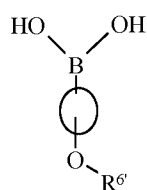
Formula 23

- d) protecting a compound of Formula 23 (when $R_{k'}$ is halogen) at hydroxyl group to give a compound of Formula 24

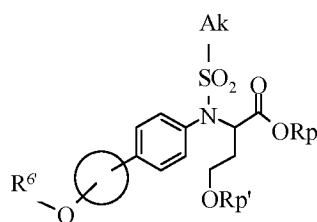


Formula 24

- e) coupling of a compound of Formula 24 with a compound of Formula 24a, to give a compound of Formula 25

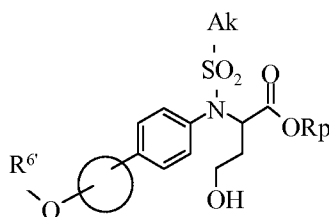


Formula 24a



Formula 25

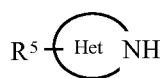
- f) deprotecting a compound of Formula 25 to give a compound of Formula 26



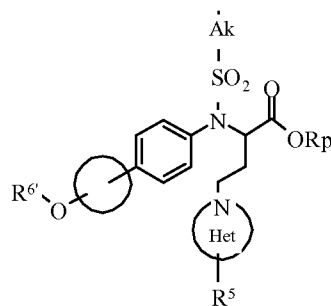
Formula 26

103

- 28 g) reacting a compound of Formula 26 with a compound of Formula 27, to give
 29 a compound of Formula 26a

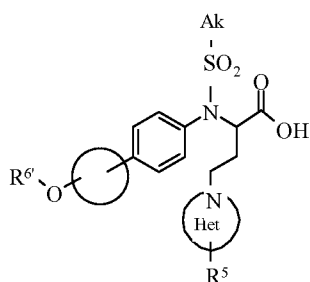


Formula 27



Formula 26a

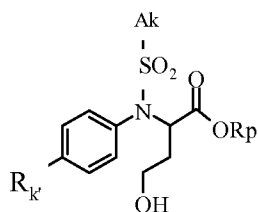
- 32 h) deprotecting a compound of Formula 26a to give a compound of Formula
 33 26b



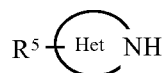
Formula 26b

36 or

- 37 i) reacting a compound of Formula 23 (when R_{k'} is
 38 alkoxy/aryloxy/halogen/hydrogen) with a compound of Formula 27



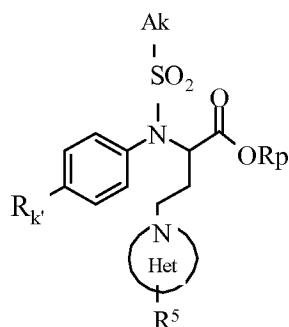
Formula 23



Formula 27

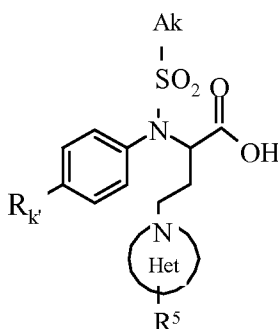
41 to give a compound of Formula 28

104



Formula 28

j) deprotecting a compound of Formula 28 to give a compound of Formula 29;



Formula 29

wherein,

Ak is C₁₋₆alkyl;

R_p is carboxy protecting group such as methyl, ethyl, allyl, benzyl, t-butyl, silyl, BOC anhydride;

R_p is hydroxyl protecting group such as benzoyl, silyl groups *tert*-butyldimethylsilyl, trimethylsilyl, *tert*-butyldimethylsilyloxymethyl, triisopropylsilyl;

 is a heteroaryl ring;

R_k is hydrogen, halogen, alkoxy, aryloxy, aryl, carboxy;

R⁵ is alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno-C₁-C₆ alkyl, halogeno-C₁-C₆ alkoxy, azido, thiol, alkylthiol, -(CH₂)_n-OR_f, -C(=O)-R_f, -

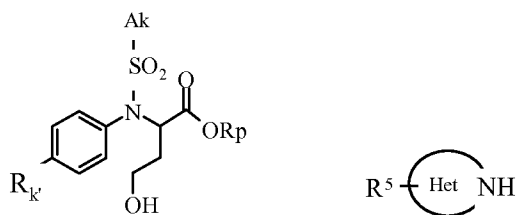
58 COOR_f, -NR_fR_q, -(CH₂)_n-C(=O)NR_fR_q, -(CH₂)_n-NHC(=O)-R_f, -(CH₂)_n-O-
 59 C(=O)-NR_fR_q, (CH₂)_n NHC(=O)NR_fR_q, -(CH₂)_n-O-C(=O)-R_f, -(CH₂)_n-NH-
 60 C(=O)-R_f or -(CH₂)_nS(=O)_m-NR_fR_q {wherein R_f and R_q are independently
 61 selected from hydrogen, alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclyl,
 62 alkylaryl, alkylheteroaryl and alkylheterocyclyl; n can be zero or an integer
 63 between 1 and 2 and m is an integer 0-2}.

64  is aryl or heteroaryl ring;

65 **OR^{6'}** wherein **R^{6'}** is hydrogen, alkyl, halogen, alkoxy or halogeno-C₁-C₆
 66 alkyl.

1 10. A process for preparing a compound of Formula 31 (Formula 1 when R³ is
 2 heteroaryl, L¹ is bond, R² is SO₂-C₁₋₆-alkyl and R¹ is aryl/heteroaryl substituted with
 3 halogen) and Formula 36 (Formula 1 when R³ is heteroaryl, L¹ is -CONH-, R² is SO₂-Ak
 4 and R¹ is aryl/heteroaryl) comprising:

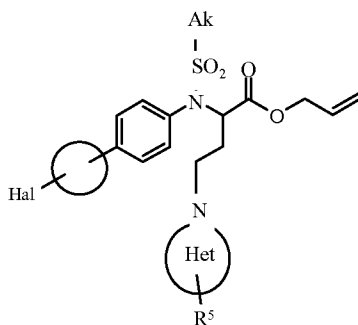
5 a) reacting a compound of Formula 23 (when R_{k'} is aryl/heteroaryl substituted
 6 with halogen and Rp is allyl) with a compound of Formula 27



Formula 23

Formula 27

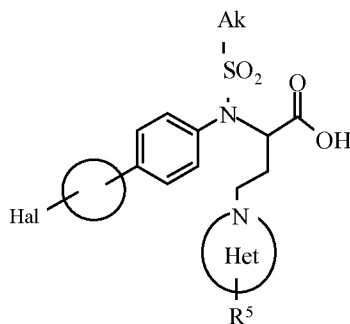
9 to give a compound of Formula 30



106

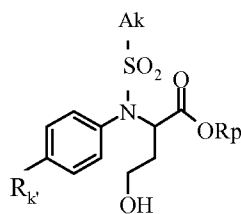
Formula 30

b) deprotecting a compound of Formula 30 to give a compound of Formula 31;

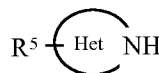


Formula 31

or

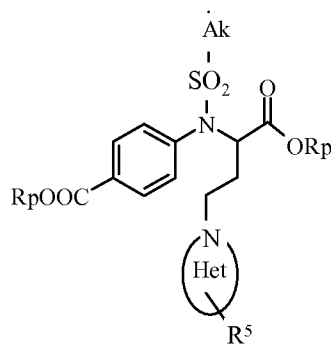
c) reacting a compound of Formula 23 (when $R_{k'}$ is $-\text{COOR}_p$) with a compound of Formula 27

Formula 23



Formula 27

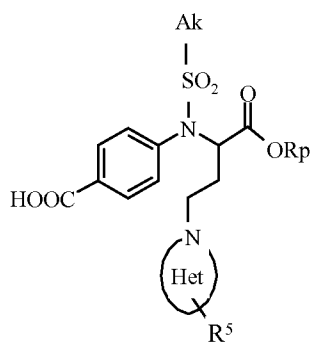
to give a compound of Formula 32;



Formula 32

107

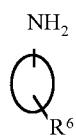
- 23 d) deprotecting a compound of Formula 32 to give a compound of Formula 33;



24

25 Formula 33

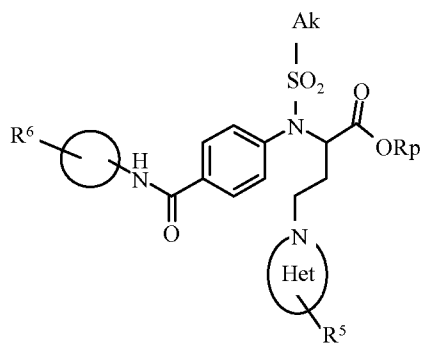
- 26 e) coupling of a compound of Formula 33 with a compound of Formula 34



27

28 Formula 34

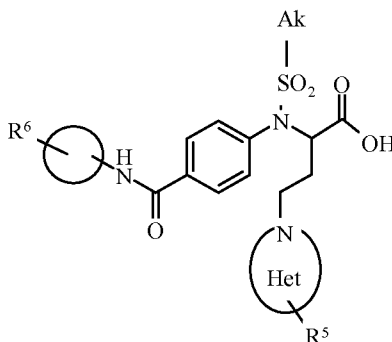
- 29 to give a compound of Formula 35



30

31 Formula 35

32 f) deprotecting a compound of Formula 35 to give a compound of Formula 36;



33
34 Formula 36

35 wherein,

36 Ak is C₁₋₆alkyl;

37 Hal is F, Cl, Br, I;

38 **R_p** is carboxy protecting group such as methyl, ethyl, allyl, benzyl, t-butyl,
39 silyl, BOC anhydride;

40 is aryl or heteroaryl ring;

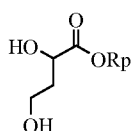
41 is a heteroaryl ring;

42 **R⁵** is alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno-C₁-C₆ alkyl,
43 halogeno-C₁-C₆ alkoxy, azido, thiol, alkylthiol, -(CH₂)_n-OR_f, -C(=O)-R_f, -
44 COOR_f, -NR_fR_q, -(CH₂)_n-C(=O)NR_fR_q, -(CH₂)_n-NHC(=O)-R_f, -(CH₂)_n-O-
45 C(=O)-NR_fR_q, (CH₂)_n NHC(=O)NR_fR_q, -(CH₂)_n-O-C(=O)-R_f, -(CH₂)_n-NH-
46 C(=O)-R_f or -(CH₂)_nS(=O)_m-NR_fR_q {wherein R_f and R_q are independently
47 selected from hydrogen, alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclyl,
48 alkylaryl, alkylheteroaryl and alkylheterocyclyl; n can be zero or an integer
49 between 1 and 2 and m is an integer 0-2};

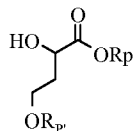
50 **R⁶** is hydrogen, alkyl, halogen, alkoxy or halogeno-C₁-C₆ alkyl.

1 11. A process for preparing a compound of Formula 43 (Formula 1 when R³ is
2 heteroaryl, L¹ is bond, R² is SO₂-C₁₋₆-alkyl and R¹ is aryl/heteroaryl) comprising:

- a) protecting a compound of Formula 37, to give compound of Formula 38



Formula 37

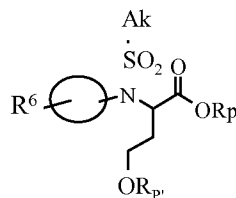


Formula 38

- c) reacting a compound of Formula 38 with a compound of Formula 39 to give a compound of Formula 40

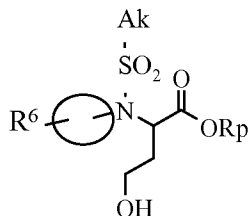


Formula 39



Formula 40

- d) deprotecting a compound of Formula 40 to give a compound of Formula 41

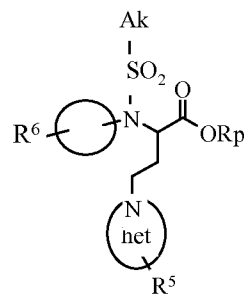


Formula 41

- e) reacting a compound of Formula 41 with a compound of Formula 27 to give a compound of Formula 42

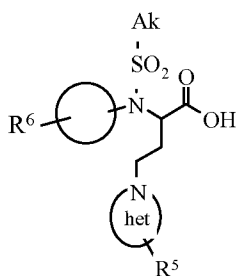


Formula 27



Formula 42

- 17 f) deprotecting a compound of Formula 42 to give a compound of Formula 43



18

19 Formula 43

20 wherein,

21 Ak is C₁₋₆ alkyl:22  is aryl or heteroaryl ring;23 **R_p** is carboxy protecting group such as methyl, ethyl, allyl, benzyl, t-butyl,

24 silyl, BOC anhydride;

25 **R_p** is hydroxyl protecting group such as benzoyl, silyl groups *tert*-26 butyldimethylsilyl, trimethylsilyl, *tert*-butyldimethylsilyloxymethyl,

27 triisopropylsilyl;

28  is a heteroaryl ring;29 **R⁵** is alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno-C₁-C₆ alkyl,30 halogeno-C₁-C₆ alkoxy, azido, thiol, alkylthiol, -(CH₂)_n-OR_f, -C(=O)-R_f, -31 COOR_f, -NR_fR_q, -(CH₂)_n-C(=O)NR_fR_q, -(CH₂)_n-NHC(=O)-R_f, -(CH₂)_n-O-32 C(=O)-NR_fR_q, (CH₂)_n NHC(=O)NR_fR_q, -(CH₂)_n-O-C(=O)-R_f, -(CH₂)_n-NH-33 C(=O)-R_f or -(CH₂)_nS(=O)_m-NR_fR_q {wherein R_f and R_q are independently

34 selected from hydrogen, alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclyl,

35 alkylaryl, alkylheteroaryl and alkylheterocyclyl; n can be zero or an integer

36 between 1 and 2 and m is an integer 0-2};

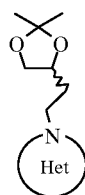
37 **R⁶** is hydrogen, alkyl, halogen, alkoxy or halogeno-C₁-C₆ alkyl.

12. A process for preparing a compound of Formula 52 (Formula 1 when R³ is heteroaryl, L¹ is bond, R² is SO₂-C₁₋₆-alkyl and R¹ is substituted aryl/heteroaryl) comprising:

a) reacting a compound of Formula 44 with 4-(2-hydroxyethyl)-2,2-dimethyl 1,3-dioxolane to give a compound of Formula 45

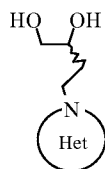


Formula 44



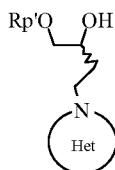
Formula 45

b) ring opening of a compound of Formula 45 to give a compound of Formula 46



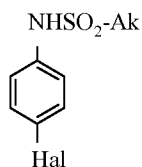
Formula 46

c) protecting a compound of Formula 46 to give a compound of Formula 47

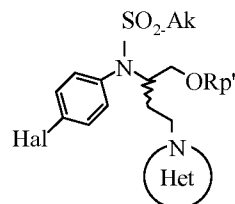


Formula 47

d) reacting a compound of Formula 47 with a compound of Formula 48 to give a compound of Formula 49

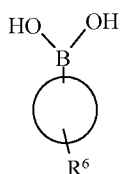


Formula 48

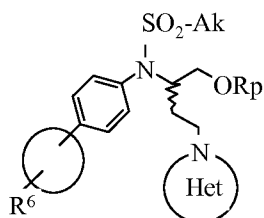


Formula 49

- e) coupling of a compound of Formula 49 with a compound of Formula 2 to give a compound of Formula 50

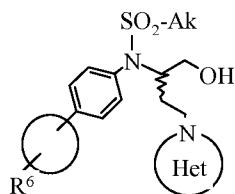


Formula 2



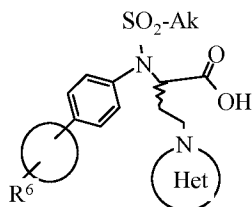
Formula 50

- f) deprotecting a compound of Formula 50 to give a compound of Formula 51



Formula 51

- g) oxidizing a compound of Formula 51 to give a compound of Formula 52



Formula 52

wherein,

Ak is C₁₋₆ alkyl:

31  is aryl or heteroaryl ring;

32 **R_p'** is hydroxyl protecting group such as benzoyl, silyl including *tert*-
 33 butyldimethylsilyl, trimethylsilyl, *tert*-butyldimethylsilyloxymethyl,
 34 triisopropylsilyl;

35  is a heteroaryl ring;

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

37 **R⁶** is hydrogen, alkyl, halogen, alkoxy or halogeno-C₁-C₆ alkyl.

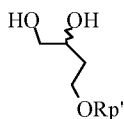
1 13. A process for preparing a compound of Formula 61 (Formula 1 when **R³** is
 2 heteroaryl, **L¹** is bond, **R²** is SO₂-C₁₋₆-alkyl and **R¹** is substituted aryl/heteroaryl)
 3 comprising:

4 a) protecting 4-(2-hydroxyethyl)-2,2-dimethyl 1,3-dioxolane to give a
 5 compound of Formula 53;



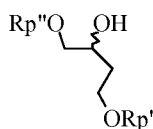
6
7 Formula 53

8 b) ring opening of a compound of Formula 53 to give a compound of Formula
 9 54;



10
11 Formula 54

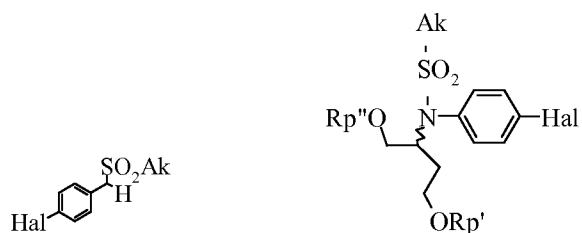
12 c) protecting a compound of Formula 54 to give a compound of Formula 55;



13
14 Formula 55

114

- 15 d) reacting a compound of Formula 55 with a compound of Formula 48 to give
 16 a compound of Formula 56;



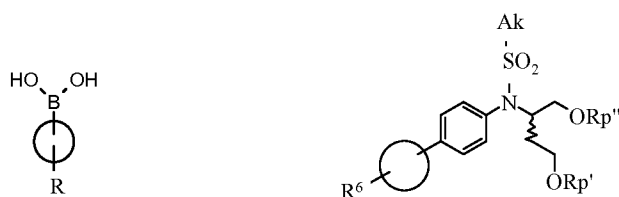
17

18

Formula 48

Formula 56

- 19 e) coupling of a compound of Formula 56 with a compound of Formula 2 to
 20 give a compound of Formula 57



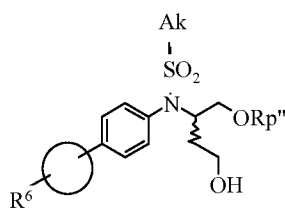
21

22

Formula 2

Formula 57

- 23 f) deprotecting a compound of Formula 57 to give a compound of Formula 58



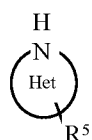
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25

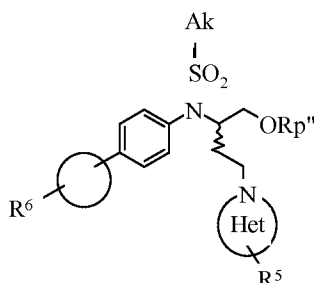
Formula 58

- 26 g) reacting a compound of Formula 58 with a compound of Formula 27 to give
 27 a compound of Formula 59

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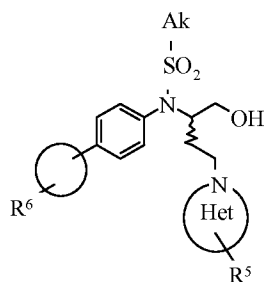


Formula 27



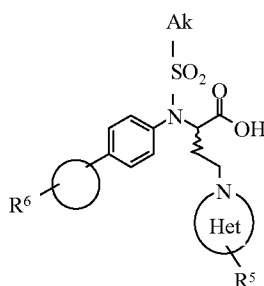
Formula 59

h) deprotecting a compound of Formula 59 to give a compound of Formula 60



Formula 60

i) oxidizing a compound of Formula 60 to give a compound of Formula 61



Formula 61

wherein,

Ak is C₁₋₆ alkyl;

⊖ is aryl or heteroaryl ring;

39 R_p and R_p is hydroxyl protecting group such as benzoyl, silyl groups *tert*-
 40 butyldimethylsilyl, trimethylsilyl, *tert*-butyldimethylsilyloxymethyl,
 41 triisopropylsilyl;

42  is a heteroaryl ring;

43 R^5 is alkyl, alkenyl, alkynyl, cyano, nitro, halogen, halogeno- C_1 - C_6 alkyl,
 44 halogeno- C_1 - C_6 alkoxy, azido, thiol, alkylthiol, $-(CH_2)_n-OR_f$, $-C(=O)-R_f$, -
 45 $COOR_f$, $-NR_fR_q$, $-(CH_2)_n-C(=O)NR_fR_q$, $-(CH_2)_n-NHC(=O)-R_f$, $-(CH_2)_n-O-$
 46 $C(=O)-NR_fR_q$, $(CH_2)_n NHC(=O)NR_fR_q$, $-(CH_2)_n-O-C(=O)-R_f$, $-(CH_2)_n-NH-$
 47 $C(=O)-R_f$ or $-(CH_2)_nS(=O)_m-NR_fR_q$ {wherein R_f and R_q are independently
 48 selected from hydrogen, alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclyl,
 49 alkylaryl, alkylheteroaryl and alkylheterocyclyl; n can be zero or an integer
 50 between 1 and 2 and m is an integer 0-2};

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

52 R^6 is hydrogen, alkyl, halogen, alkoxy or halogeno- C_1 - C_6 alkyl.