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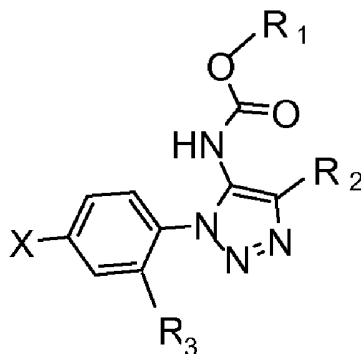
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(54) Title: N-ARYLTRIAZOLE COMPOUNDS AS LPAR ANTAGONISTS



(I)

(57) Abstract: Provided herein are compounds of the formula (I): as well as pharmaceutically acceptable salts thereof, wherein the substituents are as those disclosed in the specification. These compounds, and the pharmaceutical compositions containing them, are useful for the treatment of inflammatory diseases and disorders such as, for example, pulmonary fibrosis.

N-ARYLTRIAZOLE COMPOUNDS AS LPAR ANTAGONISTS

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal of an inflammatory disease or disorder, and in particular to N-aryltriazole compounds, their manufacture, pharmaceutical compositions containing them and their use as lysophosphatidic acid (LPA) antagonists.

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LPA is a family of bioactive phosphate lipids which function like a growth factor mediator by interacting with LPA receptors, a family of G-protein-coupled receptors (GPCRs). The lipid family has long chain saturated (such as C18:0 or C16:0) or unsaturated (C18:1 or C20:4) carbon chains attached to the glycerol through an ester linkage. In biological systems, LPA is produced by multi-step enzymatic pathways through the de-esterification of membrane phospholipids. Enzymes that contribute to LPA synthesis include lysophospholipase D (lysoPLD), autotaxin (ATX), phospholipase A1 (PLA1), phospholipase A2 (PLA2) and acylglycerol kinase (AGK) (British J. of Pharmacology 2012, 165, 829-844).

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There are at least six LPA receptors identified (LPAR1-6). LPA signaling exerts a broad range of biological responses on many different cell types, which can lead to cell growth, cell proliferation, cell migration and cell contraction. Up regulation of the LPA pathway has been linked to multiple diseases, including cancer, allergic airway inflammation, and fibrosis of the kidney, lung and liver. Therefore, targeting LPA receptors or LPA metabolic enzymes could provide new approaches towards the treatment of medically important diseases that include neuropsychiatric disorders, neuropathic pain, infertility, cardiovascular disease, inflammation, fibrosis, and cancer (Annu. Rev. Pharmacol. Toxicol. 2010, 50, 157-186; J. Biochem. 2011, 150, 223-232).

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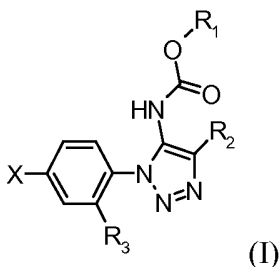
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Fibrosis is the result of an uncontrolled tissue healing process leading to excessive accumulation of extracellular matrix (ECM). Recently it was reported that the LPA1 receptor was over expressed in idiopathic pulmonary fibrosis (IPF) patients. Mice with LPA1 receptor knock-out were protected from bleomycin-induced lung fibrosis (Nature Medicine 2008, 14, 45-54).

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Thus, antagonizing LPA1 receptor may be useful for the treatment of fibrosis, such as renal fibrosis, pulmonary fibrosis, arterial fibrosis and systemic sclerosis.

In an embodiment of the present invention, provided are compounds of general formula (I):

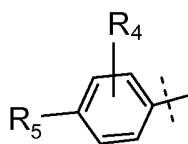


wherein:

R₁ is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or -CF₃;

R₂ is hydrogen or lower alkyl;

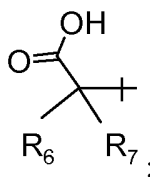
R₃ is hydrogen, fluorine or -OCH₃;



X is cycloalkyl acetic acid or

R₄ is hydrogen or halogen;

R₅ is hydrogen, cyano, tetrazole-cyclopropyl, methanesulfonylaminocarbonyl-cyclopropyl or

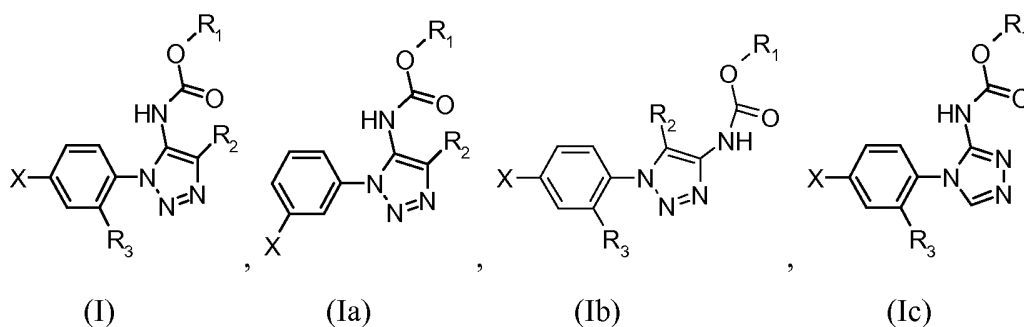


R₆ and R₇ are, independently of each other, hydrogen or lower alkyl; or

R₆ and R₇, together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, provided are compounds of general formula (I), (Ia), (Ib) or (Ic):

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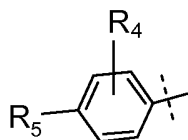
wherein:

R₁ is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cyclo-
 alkyl, unsubstituted phenyl or phenyl substituted with halogen or -CF₃;

R₂ is hydrogen or lower alkyl;

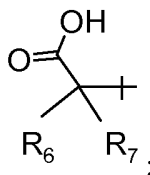
R₃ is hydrogen, fluorine or -OCH₃;

X is cycloalkyl acetic acid or



R₄ is hydrogen or halogen;

R₅ is hydrogen, cyano, tetrazole-cyclopropyl, methanesulfonylaminocarbonyl-cyclopropyl or

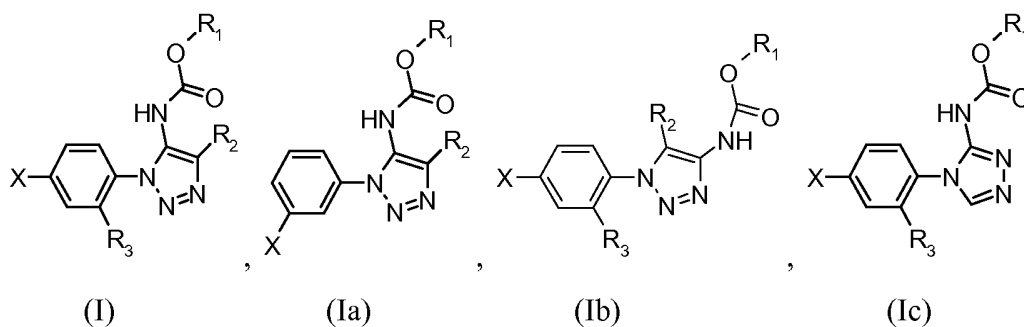


R₆ and R₇ are, independently of each other, hydrogen or lower alkyl; or

R₆ and R₇, together with the carbon to which they are attached, form a cycloalkyl group,

or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, provided are compounds of general formula (I), (Ia), (Ib) or (Ic):



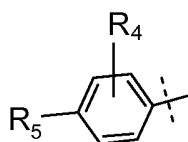
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wherein:

R₁ is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or -CF₃;

R₂ is hydrogen or lower alkyl;

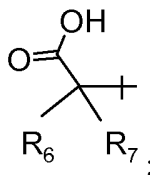
5 R₃ is hydrogen, fluorine or -OCH₃;



X is cycloalkyl acetic acid or

R₄ is hydrogen or halogen;

R₅ is hydrogen, cyano, tetrazole-cyclopropyl, methanesulfonylaminocarbonyl-cyclopropyl or



10

R₆ and R₇ are, independently of each other, hydrogen, lower alkyl or lower alkenyl; or

R₆ and R₇, together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

15 In a further embodiment of the invention, provided is a pharmaceutical composition comprising a therapeutically effective amount of a compound according to formula (I) and a therapeutically inert carrier.

20 In a still further embodiment of the invention, provided is a method for the treatment or prophylaxis of pulmonary fibrosis, which method comprises the step of administering a therapeutically effective amount of a compound according to formula (I) to a patient in need thereof.

All documents cited to or relied upon below are expressly incorporated herein by reference.

25

Unless otherwise indicated, the following specific As used herein, the term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated

aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms.

The term “lower alkyl”, alone or in combination with other groups, refers to a branched or straight-chain alkyl radical of one to nine carbon atoms, preferably one to six carbon atoms, more preferably one to four carbon atoms. This term is further exemplified by radicals such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, isobutyl, *t*-butyl, *n*-pentyl, 3-methylbutyl, *n*-hexyl, 2-ethylbutyl and the like.

The term “cycloalkyl” refers to a monovalent mono- or polycarbocyclic radical of three to ten, preferably three to six carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl and the like. In a preferred embodiment, the “cycloalkyl” moieties can optionally be substituted with one, two, three or four substituents, with the understanding that said substituents are not, in turn, substituted further. Each substituent can independently be, alkyl, alkoxy, halogen, amino, hydroxyl or oxygen (O=) unless otherwise specifically indicated. Examples of cycloalkyl moieties include, but are not limited to, optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted cyclohexyl, optionally substituted cycloheptyl, and the like or those which are specifically exemplified herein.

The term “heterocycloalkyl” denotes a mono- or polycyclic alkyl ring, wherein one, two or three of the carbon ring atoms is replaced by a heteroatom such as N, O or S. Examples of heterocycloalkyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxanyl and the like. The heterocycloalkyl groups may be unsubstituted or substituted and attachment may be through their carbon frame or through their heteroatom(s) where appropriate, with the understanding that said substituents are not, in turn, substituted further.

The term “aryl” refers to an aromatic mono- or polycarbocyclic radical of 6 to 12 carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalene, 1,2-dihydronaphthalene, indanyl, 1H-indenyl and the like.

The term "heteroaryl," refers to an aromatic mono- or polycyclic radical of 5 to 12 atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, and S, with the remaining ring atoms being C. Examples of such groups include, but are not limited to, pyridine, thiazole and pyranyl.

The alkyl, lower alkyl, aryl and heteroaryl groups described above may be substituted independently with one, two, or three substituents, with the understanding that said substituents are not, in turn, substituted further. Substituents may include, for example, halogen, lower alkyl, -CF₃, -SO₂CH₃, alkoxy, -C(O)CH₃, -OH, -SCH₃ and -CH₂CH₂OH.

As used herein, the term "alkoxy" means alkyl-O-; and "alkoyl" means alkyl-CO-. Alkoxy substituent groups or alkoxy-containing substituent groups may be substituted by, for example, one or more alkyl groups, with the understanding that said substituents are not, in turn, substituted further.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine, chlorine or bromine radical, and more preferably a fluorine or chlorine radical.

Compounds of formula I can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbents or eluant). The invention embraces all of these forms.

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic,

hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, *p*-toluenesulfonic and the like. Particularly preferred are fumaric, hydrochloric, hydrobromic, phosphoric, succinic, sulfuric and methanesulfonic acids. Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminum salts.

In the practice of the method of the present invention, an effective amount of any one of the compounds of this invention or a combination of any of the compounds of this invention or a pharmaceutically acceptable salt thereof, is administered via any of the usual and acceptable methods known in the art, either singly or in combination. The compounds or compositions can thus be administered orally (e.g., buccal cavity), sublingually, parenterally (e.g., intramuscularly, intravenously, or subcutaneously), rectally (e.g., by suppositories or washings), transdermally (e.g., skin electroporation) or by inhalation (e.g., by aerosol), and in the form or solid, liquid or gaseous dosages, including tablets and suspensions. The administration can be conducted in a single unit dosage form with continuous therapy or in a single dose therapy ad libitum. The therapeutic composition can also be in the form of an oil emulsion or dispersion in conjunction with a lipophilic salt such as pamoic acid, or in the form of a bio-degradable sustained-release composition for subcutaneous or intramuscular administration.

Useful pharmaceutical carriers for the preparation of the compositions hereof, can be solids, liquids or gases. Thus, the compositions can take the form of tablets, pills, capsules, suppositories, powders, enterically coated or other protected formulations (e.g. binding on ion-exchange resins or packaging in lipid-protein vesicles), sustained release formulations, solutions, suspensions, elixirs, aerosols, and the like. The carrier can be selected from the various oils including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly (when isotonic with the blood) for injectable solutions. For example, formulations for intravenous administration comprise sterile aqueous solutions of the active ingredient(s) which are prepared by dissolving solid active ingredient(s) in water to produce an aqueous solution, and rendering the solution sterile. Suitable pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, talc, gelatin, malt, rice, flour, chalk, silica, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The

compositions may be subjected to conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting or emulsifying agents, salts for adjusting osmotic pressure, buffers and the like. Suitable pharmaceutical carriers and their formulation are described in **Remington's Pharmaceutical Sciences** by E. W. Martin. Such compositions will, in any event, contain an effective amount of the active compound together with a suitable carrier so as to prepare the proper dosage form for proper administration to the recipient.

The dose of a compound of the present invention depends on a number of factors, such as, for example, the manner of administration, the age and the body weight of the subject, and the condition of the subject to be treated, and ultimately will be decided by the attending physician or veterinarian. Such an amount of the active compound as determined by the attending physician or veterinarian is referred to herein, and in the claims, as a "therapeutically effective amount". For example, the dose of a compound of the present invention is typically in the range of about 1 to about 1000 mg per day. Preferably, the therapeutically effective amount is in an amount of from about 1 mg to about 500 mg per day.

In one embodiment of the present invention, provided is a compound of formula (I) wherein R_1 is dimethylpropyl, butyl or isopropyl.

In another embodiment of the present invention, provided is a compound of formula (I) wherein R_1 is lower alkyl substituted with cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or $-CF_3$.

In another embodiment of the present invention, provided is a compound of formula (I) wherein R_1 is $-CH(CH_3)$ -phenyl, $-CH(CH_3)$ -fluorophenyl, $-CH(CH_3)$ -trifluoromethylphenyl, ethyl-cyclopropyl or ethyl-cyclobutyl.

In another embodiment of the present invention, provided is a compound of formula (I) wherein R_2 is lower alkyl.

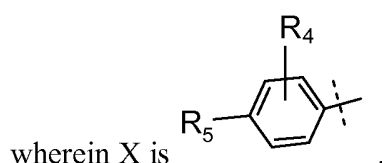
In another embodiment of the present invention, provided is a compound of formula (I) wherein R_2 is methyl.

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In another embodiment of the present invention, provided is a compound of formula (I) wherein R_3 is hydrogen.

5 In another embodiment of the present invention, provided is a compound of formula (I) wherein X is cyclohexyl acetic acid.

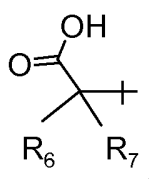
In another embodiment of the present invention, provided is a compound of formula (I)



10 In another embodiment of the present invention, provided is a compound of formula (I) wherein R_4 is hydrogen or fluorine.

In another embodiment of the present invention, provided is a compound of formula (I) wherein R_5 is hydrogen, cyano, tetrazole-cyclopropyl or methanesulfonylaminocarbonyl-
15 cyclopropyl.

In another embodiment of the present invention, provided is a compound of formula (I) wherein R_5 is



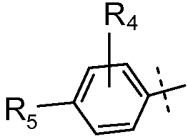
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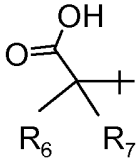
In another embodiment of the present invention, provided is a compound of formula (I) wherein R_6 and R_7 are, independently of each other, hydrogen or methyl.

In another embodiment of the present invention, provided is a compound of formula (I)
25 wherein R_6 and R_7 , together with the carbon to which they are attached, form a cyclopropyl group.

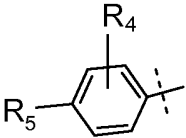
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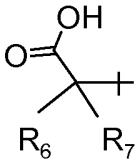
In another embodiment of the present invention, provided are compounds of general formula (I) wherein R_1 is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cycloalkyl or unsubstituted phenyl; R_2 is hydrogen or lower alkyl; R_3 is hydrogen,

fluorine or $-OCH_3$; X is cycloalkyl acetic acid or ; wherein R_4 is hydrogen or halogen and R_5 is hydrogen, cyano, tetrazole-cyclopropyl, methanesulfonylamino-carbonyl-

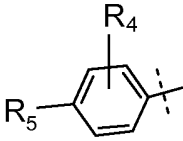
cyclopropyl or ; wherein R_6 and R_7 are, independently of each other, hydrogen or lower alkyl; or R_6 and R_7 , together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

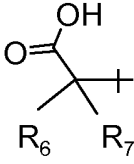
In another embodiment of the present invention, provided are compounds of general formula (I) wherein R_1 is lower alkyl being substituted with unsubstituted phenyl; R_2 is hydrogen or lower alkyl; R_3 is hydrogen, fluorine or $-OCH_3$; X is cycloalkyl acetic acid or

; wherein R_4 is hydrogen or halogen and R_5 is hydrogen, cyano, tetrazole-

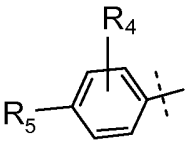
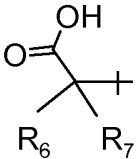
cyclopropyl, methanesulfonylamino-carbonyl-cyclopropyl or ; wherein R_6 and R_7 are, independently of each other, hydrogen or lower alkyl; or R_6 and R_7 , together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, provided are compounds of general formula (I) wherein R_1 is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or $-CF_3$; R_2 is ethyl;

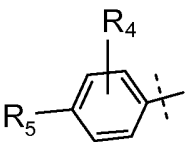
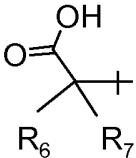
R₃ is hydrogen, fluorine or –OCH₃; X is cycloalkyl acetic acid or ; wherein R₄ is hydrogen or halogen and R₅ is hydrogen, cyano, tetrazole-cyclopropyl, methanesulf-

onfylaminocarbonyl-cyclopropyl or ; wherein R₆ and R₇ are, independently of each other, hydrogen or lower alkyl; or R₆ and R₇, together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, provided are compounds of general formula (I) wherein R₁ is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or –CF₃; R₂ is hydrogen or lower alkyl; R₃ is hydrogen, fluorine or –OCH₃; X is cycloalkyl acetic acid or

; wherein R₄ is hydrogen or halogen and R₅ is ; wherein R₆ and R₇, together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

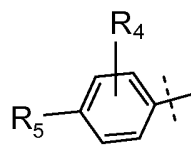
In another embodiment of the present invention, provided are compounds of general formula (I) wherein R₁ is lower alkyl being substituted with unsubstituted phenyl; R₂ is hydrogen or lower alkyl; R₃ is hydrogen, fluorine or –OCH₃; X is cycloalkyl acetic acid or

; wherein R₄ is hydrogen or halogen and R₅ is ; wherein R₆ and R₇, together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, provided are compounds of general formula (I) wherein R₁ is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted

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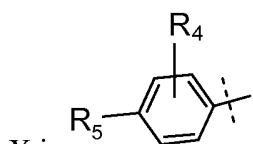
with cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or $-\text{CF}_3$; R_2 is hydrogen or lower alkyl; R_3 is hydrogen, fluorine or $-\text{OCH}_3$; X is cycloalkyl acetic acid or

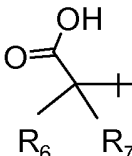
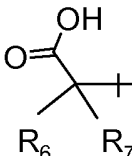


; wherein R_4 is hydrogen or halogen and R_5 is methanesulfonylamino-carbonyl-cyclopropyl, or a pharmaceutically acceptable salt thereof.

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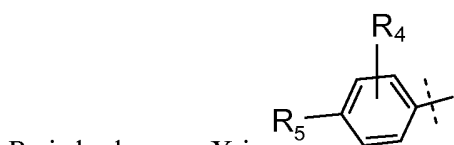
In another embodiment of the present invention, provided are compounds of general formula (Ia) wherein R_1 is lower alkyl being substituted with unsubstituted phenyl; R_2 is lower alkyl;

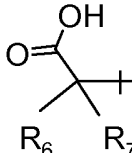
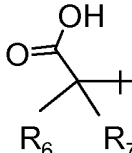


X is ; wherein R_4 is hydrogen and R_5 is ; R_6 and R_7 are hydrogen or R_6 and R_7 , together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

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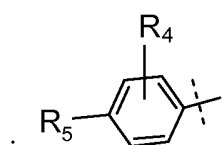
In another embodiment of the present invention, provided are compounds of general formula (Ib) wherein R_1 is lower alkyl being substituted with unsubstituted phenyl; R_2 is lower alkyl;

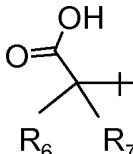
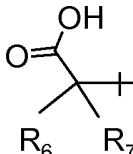


R_3 is hydrogen; X is ; wherein R_4 is hydrogen and R_5 is ; wherein R_6 and R_7 are hydrogen or R_6 and R_7 , together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

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In another embodiment of the present invention, provided are compounds of general formula (Ic) wherein R_1 is lower alkyl being substituted with unsubstituted phenyl; R_3 is hydrogen; X



is ; wherein R_4 is hydrogen and R_5 is ; wherein R_6 and R_7 , together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

20

Particular compounds of formula (I) include the following:

1-{4'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

{4'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid;

1-{4'-[5-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

{4'-[5-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid;

1-(4'-{5-[(R)-1-(2-Fluoro-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid;

1-(4'-{4-Methyl-5-[(R)-1-(2-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid;

1-(4'-{4-Methyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid;

1-{4'-[5-((R)-Indan-1-yloxy carbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

1-{4'-[5-((R)-1,2-Dimethyl-propoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

1-{4'-[5-((R)-*sec*-Butoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

1-[4'-(5-*iso*-Propoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid;

1-{4'-[5-(1-Cyclopropyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

1-{4'-[5-(1-Cyclobutyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

1-[4'-(5-*tert*-Butoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid;

1-{3-Fluoro-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

1-{3'-Methoxy-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

1-{4'-[4-Ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

{4'-[4-Ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid;

5 1-(4'-{4-Ethyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid;

{4'-[4-Ethyl-5-((R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid;

10 1-{4'-[5-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

{4'-[5-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid;

2-Methyl-2-{4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-propionic acid;

15 (R)-1-(4'-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-3-yl)cyclopropanecarboxylic acid;

1-{3'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

{3'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid;

20 (3-Biphenyl-4-yl-5-methyl-3*H*-[1,2,3]triazol-4-yl)-carbamic acid (R)-1-phenyl-ethyl ester;
[3-(4'-Cyano-biphenyl-4-yl)-5-methyl-3*H*-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester;

(R)-1-Phenyl-ethyl-1-(4'-(1-(1*H*-tetrazol-5-yl)cyclopropyl)biphenyl-4-yl)-4-methyl-1*H*-1,2,3-triazol-5-ylcarbamate;

25 {3-[4'-(1-Methanesulfonylaminocarbonyl-cyclopropyl)-biphenyl-4-yl]-5-methyl-3*H*-[1,2,3]triazol-4-yl}-carbamic acid (R)-1-phenyl-ethyl ester;

1-{4'-[3-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,4]triazol-4-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

30 (R)-1-(4'-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-4-yl)cyclobutanecarboxylic acid;

(R)-2-{4'-[4-Methyl-5-(-1-phenylethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-pent-4-enoic acid;

(R)-2-(4-(4-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)phenyl)cyclohexyl)acetic acid; or
{3-[4'-(1-Methanesulfonylamino-carbonyl-cyclopropyl)-biphenyl-4-yl]-5-methyl-3*H*-[1,2,3]triazol-4-yl}-carbamic acid (R)-1-(3-trifluoromethyl-phenyl)-ethyl ester.

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In another embodiment of the invention, provided is a compound of formula (I) for use as a therapeutically active substance.

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In another embodiment of the invention, provided is pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) and a therapeutically inert carrier.

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In another embodiment of the invention, provided is a use of a compound according to formula (I) for the treatment or prophylaxis of pulmonary fibrosis.

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In another embodiment of the invention, provided is a use of a compound according to formula (I) for the preparation of a medicament for the treatment or prophylaxis of pulmonary fibrosis.

In another embodiment of the invention, provided is a compound according to formula (I) for the treatment or prophylaxis of pulmonary fibrosis.

25

In another embodiment of the invention, provided is a compound according formula (I), when manufactured according to a process below.

In another embodiment of the invention, provided is a method for the treatment or prophylaxis of pulmonary fibrosis, which method comprises the step of administering a therapeutically effective amount of a compound of formula (I) to a patient in need thereof.

30

In another embodiment of the invention, provided is an invention as hereinbefore described.

It will be appreciated, that the compounds of general formula I in this invention may be derivatized at functional groups to provide derivatives which are capable of conversion back to the parent compound *in vivo*. Physiologically acceptable and metabolically labile

derivatives, which are capable of producing the parent compounds of general formula I *in vivo* are also within the scope of this invention.

Compounds of the present invention can be prepared beginning with commercially available
5 starting materials, or utilizing general synthetic techniques and procedures known to those
skilled in the art. Chemicals may be purchased from companies such as for example Aldrich,
Argonaut Technologies, VWR, Lancaster, Princeton, Alfa, Oakwood, TCI, Fluorochem,
Apollo, Matrix, Maybridge or Meinoah. Chromatography supplies and equipment may be
10 purchased from such companies as for example AnaLogix, Inc, Burlington, WI; Biotage AB,
Charlottesville, VA; Analytical Sales and Services, Inc., Pompton Plains, NJ; Teledyne Isco,
Lincoln, NE; VWR International, Bridgeport, NJ; Varian Inc., Palo Alto, CA, and Multigram
II Mettler Toledo Instrument Newark, DE. Biotage, ISCO and Analogix columns are pre-
packed silica gel columns used in standard chromatography. Final compounds and
15 intermediates were named using the AutoNom2000 feature in the MDL ISIS Draw
application.

The present invention is also directed to the administration of a therapeutically effective
amount of a compound of formula I in combination or association with other drugs or active
agents for the treatment of inflammatory or allergic diseases and disorders. In one
20 embodiment, the present invention relates to a method for the treatment and/or prevention of
such diseases or disorders comprising administering to a human or animal simultaneously,
sequentially, or separately, a therapeutically effective amount of a compound of formula I
and another drug or active agent (such as another anti-inflammatory or anti-allergic drug or
agent). These other drugs or active agents may have the same, similar, or a completely
25 different mode of action. Suitable other drugs or active agents may include, but are not
limited to: Beta2-adrenergic agonists such as albuterol or salmeterol; corticosteroids such as
dexamethasone or fluticasone; antihistamines such as loratidine; leukotriene antagonists such
as montelukast or zafirlukast; anti-IgE antibody therapies such as omalizumab; anti-
infectives such as fusidic acid (particularly for the treatment of atopic dermatitis); anti-
30 fungals such as clotrimazole (particularly for the treatment of atopic dermatitis);
immunosuppressants such as tacrolimus and pimecrolimus; other antagonists of PGD2 acting
at other receptors such as DP antagonists; inhibitors of phosphodiesterase type 4 such as
cilomilast; drugs that modulate cytokine production such as inhibitors of TNF-alpha
converting enzyme (TACE); drugs that modulate the activity of Th2 cytokines IL-4 and IL-5

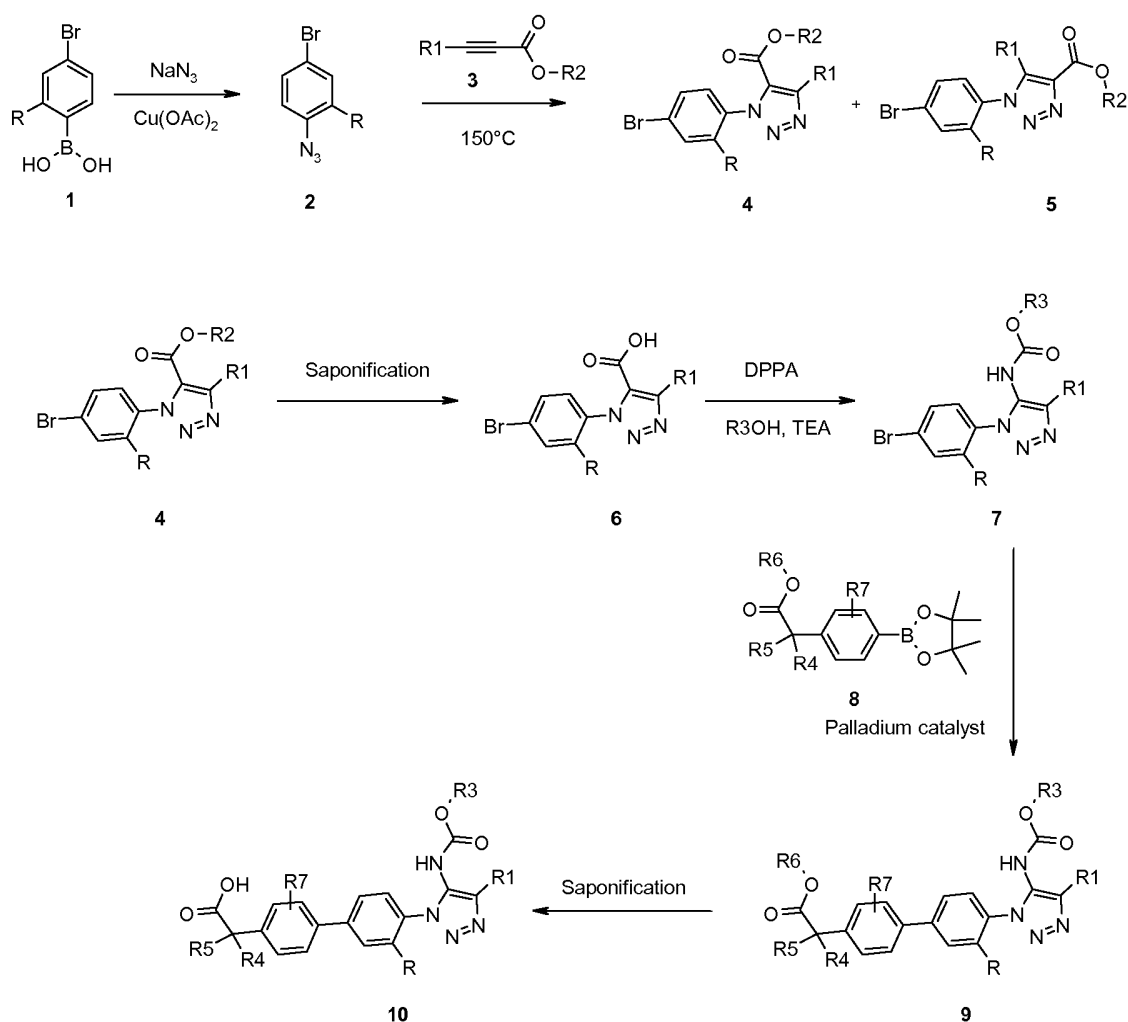
such as blocking monoclonal antibodies and soluble receptors; PPAR-gamma agonists such as rosiglitazone; and 5-lipoxygenase inhibitors such as zileuton.

The compounds of the present invention can be prepared by any conventional means.

- 5 Suitable processes for synthesizing these compounds are provided in the examples. Generally, compounds of formula **I** can be prepared according to the schemes illustrated below. For example, certain compounds of the invention may be made using the approach outlined in Scheme 1.

10

Scheme 1



The compounds of the present invention of formula **10** can be prepared according to Scheme 1. Starting with 4-bromophenylboronic acid **1**, the coupling reaction can be carried out with sodium azide in the presence of copper acetate to provide the azide intermediate **2** in protic

solvents such as methanol at room temperature. The best yields can be obtained when the reaction mixture opened to the atmosphere. This azide intermediate is stable under cold conditions, but ideally it should be used immediately in the cycloaddition reaction.

The crucial 3+2 cycloaddition reaction between the azide intermediate **2** and the alkynoate **3** can be performed in toluene at higher temperature, preferably at 150°C for 2-15 h. The reaction times can depend on the R1 groups of alkynoate, which can be hydrogen, lower alkyl, preferably methyl and ethyl groups. The ratio of both triazole regioisomers **4** and **5** depend on the R1 group and when the R1 group is methyl or ethyl the ratio generally should be 1:1.2 and when the R1 is hydrogen the ratio would be 1:4, the wrong isomer can form predominantly. The reaction temperature can be lowered if the reaction performed in the presence of a copper catalyst.

The two regioisomers can be converted to the final compounds separately. Hydrolysis of ester **4** to the corresponding acid **6** can be accomplished in the presence of a base such as lithium hydroxide in an inert solvent such as tetrahydrofuran and water at room temperature for several hours.

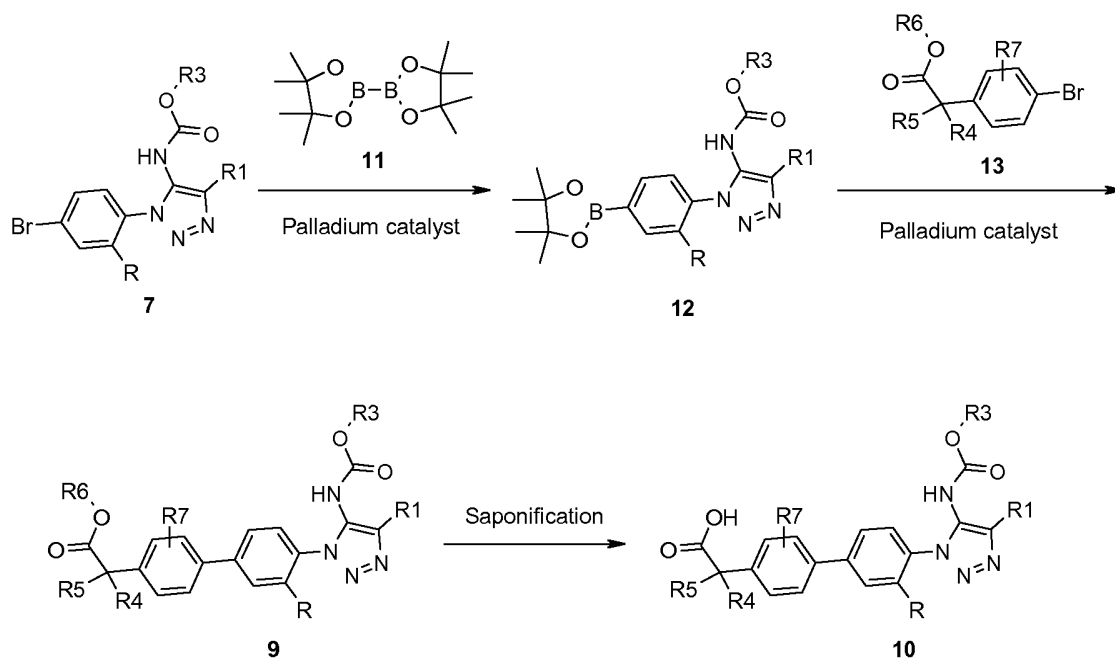
The acid **6** can be converted to a carbamate **7** using the Curtis rearrangement conditions such as diphenylphosphorylazide (DPPA) and a base such as triethylamine in the presence of an alcohol R3OH in an inert solvent such as toluene at 65-80 °C for several hours. The R3 can be a simple alkyl, cycloalkyl, or aryl-substituted alkyl.

The cross-coupling reaction between compounds **7** and **8** to provide the biaryl intermediate **9** can be accomplished in the presence of a palladium catalyst such as palladium(II) acetate and a phosphine ligand such as 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos) in the presence of a base such as potassium phosphate tribasic in a mixture of solvents for example toluene and water. This reaction can be carried out at higher temperature, preferably at 100-105°C for several hours.

The final compounds **10** of the invention can be obtained by hydrolysis of ester **9** in the presence of a base such as lithium hydroxide or sodium hydroxide in an inert solvent such as tetrahydrofuran, ethanol, and water at room temperature for several hours.

-19-

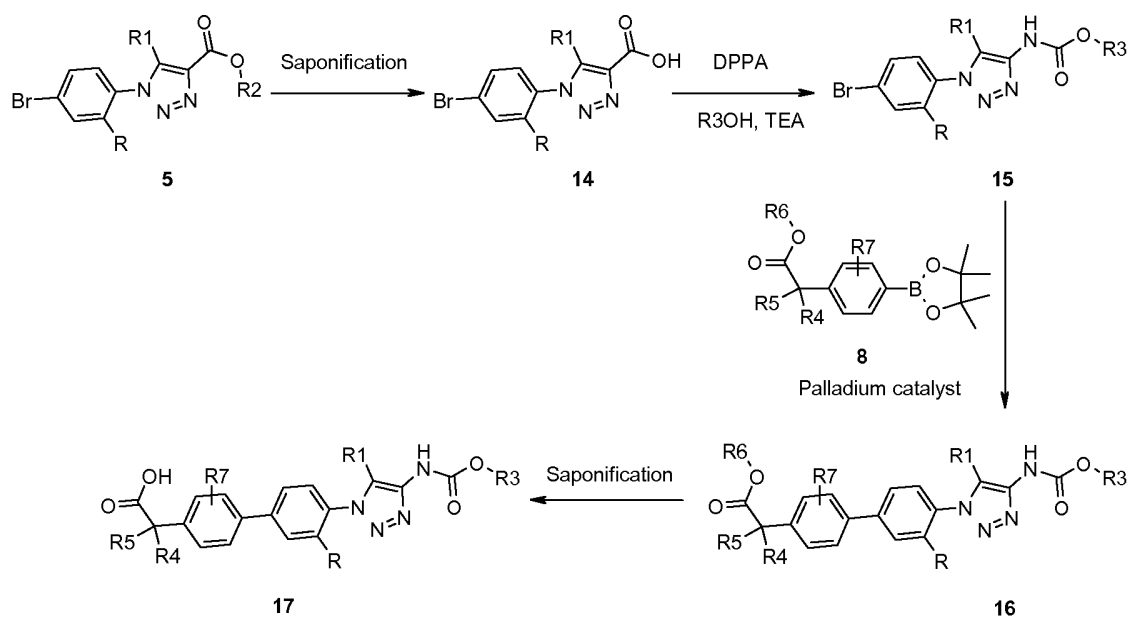
Scheme 2



Alternatively, as described in Scheme 2, the bromo intermediate **7** can be converted to the corresponding pinacolatoboronate intermediate **12** using bispinacolatodiboron **11** in the presence of a palladium catalyst such as 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) in the presence of a suitable base such as potassium acetate. The preferred solvent for this reaction can be 1,4-dioxane at 80°C for several hours. The pinacolatoborane intermediate **12** then undergoes a cross-coupling reaction with bromo intermediates such as **13** under palladium mediated coupling conditions to provide compound **9** which then can give the final compound **10** after treatment with regular hydrolysis conditions.

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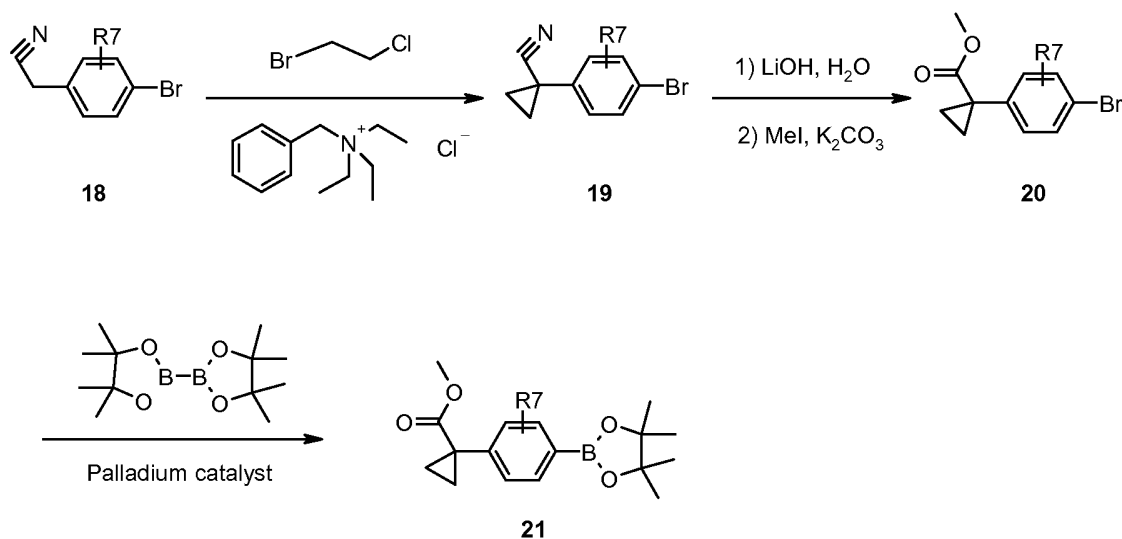
Scheme 3



Scheme 3 described the conversion of other regioisomer **5** to the corresponding final compounds **17** following the same reaction conditions as mentioned above.

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Scheme 4



Scheme 4 described the synthesis of commercially unavailable substituted arylboronate intermediates. The 4-bromophenylacetonitrile **18** can be converted to compound **19** by treatment with 1-bromo-2-chloroethane and sodium hydroxide in the presence of a phase transfer catalyst such as benzyltriethylammonium chloride at 50°C for several hours. Then, the cyano group of **19** can be hydrolyzed to the corresponding acid which can be treated with

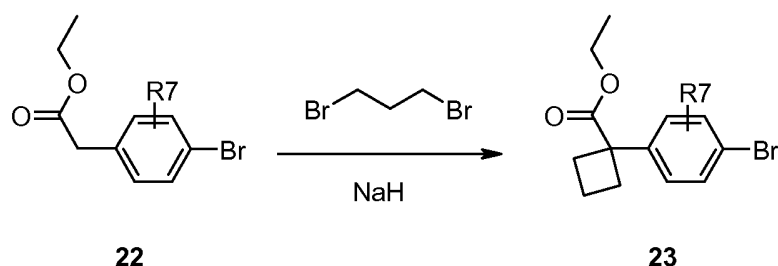
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-21-

methyl iodide in the presence of a base such as potassium carbonate to obtain compound **20**. The bromo intermediate **20** can be reacted with a bispinacolatodiboron using a palladium mediated reaction conditions to form the boronate intermediate **21**.

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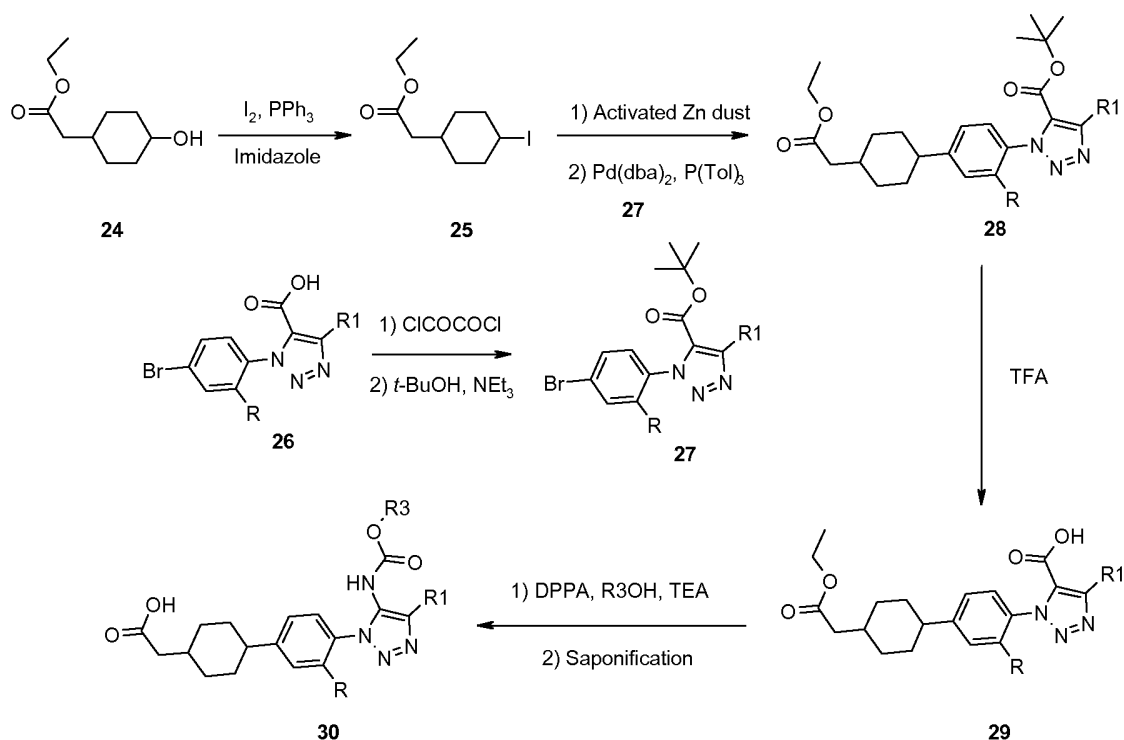
Scheme 5



As shown in Scheme 5, the 1-(4-bromophenyl)cyclobutane or cyclopentane carboxylate intermediates such as **23** can be prepared from ethyl 2-(4-bromophenyl)acetate **22** and 1,3-dibromopropane or 1,4-dibromobutane in the presence of a strong base such as sodium hydride in aprotic solvents such as DMF at 0°C to room temperature for several hours.

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Scheme 6



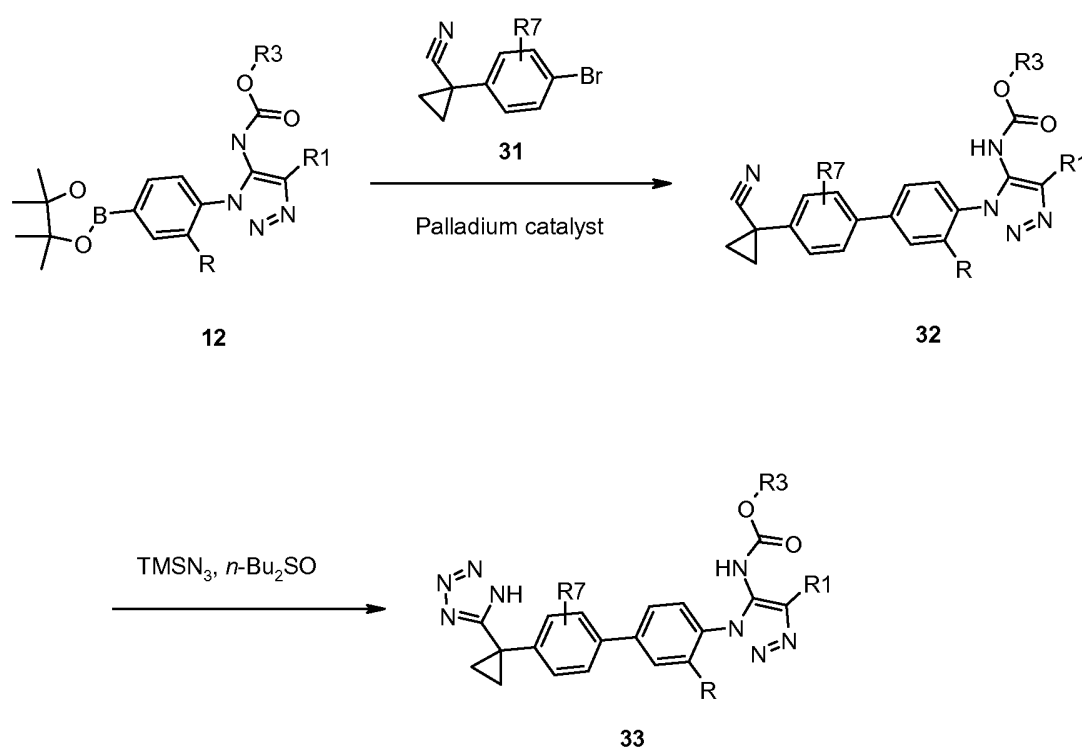
Compounds of the present invention of formula 30 can be prepared according to Scheme 6. The desired ethyl 2-(4-iodocyclohexyl)acetate **25** can be prepared from ethyl 2-(4-hydroxycyclohexyl)acetate **24** using iodine and triphenylphosphine in the presence of

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-22-

imidazole in dichloromethane. Then, ethyl 2-(4-iodocyclohexyl)acetate **25** can be reacted with an activated zinc dust in anhydrous THF at 60°C for few hours to give the zinc intermediate which can undergo a cross-coupling reaction with bromo intermediate **27** in the presence of Pd(dba)₂ and tri-*o*-tolylphosphine in anhydrous THF at 60°C to provide coupling product **28**. The *tert*-butyl ester of **28** can be hydrolyzed to the acid **29** in the presence of TFA. Then, the Curtius rearrangement and saponification conditions were described in the Scheme 1 to obtain compound **30**.

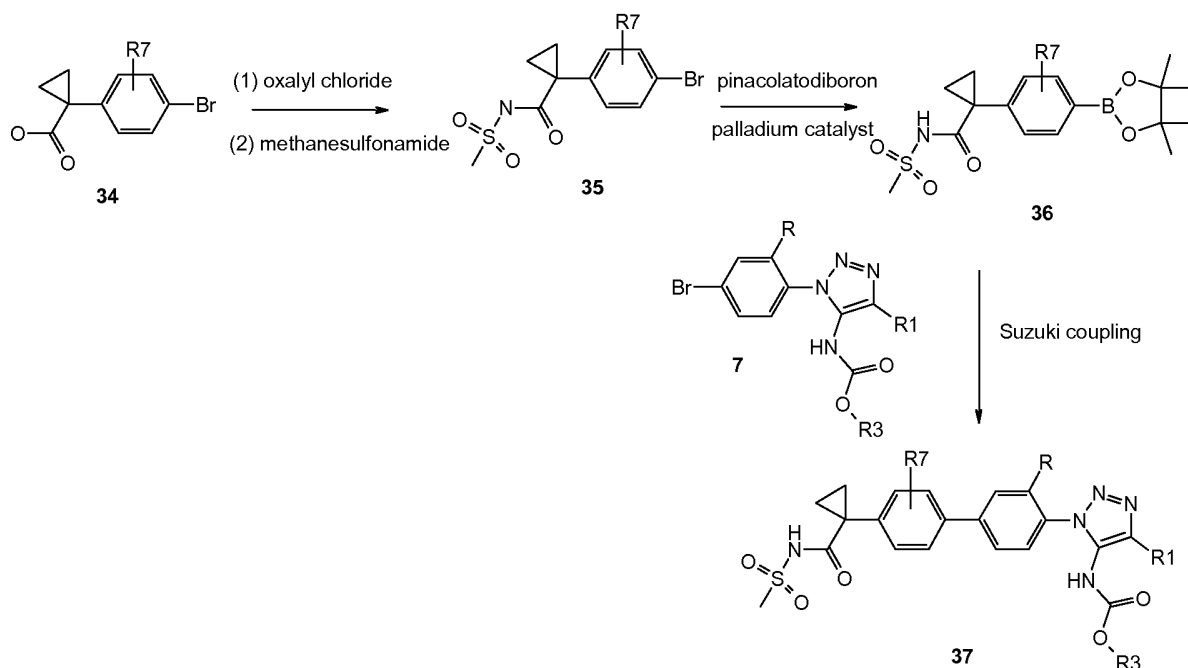
Scheme 7



Compounds of the present invention of formula **33** can be prepared according to Scheme 7. The pinacolboronate intermediate **12** can be reacted with bromo intermediate **31** in the presence of a palladium catalyst such as palladium(II) acetate and a phosphine ligand such as 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-phos) in a mixed solvent system such as toluene and water at 105°C to give compound **32**. Compound **32** can be converted to the compound of interest **33** using azidotrimethylsilane and di-*n*-butyltin oxide in toluene at 100°C for several hours.

-23-

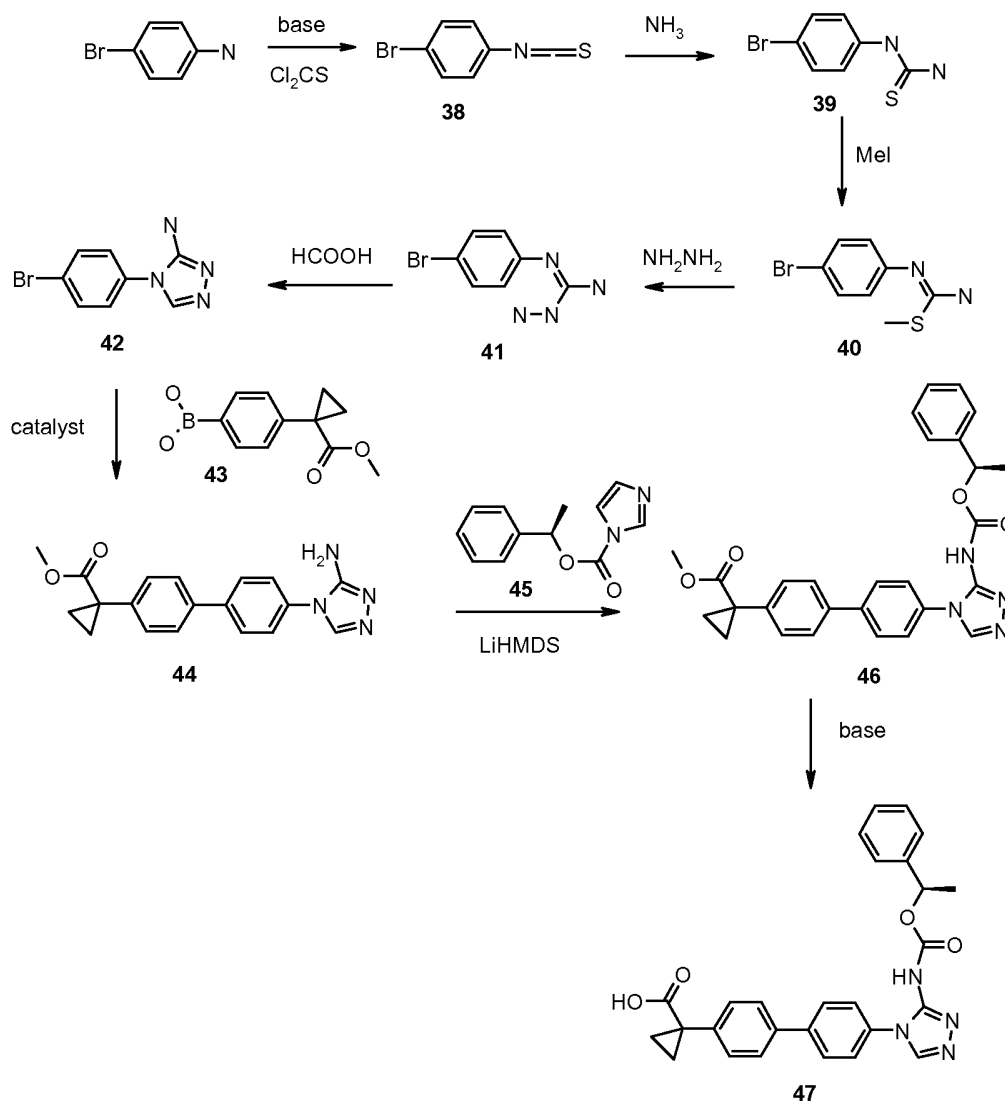
Scheme 8



Scheme 8 described the synthesis of acyl methanesulfonamides and their resulting final compounds. The acid **34** can be converted to the acid chloride which can be reacted with methanesulfonamide in the presence of base, such as sodium hydride, to give N-acylsulfonamide **35**. The arylboronate intermediate **36** can be prepared from aryl bromide **35**. The final cross-coupling step with compound **7** can be accomplished in the presence of a palladium catalyst, such as $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$, DPPF ligand, and a base such as sodium carbonate in a mixture of solvents, for example DMF and water. This reaction can be carried out at higher temperature, preferably at 85°C for several hours to yield the final compound **37**.

-24-

Scheme 9



Compound of N-aryl-1,2,4-triazole derivative **47** can be prepared according to Scheme 9. 4-Bromoaniline can react with thiophosgene under basic condition to provide isothiocyanate **38**, which can be converted to thiourea **39** by reacting with ammonia. Methylation of thiourea can be achieved in the presence of methyl iodide to provide the intermediate **40**, which can be converted to 1N-amino-2N-arylguanidine **41** through the reaction with hydrazine. Treatment of aminoguanidine **41** with formic acid can lead to the key 4N-aryl-4H-3-amino-1,2,3-triazole **42**. Under Suzuki coupling conditions, **42** can be coupled with boronic acid **43** to provide compound **44** in the presence of palladium catalyst. Compound **44** can be first deprotonated by lithium bis(hexamethyldisilyl)amide and then reacted with imidazolecarbamate **45** to provide the key carbamate **46**. Imidazolecarbamate **45** can be prepared from the corresponding phenylethanol and carbonyldiimidazole (CDI). Under basic

conditions, hydrolysis of **46** can lead to 4N-aryl-4H-1,2,3-triazole derivative **47**. Other analogs in this chemical class can be prepared using the same method described in Scheme 9.

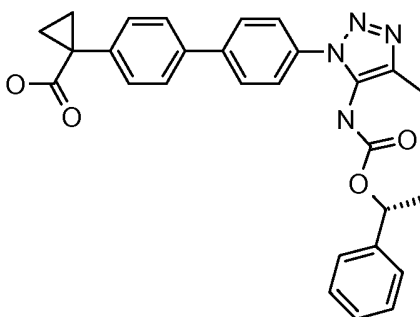
EXAMPLES

Although certain exemplary embodiments are depicted and described herein, the compounds of the present invention can be prepared using appropriate starting materials according to the methods described generally herein and/or by methods available to one of ordinary skill in the art.

Definition of abbreviations: DPPA: diphenylphosphorylazide; DPPF: 1,1'-bis(diphenylphosphino)ferrocene; S-Phos: dicyclohexyl(2',6'-dimethoxy[1,1'-biphenyl]-2-yl)-phosphine; DBA: dibenzylideneacetone; DCM: dichloromethane; DMF: dimethylformamide; EA: ethyl acetate; ACN: acetonitrile; LiHMDS: lithium bis(trimethylsilyl)amide; TEA: triethylamine; THF: tetrahydrofuran; TLC: thin layer chromatography

Example 1

1-{4'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid



Step 1: 1-Azido-4-bromo-benzene

In a 350 mL reaction vial, 4-bromo-phenylboronic acid (21.17 g, 105 mmol), sodium azide (10.3 g, 158 mmol), and copper (II) acetate (1.91 g, 10.5 mmol) were combined with MeOH (200 mL) to give a brown suspension. The reaction was stirred at room temperature overnight open to the atmosphere, 23 hr. The reaction was concentrated, diluted with ethyl ether / hexanes (380/20 mL, first organic layer) and washed with water (100 mL, first aqueous layer) and saturated NH₄Cl / concentrate NH₄OH (200/300 mL, second aqueous layer). To the first aqueous layer was added saturated NH₄Cl and concentrated NH₄OH

(60/40 mL) and the resulting organic layer was separated, washed with the second aqueous layer, and combined with the first organic layer. The first aqueous layer was extracted a second time with ether (300 mL) and the organic layer was washed with the second aqueous layer. The organic layers were combined, dried over MgSO_4 and stored in the refrigerator overnight. The crude material was warmed to room temperature, filtered, concentrated to a red/yellow oil, dissolved in hexanes (20 mL) and purified by silica gel (120 g Redisep) and eluted with hexanes to obtain 1-azido-4-bromo-benzene (19.5 g, 93.4% yield) as a yellow oil. LC/MS calcd. for $\text{C}_6\text{H}_4\text{BrN}_3$ (m/e) 197/199, obsd. 170/172 ($\text{M}-\text{N}_2+\text{H}$, ES^+).

Step 2: 3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid methyl ester

In 350 mL reaction vial 1-azido-4-bromo-benzene (10 g, 50.5 mmol) and methyl but-2-ynoate (5.45 g, 5.56 mL, 55.5 mmol) were combined with Toluene (106 mL) to give a yellow suspension. The vial was sealed and heated in an oil bath at 150°C for 4.5 h. Cooled and stored at room temperature for 6 days. The reaction was filtered and the solid was washed with toluene and EtOAc (3 x 15 mL). The filtrate was concentrated, dissolved in minimal DCM, and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes to give 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid methyl ester (4.5 g, 30.1% yield) as a light brown solid. LC/MS calcd. for $\text{C}_{11}\text{H}_{10}\text{BrN}_3\text{O}_2$ (m/e) 295/297, obsd. 296/298 ($\text{M}+\text{H}$, ES^+).

Step 3: 3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid

To 1 L round bottom flask containing 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid methyl ester (4.5 g, 11.5 mmol) dissolved in THF (200 mL) (brown solution) was added LiOH (2.77 g, 115 mmol) mostly dissolved in water (75 mL, with heat). The solution was stirred at room temperature for 16 h. The reaction was concentrated, diluted in water (total volume, 400mL) extracted with ethyl ether (2 x 100mL). The aqueous layer was acidified with 1 N HCl and the resulting precipitate was filtered, washed with water and hexanes, and dried over house vacuum. The white solid was partially dissolved in DCM and ACN, transferred to a round bottom flask, and dried to provide 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (3.6 g, 110% yield) as an off-white solid. LC/MS calcd. for $\text{C}_{10}\text{H}_8\text{N}_3\text{O}_2$ (m/e) 281/283, obsd. 281/284 ($\text{M}+\text{H}$, ES^+).

Step 4: [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester

In a 350 mL reaction vial, 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (3.6 g, 12.8 mmol), (R)-1-phenylethanol (3.04 g, 3 mL, 24.9 mmol) and triethylamine (3.27 g, 4.5 mL, 32.3 mmol) were combined with toluene (100 mL) to give a yellow solution and to this was added diphenylphosphorazidate (8.94 g, 7 mL, 32.5 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 65°C for 2 h, and cooled to room temperature overnight. The reaction was concentrated as yellow viscous oil, diluted with DCM, and purified by flash chromatography (silica gel, 0-50% EtOAc in hexanes). Appropriate fractions combined, concentrated, dried from DCM / hexanes, to obtain [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (4.07 g, 79.5% yield) as white solid. LC/MS calcd. for $C_{18}H_{17}BrN_4O_2$ (m/e) 400/402, obsd. 401/403 (M+H, ES⁺).

Step 5: 1-(4-Bromo-phenyl)-cyclopropanecarbonitrile

In a 1 L round-bottomed flask, 2-(4-bromophenyl)acetonitrile (59.57 g, 304 mmol) (semi-melted at 60°C to transfer), 1-bromo-2-chloroethane (65.4 g, 456 mmol) and N-benzyl-N,N-triethylethanaminium chloride (5.54 g, 24.3 mmol) were combined, heated in an oil bath at 50°C to give a light brown solution. To this was added drop wise a just prepared solution of NaOH (72.9 g, 1.82 mol) in 72 mL of water (not completely dissolved). The NaOH flask and addition funnel were rinsed with water and the washings were added as well. This reaction was stirred in the oil bath at 50°C with a condenser overnight, 22 hr. The reaction was cooled, diluted with water (500 mL), extracted with DCM (2 x 300 mL). The organic layers were washed with water (2 x 300 mL), 1 N HCl (2 x 300 mL) and brine (300 mL), dried over MgSO₄, filtered, concentrated, and dried yielding 1-(4-bromo-phenyl)cyclopropanecarbonitrile (66.8 g, 99% yield) as a yellow solid. LC/MS calcd. for $C_{10}H_8BrN$ (m/e) 221/223, obsd. 222/224 (M+H, ES⁺), 263/265 (M+ACN+H, ES⁺).

Step 6: 1-(4-Bromo-phenyl)-cyclopropanecarboxylic acid

In a 2 L round-bottomed flask, 1-(4-bromo-phenyl)cyclopropanecarbonitrile (66.8 g, 301 mmol) was combined with LiOH (144 g, 6.02 mol) partially dissolved in water (1.1 L) to give a red suspension and stirred in an oil bath heated at reflux for 7 h. The reaction was cooled to room temperature over the weekend. The off white/grey mixture was diluted with water (~ 1L) and extracted with EtOAc (2 x 400 mL) keeping solid in aqueous layer. The aqueous layer was acidified with concentrate HCl to pH ~ 3 and the resulting precipitate was filtered and washed with hexanes (4 x total 0.9 L) yielding, 1-(4-bromo-phenyl)cyclopropanecarboxylic acid (73.3 g, 101% yield) as an off-white solid. LC/MS

calcd. for $C_{10}H_9BrO_2$ (m/e) 240/242, obsd. 241/243 ($M+H$, ES^+), 239/241 ($M-H$, ES^-).

Step 7: 1-(4-Bromo-phenyl)-cyclopropanecarboxylic acid methyl ester

In a 2 L round-bottomed flask, 1-(4-bromo-phenyl)cyclopropanecarboxylic acid (73.6 g, 305 mmol) was combined with DMF (0.5 L) to give a light brown/red solution and to this magnetically stirred solution was added K_2CO_3 (127 g, 916 mmol). After about 10 min a white precipitate formed and the solution became unstirrable. The material was transferred to a 3L three-neck-flask, diluted with DMF (1L) and magnetically stirred. To this was dripped in over 1 h methyl iodide (217 g, 95.4 mL, 1.53 mol) dissolved in DMF (0.1 L). The white suspension was stirred at room temperature overnight. The reaction was split in half, and each half was partially concentrated (removed ~300 mL volume), diluted with water (1 L), and extracted with EtOAc (2 x 500 mL). Each EtOAc layer was washed with water (500 mL) and brine (250 mL), combined, dried over $MgSO_4$, filtered, concentrated, (combined with the other half), concentrated yielding 1-(4-bromophenyl)-cyclopropanecarboxylic acid methyl ester (73.3 g, 94.1% yield) as light brown oil. LC/MS calcd. for $C_{11}H_{11}BrO_2$ (m/e) 254/256, obsd. 255/257 ($M+H$, ES^+).

Step 8: 1-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester

In a 350 mL reaction vial, 1-(4-bromophenyl)-cyclopropanecarboxylic acid methyl ester (20 g, 78.4 mmol), BISPIN (23.9 g, 94.1 mmol) and potassium acetate (15.4 g, 157 mmol) were combined with 1,4-dioxane (150 mL) to give a light brown suspension. The mixture was purged with nitrogen for 5 min, $PdCl_2(dppf)$ (3.2 g, 3.92 mmol) was added and the vial was sealed and heated in an oil bath at 80 °C for 4 hr. The reaction was filtered through celite (rinsed / DCM), concentrated, diluted ethyl ether (500 mL), washed with water (2 x 500 mL) and brine (250 mL). The aqueous layer had black solid and was filtered and the solid washed with ethyl ether. This filtrate was extracted with ethyl ether (500 mL) and washed with the same brine. The ethyl ether layers were combined, dried over $MgSO_4$, filtered, and concentrated as red oil. The crude material was purified by flash chromatography (silica gel, 0% to 20% EtOAc in hexanes). The appropriate fractions were combined, concentrated, dried from DCM to provide 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (20.83 g, 87.9% yield) as a white to white/very faint yellow solid. LC/MS calcd. for $C_{17}H_{23}BO_4$ (m/e) 302, obsd. 303 ($M+H$, ES^+).

Step 9: 1-{4'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

In a 350 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (2.49 g, 8.22 mmol), [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (3.0 g, 7.48 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (921 mg, 2.24 mmol), and palladium(II) acetate (252 mg, 1.12 mmol) were combined with toluene (120 mL) (previously purged with nitrogen for 20 min) to give a light yellow solution. To this was added tripotassium phosphate (4.76 g, 22.4 mmol) dissolved in water (30.0 mL) (previously purged with nitrogen for 20 min). The vial's atmosphere was replaced with nitrogen, sealed, heated in oil bath at 100°C for 4 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc (50 mL) and water (100 mL) and filtered and rinsed with water (30 mL) and EtOAc (50 mL). The filtrate was separated by addition of brine (50 mL) and the organic layer was washed with brine (150 mL). The aqueous layer was extracted with EtOAc (2 x 150 mL) and each organic layer was washed with the same brine. The organic layers were combined, dried over MgSO₄, filtered, concentrated, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes to obtain 1-{4'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (2.65 g, 71.4% yield) as a white solid. LC/MS calcd. for C₂₉H₂₈N₄O₄ (m/e) 496, obsd. 497 (M+H, ES⁺).

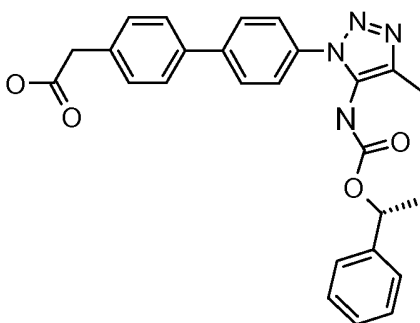
Step 10: 1-{4'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

In a 1 L round-bottomed flask, 1-{4'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (2.65 g, 5.34 mmol) was combined with THF (50 mL) to give a yellow solution. To this was dripped in LiOH (1.28 g, 53.4 mmol) dissolved in water (12.5 mL, heated to partially dissolve). The reaction flask sealed and heated in an oil bath at 60 °C for 5 h. The reaction cooled to room temperature overnight. The reaction was diluted with water (100 mL), concentrated, diluted with more water (500 mL) and acidified with 1 N HCl. The resulting precipitate was filtered, washed with water and hexanes and dried over house vacuum and in a desiccator. The crude product (2.8 g), as a white solid, was triturated from hot ACN and recrystallized from EtOAc, EtOH / water, and IPA / water. These attempted purifications were unsuccessful and the resulting solid (2.0 g) was purified by flash reverse phase chromatography (C18 Silicycle 120 g, 60 mL min 20-100% ACN/H₂O 20 min). Appropriate fractions combined,

concentrated, diluted with water, and the resulting precipitate was filtered and washed with water and hexanes yielding 1.65 g of a white solid. The solid was crystallized from ACN to give 1-{4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid (1.48 g, 57.5% yield) as a white solid. LC/MS calcd. for $C_{28}H_{26}N_4O_4$ (m/e) 482, obsd. 483 (M+H, ES^+). 1H NMR (DMSO- d_6) δ : 12.40 (br. s., 1H), 9.69 (br. s., 1H), 7.83 (d, J = 7.0 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.00 - 7.42 (m, 5H), 5.71 (br. s., 1H), 2.18 (s, 3H), 1.29 - 1.69 (m, 5H), 1.13 - 1.26 (m, 2H).

Example 2

{4'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid



Step 1: [4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid ethyl ester

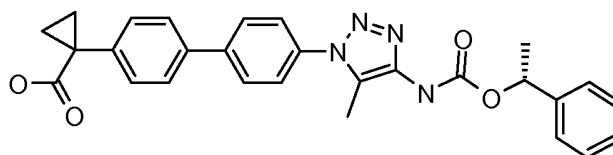
In a 350 mL reaction vial, ethyl 2-(4-bromophenyl)acetate (25 g, 103 mmol), BISPIN (31.3 g, 123 mmol) and potassium acetate (20.2 g, 206 mmol) were combined with 1,4 dioxane (190 mL) to give a white suspension. The mixture was purged with nitrogen for 5 min, $PdCl_2(dppf)$ (4.2 g, 5.14 mmol) was added and the vial was sealed and heated in an oil bath at 80 °C for 3 h. The reaction was filtered, rinsed with ethyl ether, concentrated, diluted with water (500 mL) and extracted with ethyl ether (2 x 300 mL), and the organic layers washed with brine (250 mL). The ethyl ether layers were combined, dried over $MgSO_4$, filtered, and concentrated as red oil. The crude material was purified by flash chromatography (silica gel, 0% to 20% EtOAc in hexanes). The appropriate fractions were combined, concentrated, dried from DCM to obtain [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid ethyl ester (25.14 g, 84.2% yield) as a white solid/oil. LC/MS calcd. for $C_{16}H_{23}BO_4$ (m/e) 290, obsd. 291 (M+H, ES^+).

Step 2: {4'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester

In a 20 mL vial, [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid ethyl ester (79.5 mg, 0.274 mmol), [1-(4-bromo-phenyl)-5-methyl-1H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (100 mg, 0.249 mmol), tripotassium phosphate (159 mg, 0.748 mmol), 2-dicyclohexyphosphino-2',6'-dimethoxybiphenyl (SPhos) (30.7 mg, 0.0748 mmol), and palladium(II) acetate (8.4 mg, 0.037 mmol) were combined with toluene (2mL) and water (0.5 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was replaced with nitrogen, sealed, heated in a dry block at 100 °C for 6 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc (50 mL) and washed with water (50 mL) and brine. The aqueous layers were extracted with EtOAc (50 mL). The organic layers were combined, dried over MgSO₄, filtered, concentrated, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 60% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes to obtain {4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester (40 mg, 0.0826 mmol, 33.1 % yield) as a colorless waxy solid. LC/MS calcd. for C₂₈H₂₈N₄O₄ (m/e) 484, obsd. 485 (M+H, ES⁺).

Step 3: {4'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid

In a 200 mL round-bottomed flask, {4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester (34 mg, 0.0702 mmol) was combined with THF (2 mL) to give a yellow solution. To this was dripped in LiOH (16.8 mg, 0.702 mmol) dissolved in water (0.5 mL, heated to partially dissolve). The reaction flask sealed and heated in an oil bath at 60 °C for 11 h. The reaction cooled to room temperature, diluted with water, and acidified with 1 N HCl. The resulting precipitate was filtered, washed with water, and hexanes and dried over house vacuum yielding 1-{4'-[5-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid (40 mg, 62.4% yield) as an off-white solid. LC/MS calcd. for C₂₆H₂₄N₄O₄ (me) 456, obsd. 457 (M+H, ES⁺). ¹H NMR (DMSO-d₆) δ: 12.42 (br. s., 1H), 9.19 - 9.80 (m, 1H), 7.83 (d, J = 6.5 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 7.3 Hz, 2H), 7.08 - 7.47 (m, 7H), 5.69 (br. s., 1H), 3.65 (s, 2H), 2.16 (s, 3H), 1.13 - 1.64 (m, 3H)

Example 3**1-{4'-[5-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid****5 Step 1: 1-(4-Bromo-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid methyl ester**

In 20 mL reaction vial, 1-azido-4-bromo-benzene (1.647 g, 8.32 mmol and methyl but-2-ynoate (0.816 g, 0.8 mL, 8.32 mmol) were combined with Toluene (15 mL) to give a yellow solution. The vial's atmosphere was purged with nitrogen, the vial sealed, and microwaved at 150 °C for 1 h. The resulting solid in the reaction was filtered, and washed with toluene yielding 1-(4-Bromo-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid methyl ester (0.33g, 1.11 mmol, 13.3 % yield). The filtrate was concentrated, transferred to a reaction vial with toluene (10 mL), methyl but-2-ynoate (816 mg, 0.8 mL, 8.32 mmol) was added, and the reaction was performed the same as above. The reaction with minimal solid was supported on silica gel and purified by flash chromatography (silica gel, 0% to 40% EtOAc in hexanes). Appropriate fractions were combined, concentrated, and dried from DCM / hexanes yielding 1-(4-Bromo-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid methyl ester (0.87 g, 35.3% yield) as a light brown solid. The precipitate from the reaction was not combined with the isolated product from the column. LC/MS calcd. for C₁₁H₁₀BrN₃O₂ (m/e) 295/297, obsd. 296/298 (M+H, ES⁺).

20 Step 2: 1-(4-Bromo-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid

To 500 mL round bottom flask containing 1-(4-bromo-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid methyl ester (0.87 g, 2.9 mmol) dissolved in THF (30 mL) (brown solution) was added LiOH (0.71 g, 30 mmol) mostly dissolved in water (7 mL, with heat). The solution was stirred at room temperature overnight. The reaction was concentrated, diluted in water (total volume, 100mL), and extracted with ethyl ether (2 x 100mL). The aqueous layer was acidified with 1 N HCl. The resulting precipitate was filtered, washed with water and hexanes, and dried over house vacuum and on lypholizer to obtain 1-(4-bromo-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid (3.6 g, 110% yield) as a brown solid. LC/MS calcd. for C₁₀H₈N₃O₂ (m/e) 281/283, obsd. 281/284 (M+H, ES⁺).

30 Step 3: [1-(4-Bromo-phenyl)-5-methyl-1H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester

In a 20 mL reaction vial, 1-(4-bromo-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid (0.67 g, 2.38 mmol), (R)-1-phenylethanol (0.29 g, 0.29 mL, 2.4 mmol) and triethylamine (0.24 g, 0.33 mL, 2.4 mmol) were combined with toluene (100 mL) to give a yellow solution and to this was added diphenylphosphorylazide (0.65 g, 0.5 mL, 2.4 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in a dry block at 80 °C for 4 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc (100 mL) and washed with water (100 mL) and brine (50 mL). The aqueous layers were extracted with EtOAc (100 mL). The organic layers were combined, dried over MgSO₄, filtered, concentrated, dissolved in minimal DCM, and purified by flash chromatography (silica gel, 0% to 25% EtOAc in hexanes). Appropriate fractions combined, concentrated, dried from DCM / hexanes, to give [1-(4-bromo-phenyl)-5-methyl-1H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (0.507 g, 53.2% yield) as an off-white solid. LC/MS calcd. for C₁₈H₁₇BrN₄O₂ (m/e) 400/402, obsd. 401/403 (M+H, ES⁺).

Step 4: 1-{4'-[5-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (75.3 mg, 0.249 mmol), [1-(4-bromo-phenyl)-5-methyl-1H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (100 mg, 0.249 mmol), tripotassium phosphate (159 mg, 0.748 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (30.7 mg, 0.0748 mmol), and Pd(OAc)₂ (8.4 mg, 0.037 mmol) were combined with toluene (2mL) and water (0.5 mL) (previously purged with nitrogen for 20 min) to give a light yellow solution. The vial's atmosphere was purged with nitrogen, sealed, heated in a dry block at 100 °C for 5 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc (50 mL) and washed with water (50 mL) and brine. The aqueous layers were extracted with EtOAc (50 mL). The organic layers were combined, dried over MgSO₄, filtered, concentrated, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 100% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes to give 1-{4'-[5-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (74 mg, 59.8% yield) as a white solid. LC/MS calcd. for C₂₉H₂₈N₄O₄ (m/e) 496, obsd. 497 (M+H, ES⁺).

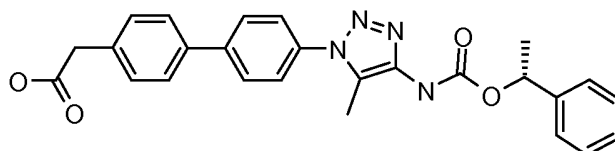
Step 5: 1-{4'-[5-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

-34-

In a 200 mL round-bottomed flask, 1-{4'-[5-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (66 mg, 0.133 mmol) was combined with THF (3 mL) to give a yellow solution. To this was dripped in LiOH (31.8 mg, 1.334 mmol) in water (1 mL), partially dissolved with heat. The reaction flask sealed and heated in an oil bath at 60 °C for 11 h. The reaction cooled to room temperature diluted with water and acidified with 1 N HCl. The resulting precipitate was filtered, washed with water, ethyl ether, and hexanes and dried over house vacuum yielding 1-{4'-[5-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid (40 mg, 62.4% yield) as an off-white solid. LC/MS calcd. for C₂₈H₂₆N₄O₄ (m/e) 482, obsd. 483 (M+H, ES⁺). ¹H NMR (DMSO-d₆) δ: 12.39 (br. s., 1H), 9.59 (br. s., 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.69 (dd, J = 8.3, 5.3 Hz, 4H), 7.28 - 7.49 (m, 7H), 5.79 (q, J = 6.5 Hz, 1H), 2.21 (s, 3H), 1.43 - 1.63 (m, 5H), 1.14 - 1.25 (m, 2H).

Example 4

{4'-[5-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid



Step 1: {4'-[5-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid methyl ester

In a 20 mL vial, [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid ethyl ester (86.8 mg, 0.299 mmol), [1-(4-bromo-phenyl)-5-methyl-1H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (100 mg, 0.249 mmol), tripotassium phosphate (159 mg, 0.748 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (30.7 mg, 0.0748 mmol), and Pd(OAc)₂ (8.4 mg, 0.037 mmol) were combined with Toluene (2mL) and water (0.5 mL) (previously purged with nitrogen for 20 min) to give a light yellow solution. The vial's atmosphere was purged with nitrogen, sealed, heated in a dry block at 100 °C for 16 h, and cooled to room temperature overnight. The reaction was filtered through celite, concentrated, dissolved in DCM / EtOAc / MeOH, supported on silica gel and purified by flash chromatography (silica gel, 0% to 40% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes to give {4'-[5-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid methyl

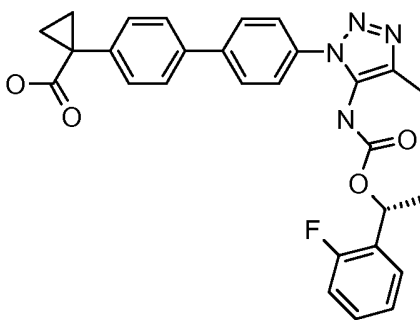
ester (56.6 mg, 54.3% yield) as a white solid. LC/MS calcd. for $C_{28}H_{28}N_4O_4$ (m/e) 484, obsd. 485 (M+H, ES^+).

Step 2: {4'-[5-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid

5 In a 200 mL round-bottomed flask, {4'-[5-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid methyl ester (59 mg, 0.122 mmol) was combined with THF (3 mL) to give a yellow solution. To this was dripped in LiOH (29.2 mg, 1.22 mmol) in water (1 mL), heated to partially dissolve. The reaction flask was sealed, heated in an oil bath at 60 °C for 3.5 h, and cooled to room temperature overnight. The
10 reaction was diluted with water and acidified with 1 N HCl. The resulting precipitate was extracted with EtOAc (2 x 75 mL). The organic layers were washed with brine (50 mL), combined, dried over $MgSO_4$, filtered, concentrated, and dried from DCM / hexanes yielding {4'-[5-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid (50 mg, 90% yield) as an off-white solid. LC/MS calcd. for $C_{26}H_{24}N_4O_4$ (m/e) 456, obsd. 457 (M+H, ES^+). 1H NMR (DMSO- d_6) δ : 12.44 (br. s., 1H), 9.62 (br. s., 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.76 (t, J = 8.0 Hz, 4H), 7.22 - 7.59 (m, 7H), 5.85 (q, J = 6.5 Hz, 1H), 3.71 (s, 2H), 2.27 (s, 3H), 1.60 (d, J = 6.0 Hz, 3H).

Example 5

20 **1-(4'-{5-[(R)-1-(2-Fluoro-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid**



Step 1: [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(2-fluoro-phenyl)-ethyl ester

25 In a 20 mL reaction vial, 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (100 mg, 0.354 mmol), (R)-1-(2-fluorophenyl)ethanol (49.6 mg, 49 μ L, 0.354 mmol) and triethylamine (35.8 mg, 49.3 μ L, 0.354 mmol) were combined with toluene (2.5 mL) to give a yellow suspension and to this was added diphenylphosphoryl azide (97.4 mg, 76.3 μ L,

0.354 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 80 °C for 4 h, and cooled to room temperature overnight. Additional reagents were added, (R)-1-(2-fluorophenyl)ethanol (24.8 mg, 24.5 µL, 0.177 mmol), triethylamine (72.6 mg, 100 µL, 0.717 mmol), and diphenylphosphorylazide (97.4 mg, 76.3 µL, 0.354 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 80 °C for 2 h, and cooled to room temperature. The reaction was supported on celite and purified by flash chromatography (silica gel, 12 g Redisep, 20 mL/min, 0% to 40% EtOAc in hexanes). Appropriate fractions combined, concentrated, dried from DCM / hexanes, to obtain [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(2-fluoro-phenyl)-ethyl ester (95.7 mg, 64.4% yield) as solid. LC/MS calcd. for C₁₈H₁₆BrFN₄O₂ (m/e) 418/420, obsd. 419/421 (M+H, ES⁺).

Step 2: 1-(4'-{5-[(R)-1-(2-Fluoro-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid methyl ester

In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (74.4 mg, 0.246 mmol), [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(2-fluoro-phenyl)-ethyl ester (86 mg, 0.205 mmol), tripotassium phosphate (131 mg, 0.615 mmol), 2-dicyclohexyphosphino-2',6'-dimethoxybiphenyl (SPhos) (25.3 mg, 0.0615 mmol), and Pd(OAc)₂ (6.91 mg, 0.0308 mmol) were combined with toluene (2 mL) and Water (0.5 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was purged with nitrogen, sealed, heated in oil bath at 100 °C for 4 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc (8 mL), filtered through celite, rinsed with EtOAc (2 x 6 mL), dried, dissolved in minimal DCM, and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 1-(4'-{5-[(R)-1-(2-fluoro-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid methyl ester (47.8 mg, 45.3% yield) as a white solid. LC/MS calcd. for C₂₉H₂₇FN₄O₄ (m/e) 514, obsd. 515 (M+H, ES⁺).

Step 3: 1-(4'-{5-[(R)-1-(2-Fluoro-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid

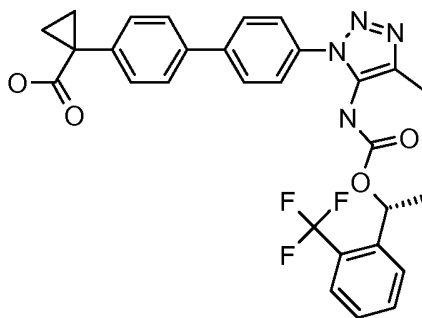
In a 20 mL round-bottomed flask, 1-(4'-{5-[(R)-1-(2-fluoro-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid methyl ester (42 mg, 0.0816 mmol) was combined with THF (2 mL) to give a yellow solution. To this was

-37-

dripped in LiOH (34.3 mg, 0.816 mmol) in water (0.5 mL) heated to partially dissolve. The vial was sealed, heated in an oil bath at 60 °C for 11 h, and cooled to room temperature overnight. The reaction was diluted with water (35 mL) and acidified with 1 N HCl. The resulting precipitate was filtered, washed with water and hexanes, and dried over house vacuum and in a desiccator to produce 1-(4'-{5-[(R)-1-(2-fluoro-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid (44 mg, 108% yield) as a white solid. LC/MS calcd. for C₂₈H₂₅FN₄O₄ (m/e) 500, obsd. 501 (M+H, ES⁺). ¹H NMR (DMSO-d₆) δ: 12.39 (br. s., 1H), 9.74 (br. s., 1H), 7.84 (d, J = 6.5 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 6.69 - 7.42 (m, 4H), 5.89 (br. s., 1H), 2.17 (br. s., 3H), 1.26 - 1.74 (m, 5H), 1.14 - 1.24 (m, 2H).

Example 6

1-(4'-{4-Methyl-5-[(R)-1-(2-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid



Step 1: [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(2-trifluoromethyl-phenyl)-ethyl ester

In a 20 mL reaction vial, 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (100 mg, 0.354 mmol), (R)-1-(2-trifluoromethyl-phenyl)ethanol (67.4 mg, 0.354 mmol) and triethylamine (35.8 mg, 49.3 μL, 0.354 mmol) were combined with toluene (2.5 mL) to give a yellow suspension and to this was added diphenylphosphoryl azide (97.4 mg, 76.3 μL, 0.354 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 80 °C for 4 h, and cooled to room temperature overnight. Additional reagents were added, (R)-1-(2-trifluoromethyl-phenyl)ethanol (33.7 mg, 0.177 mmol), triethylamine (72.6 mg, 100 μL, 0.354 mmol), and diphenylphosphoryl azide (97.4 mg, 76.3 μL, 0.354 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 80 °C for 2 h, and cooled to room temperature. The reaction was supported on celite and purified by flash chromatography (silica gel, 12 g Redisep, 20 mL/min, 0% to 40% EtOAc in hexanes).

Appropriate fractions combined, concentrated, dried from DCM / hexanes, to give [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(2-trifluoromethyl-phenyl)-ethyl ester (99.7 mg, 59.9% yield) as an off-white solid. LC/MS calcd. for $C_{19}H_{16}BrF_3N_4O_2$ (m/e) 468/470, obsd. 469/471 (M+H, ES^+).

Step 2: 1-(4'-{5-[(R)-1-(2-Trifluoromethyl-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid methyl ester

In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (69.4 mg, 0.230 mmol), [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(2-trifluoromethyl-phenyl)-ethyl ester (90 mg, 0.192 mmol), tripotassium phosphate (122 mg, 0.575 mmol), 2-dicyclohexyphosphino-2',6'-dimethoxybiphenyl (SPhos) (23.6 mg, 0.0575 mmol), and $Pd(OAc)_2$ (6.5 mg, 0.0288 mmol) were combined with toluene (2 mL) and water (0.5 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was purged with nitrogen, sealed, heated in oil bath at 100 °C for 4 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc (8 mL), filtered through celite, rinsed with EtOAc (2 x 6 mL), dried, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 1-(4'-{5-[(R)-1-(2-trifluoromethyl-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid methyl ester (50.3 mg, 46.5% yield) as a white solid. LC/MS calcd. for $C_{30}H_{27}F_3N_4O_4$ (m/e) 564, obsd. 565 (M+H, ES^+).

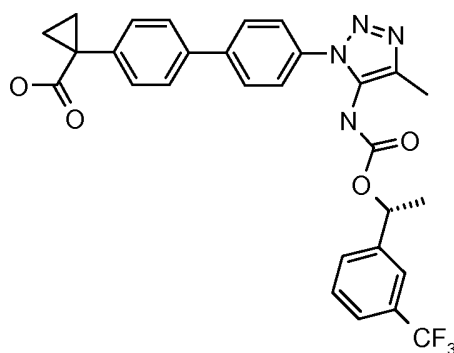
Step 3: 1-(4'-{5-[(R)-1-(2-Trifluoromethyl-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid

In a 20 mL round-bottomed flask, 1-(4'-{5-[(R)-1-(2-trifluoromethyl-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid methyl ester (45 mg, 0.0797 mmol) was combined with THF (2 mL) to give a yellow solution. To this was dripped in LiOH (33.5 mg, 0.797 mmol) in water (0.5 mL) heated to partially dissolve. The vial was sealed and heated in an oil bath at 60 °C for 11 h, and cooled to room temperature overnight. The reaction was diluted with water (35 mL) and acidified with 1 N HCl. The resulting precipitate was extracted into the organic layer with EtOAc (2 x 30 mL), washed with brine (30 mL), dried or $MgSO_4$, filtered, concentrated, and dried from DCM / hexanes, yielding 38.8 mg of impure product. The product was purified by RP-HPLC (Gilson, Pursuit 10 μm , 20 x 100 mm C18, 30 ml/min, 30 to 100 % ACN/H₂O, 8 min).

Appropriate fractions combined, concentrated, and dried from DCM / hexanes. The product was dissolved in DCM and precipitated with addition of hexanes. The solid was filtered off and washed with hexanes, dried over house vacuum yielding 1-(4'-{5-[(R)-1-(2-trifluoromethyl-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid (17.2 mg, 39.2% yield) as an off-white solid. LC/MS calcd. for $C_{29}H_{25}F_3N_4O_4$ (m/e) 550, obsd. 551 ($M+H$, ES^+). 1H NMR ($DMSO-d_6$) δ : 12.40 (br. s., 1H), 9.77 (br. s., 1H), 7.83 (d, $J = 7.3$ Hz, 2H), 7.63 - 7.78 (m, 5H), 7.39 - 7.62 (m, 5H), 5.96 (br. s., 1H), 2.15 (br. s., 3H), 1.50 (d, $J = 2.3$ Hz, 5H), 1.20 (d, $J = 2.0$ Hz, 2H).

Example 7

1-(4'-{4-Methyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid



Step 1: [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(3-trifluoromethyl-phenyl)-ethyl ester

In a 20 mL reaction vial, 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (195 mg, 0.691 mmol), (R)-1-(3-(trifluoromethyl)phenyl)ethanol (197 mg, 1.04 mmol) and triethylamine (145 mg, 0.2 mL, 1.43 mmol) were combined with toluene (10 mL) to give a yellow solution and to this was added diphenylphosphoryl azide (383 mg, 0.3 mL, 1.39 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 65 °C for 2.5 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc and washed with water, saturated ammonium chloride, and brine. The aqueous layers were extracted once with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered, concentrated, diluted with DCM, and purified by flash chromatography (silica gel, 0% to 30% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes, to obtain [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(3-trifluoromethyl-phenyl)-ethyl ester (118.1 mg, 36.4% yield) as a

colorless waxy solid. LC/MS calcd. for $C_{19}H_{16}BrF_3N_4O_2$ (m/e) 468/470, obsd. 469/471 (M+H, ES^+).

Step 2: 1-(4'-{4-Methyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid methyl ester

In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (89.6 mg, 0.297 mmol), [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(3-trifluoromethyl-phenyl)-ethyl ester (116 mg, 0.247 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (30.4 mg, 0.0742 mmol), tripotassium phosphate (157 mg, 0.742 mmol), and $Pd(OAc)_2$ (8.3mg, 0.0371 mmol) were combined with toluene (4 mL) and water (1mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was purged with nitrogen, sealed, heated in oil bath at 80 °C for 3.5 h, and cooled to room temperature overnight. Additional reagents were added 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (45 mg, 0.149 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (32 mg, 0.0779 mmol), tripotassium phosphate (57 mg, 0.269 mmol), and $Pd(OAc)_2$ (10 mg, 0.0445 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in dry block at 80 °C for 4 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc and washed with water and brine. The aqueous layers were extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered, concentrated, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 1-(4'-{4-methyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid methyl ester (63.5 mg, 45.5% yield) as a white solid.

LC/MS calcd. for $C_{30}H_{27}F_3N_4O_4$ (m/e) 564, obsd. 565 (M+H, ES^+).

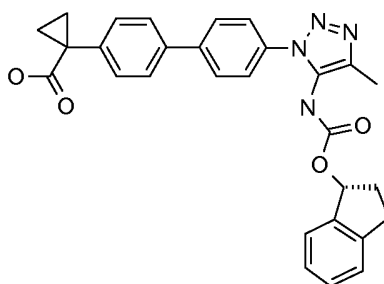
Step 3: 1-(4'-{4-Methyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid

In a 250 mL round-bottomed flask, 1-(4'-{4-methyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid methyl ester (214.5 mg, 0.452 mmol) was combined with THF (8 mL) and ethanol (8 mL) to give a yellow solution. To this was dripped in NaOH (1 N, 4.5 mL, 4.5 mmol). The reaction was stirred at room temperature overnight. The reaction was diluted with water, concentrated, diluted with more water and acidified with 1 N HCl. The resulting precipitate

was filtered, washed with water and hexanes and dried over house vacuum and in a desiccator yielding 1-(4'-{4-methyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid (174 mg, 83.6% yield) as a white solid. LC/MS calcd. for $C_{26}H_{28}N_4O_4$ (m/e) 460, obsd. 461 (M+H, ES⁺). ¹H NMR (DMSO-d₆) δ: 12.39 (br. s., 1H), 9.47 (br. s., 1H), 7.88 (d, J = 7.8 Hz, 2H), 7.64 (dd, J = 18.7, 8.2 Hz, 4H), 7.46 (d, J = 8.3 Hz, 2H), 4.67 (br. s., 1H), 2.36 (br. s., 1H), 2.20 (s, 3H), 1.54 - 2.02 (m, 6H), 1.43 - 1.53 (m, 2H), 1.17 - 1.31 (m, 2H), 1.05 (br. s., 3H).

Example 8

1-{4'-[5-((R)-Indan-1-yloxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid



Step 1: [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-indan-1-yl ester

In a 20 mL reaction vial, 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (100 mg, 0.354 mmol), (R)-2,3-dihydro-1H-inden-1-ol (47.6 mg, 0.354 mmol) and triethylamine (35.8 mg, 49.3 μL, 0.354 mmol) were combined with toluene (2.5 mL) to give a yellow suspension and to this was added diphenylphosphoryl azide (97.4 mg, 76.3 μL, 0.354 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 80 °C for 4 h, and cooled to room temperature overnight. Additional reagents were added, (R)-2,3-dihydro-1H-inden-1-ol (23.8 mg, 0.177 mmol), triethylamine (72.6 mg, 100 μL, 0.717 mmol), and diphenylphosphoryl azide (97.4 mg, 76.3 μL, 0.354 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 80°C for 2 h, and cooled to room temperature. The reaction was supported on celite and purified by flash chromatography (silica gel, 12 g Redisep, 20 mL/min, 0% to 40% EtOAc in hexanes). Appropriate fractions combined, concentrated, dried from DCM / hexanes, yielding [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-indan-1-yl ester (81.6 mg,

55.7% yield) as an off-white solid. LC/MS calcd. for $C_{19}H_{17}BrN_4O_2$ (m/e) 412/414, obsd. 413/415 (M+H, ES^+).

Step 2: 1-{4'-[5-((R)-Indan-1-yloxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (64.1 mg, 0.212 mmol), [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-indan-1-yl ester (73 mg, 0.177 mmol), tripotassium phosphate (112 mg, 0.530 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (21.8 mg, 0.0530 mmol), and $Pd(OAc)_2$ (6.0 mg, 0.0265 mmol) were combined with toluene (2 mL) and water (0.5 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was purged with nitrogen, sealed, heated in oil bath at 100 °C for 4 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc (8 mL), filtered through celite, rinsed with EtOAc (2 x 6 mL), dried, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 1-{4'-[5-((R)-indan-1-yloxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (59.5 mg, 66.2% yield) as a white solid. LC/MS calcd. for $C_{30}H_{28}N_4O_4$ (m/e) 508, obsd. 509 (M+H, ES^+).

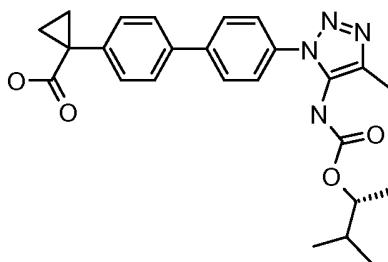
Step 3: 1-{4'-[5-((R)-Indan-1-yloxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

In a 20 mL round-bottomed flask, 1-{4'-[5-((R)-indan-1-yloxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (53 mg, 0.104 mmol) was combined with THF (2 mL) to give a yellow solution. To this was dripped in LiOH (43.8 mg, 1.04 mmol) in water (0.5 mL) heated to partially dissolve. The vial was sealed, heated in an oil bath at 60 °C for 11 h, and cooled to room temperature overnight. The reaction was diluted with water (35 mL) and acidified with 1 N HCl. The resulting precipitate was filtered off and washed with water and hexanes, and dried over house vacuum yielding 1-{4'-[5-((R)-indan-1-yloxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid (28 mg, 54.3 % yield) as a white solid. LC/MS calcd. for $C_{29}H_{26}N_4O_4$ (m/e) 494, obsd. 495 (M+H, ES^+). 1H NMR (DMSO- d_6) δ : 12.38 (br. s., 1H), 9.56 (br. s., 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.60 (br. s., 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.29 (br. s., 3H), 7.11 - 7.21 (m, 1H), 6.04 (br. s., 1H), 3.00 (br. s., 1H), 2.85

(br. s., 1H), 2.30 - 2.45 (m, 1H), 2.09 - 2.28 (m, 3H), 2.00 (br. s., 1H), 1.42 - 1.61 (m, 2H), 1.21 (d, J = 3.0 Hz, 2H).

Example 9

1-{4'-[5-((R)-1,2-Dimethyl-propoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid



Step 1: [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-2-dimethyl-propyl ester

In a 20 mL reaction vial, 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (100 mg, 0.354 mmol), (R)-3-methylbutan-2-ol (31.2 mg, 38.6 μ L, 0.354 mmol) and triethylamine (35.8 mg, 49.3 μ L, 0.354 mmol) were combined with toluene (2.5 mL) to give a yellow suspension and to this was added diphenylphosphoryl azide (97.4 mg, 76.3 μ L, 0.354 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 80 °C for 4 h, and cooled to room temperature overnight. Additional reagents were added, (R)-3-methylbutan-2-ol (15.6 mg, 19.3 μ L, 0.177 mmol), triethylamine (72.6 mg, 100 μ L, 0.717 mmol), and diphenylphosphoryl azide (97.4 mg, 76.3 μ L, 0.354 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 80 °C for 2 h, and cooled to room temperature. The reaction was supported on celite and purified by flash chromatography (silica gel, 0% to 40% EtOAc in hexanes). Appropriate fractions combined, concentrated, dried from DCM / hexanes, yielding [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-2-dimethyl-propyl ester (93.6 mg, 71.9 % yield) as an off-white solid. LC/MS calcd. for $C_{15}H_{19}BrN_4O_2$ (m/e) 366/368, obsd. 367/369 (M+H, ES⁺).

Step 2: 1-{4'-[5-((R)-1,2-Dimethyl-propoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

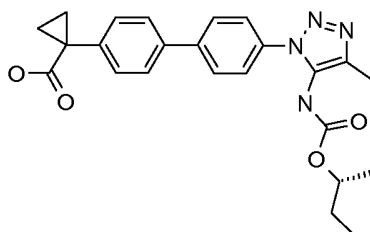
In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (82.9 mg, 0.274 mmol), [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1,2-dimethyl-propyl ester (84 mg, 0.229

mmol), tripotassium phosphate (146 mg, 0.686 mmol), 2-dicyclohexyphosphino-2',6'-dimethoxybiphenyl (SPhos) (28.2 mg, 0.0686 mmol), and Pd(OAc)₂ (7.7 mg, 0.0343 mmol) were combined with toluene (2 mL) and water (0.5 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was replaced with nitrogen, sealed, heated in oil bath at 100 °C for 4 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc (8 mL), filtered through celite, rinsed with EtOAc (2 x 6 mL), dried, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 1-{4'-[5-((R)-1,2-dimethyl-propoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (80 mg, 75.6% yield) as a white solid. LC/MS calcd. for C₂₆H₃₀N₄O₄ (m/e) 462, obsd. 463 (M+H, ES⁺).

Step 3: 1-{4'-[5-((R)-1,2-Dimethyl-propoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

In a 20 mL round-bottomed flask, 1-{4'-[5-((R)-1,2-dimethyl-propoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (45 mg, 0.0797 mmol) was combined with THF (2 mL) to give a yellow solution. To this was dripped in LiOH (33.5 mg, 0.797 mmol) in water (0.5 mL) heated to partially dissolve. The vial was sealed and heated in an oil bath at 60 °C for 6 h, and cooled to room temperature overnight. The reaction was diluted with water (35 mL) and acidified with 1 N HCl. The resulting precipitate was extracted into the organic layer with EtOAc (2 x 30 mL), washed with brine (30 mL), dried over MgSO₄, filtered, concentrated, and dried from DCM / hexanes yielding 1-{4'-[5-((R)-1,2-dimethyl-propoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid (42.4 mg, 58.3% yield) as a white solid.

LC/MS calcd. for C₂₅H₂₈N₄O₄ (m/e) 448, obsd. (M+H, ES⁺). ¹H NMR (DMSO-d₆) δ: 12.37 (br. s., 1H), 9.43 (br. s., 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.57 - 7.73 (m, 4H), 7.46 (d, J = 8.3 Hz, 2H), 4.50 (br. s., 1H), 2.21 (s, 3H), 1.71 (br. s., 1H), 1.40 - 1.57 (m, 2H), 1.00 - 1.32 (m, 5H), 0.84 (br. s., 6H).

Example 10**1-{4'-[5-((R)-*sec*-Butoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid****Step 1: [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-*sec*-butyl ester**

In a 20 mL reaction vial, 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (100 mg, 0.354 mmol), (R)-butan-2-ol (26.3 mg, 32.6 μ L, 0.354 mmol) and triethylamine (35.8 mg, 49.3 μ L, 0.354 mmol) were combined with toluene (2.5 mL) to give a yellow suspension and to this was added diphenylphosphoryl azide (97.4 mg, 76.3 μ L, 0.354 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 80 °C for 4 h, and cooled to room temperature overnight. Additional reagents were added, (R)-butan-2-ol (13.2 mg, 16.3 μ L, 0.177 mmol), triethylamine (72.6 mg, 100 μ L, 0.717 mmol), and diphenylphosphoryl azide (97.4 mg, 76.3 μ L, 0.354 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 80 °C for 2 h, and cooled to room temperature. The reaction was supported on celite and purified by flash chromatography (silica gel, 0% to 40% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes, yielding [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-*sec*-butyl ester (99.5 mg, 79.5% yield) as an off-white solid. LC/MS calcd. for $C_{14}H_{17}BrN_4O_2$ (m/e) 352/354, obsd. 353/355 ($M+H$, ES^+).

Step 2: 1-{4'-[5-((R)-*sec*-Butoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (92.4 mg, 0.306 mmol), [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-*sec*-butyl ester (90 mg, 0.255 mmol), tripotassium phosphate (162 mg, 0.764 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (31.4 mg, 0.0764 mmol), and $Pd(OAc)_2$ (8.6 mg, 0.0382 mmol) were combined with toluene (2 mL) and water (0.5 mL) (previously purged with nitrogen for 20 min) to give a light

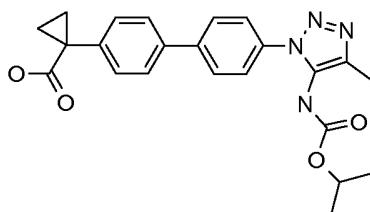
yellow suspension. The vial's atmosphere was replaced with nitrogen, sealed, heated in oil bath at 100 °C for 4 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc (8 mL), filtered through celite, rinsed with EtOAc (2 x 6 mL), dried, and dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 1-{4'-[5-((R)-*sec*-butoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (53.6 mg, 46.9% yield) as a white solid. LC/MS calcd. for C₂₅H₂₈N₄O₄ (m/e) 448, obsd. 449 (M+H, ES⁺).

Step 3: 1-{4'-[5-((R)-*sec*-Butoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

In a 20 mL round-bottomed flask, 1-{4'-[5-((R)-*sec*-butoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (37 mg, 0.0825 mmol) was combined with THF (2 mL) to give a yellow solution. To this was dripped in LiOH (34.6 mg, 0.825 mmol) in water (0.5 mL) heated to partially dissolve. The vial was sealed and heated in an oil bath at 60 °C for 6 h, and cooled to room temperature overnight. The reaction was diluted with water (35 mL) and acidified with 1 N HCl. The resulting precipitate was extracted into the organic layer with EtOAc (2 x 30 mL), washed with brine (30 mL), dried over MgSO₄, filtered, concentrated, and dried from DCM / hexanes yielding 1-{4'-[5-((R)-*sec*-butoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid (40 mg, 112% yield) as a white solid. LC/MS calcd for C₂₄H₂₆N₄O₄ (m/e) 434, obsd. 435 (M+H, ES⁺). ¹H NMR (DMSO-d₆) δ: 12.37 (br. s., 1H), 9.44 (br. s., 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.56 - 7.72 (m, 4H), 7.46 (d, J = 8.3 Hz, 2H), 4.61 (br. s., 1H), 2.21 (s, 3H), 1.38 - 1.66 (m, 4H), 1.03 - 1.34 (m, 5H), 0.85 (dd, J = 10.7, 6.9 Hz, 3H).

Example 11

1-[4'-(5-*iso*-Propoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid



Step 1: [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid isopropyl ester

In a 20 mL reaction vial, 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (100 mg, 0.354 mmol), propan-2-ol (21.3 mg, 27.1 μ L, 0.354 mmol) and triethylamine (35.8 mg, 49.3 μ L, 0.354 mmol) were combined with toluene (2.5 mL) to give a yellow suspension and to this was added diphenylphosphorylazide (97.4 mg, 76.3 μ L, 0.354 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 80 °C for 4 h, and cooled to room temperature overnight. Additional reagents were added, propan-2-ol (10.7 mg, 13.6 μ L, 0.177 mmol), triethylamine (72.6 mg, 100 μ L, 0.717 mmol), and diphenylphosphorylazide (97.4 mg, 76.3 μ L, 0.354 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 80 °C for 2 h, and cooled to room temperature. The reaction was supported on celite and purified by flash chromatography (silica gel, 0% to 40% EtOAc in hexanes). Appropriate fractions combined, concentrated, dried from DCM / hexanes, yielding [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid *iso*-propyl ester (141 mg, 60 % pure, 70.4% yield) as an off-white solid. LC/MS calcd. for $C_{13}H_{15}BrN_4O_2$ (m/e) 338/340, obsd. 339/341 (M+H, ES⁺).

Step 2: 1-[4'-(5-*iso*-Propoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid methyl ester

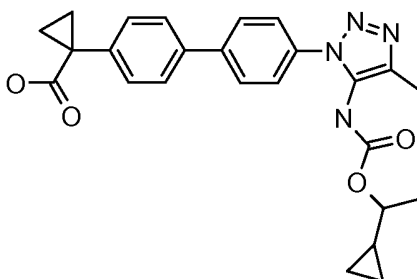
In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (83.4 mg, 0.276 mmol), [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid *iso*-propyl ester (130 mg, 0.230 mmol), tripotassium phosphate (146 mg, 0.690 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (28.3 mg, 0.069 mmol), and Pd(OAc)₂ (7.7 mg, 0.0345 mmol) were combined with toluene (2 mL) and water (0.5 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was replaced with nitrogen, sealed, heated in oil bath at 100 °C for 4 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc (8 mL), filtered through celite, rinsed with EtOAc (2 x 6 mL), dried, and dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 1-[4'-(5-*iso*-propoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid methyl ester (44.3 mg, 44.3% yield) as a solid. LC/MS calcd. for $C_{24}H_{26}N_4O_4$ (m/e) 434, obsd. 435 (M+H, ES⁺).

Step 3: 1-[4'-(5-*iso*-Propoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid

In a 20 mL round-bottomed flask, 1-[4'-(5-*iso*-propoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid methyl ester (39 mg, 0.0898 mmol) was combined with THF (2 mL) to give a yellow solution. To this was dripped in LiOH (37.7 mg, 0.898 mmol) in water (0.5 mL) heated to partially dissolve. The vial was sealed and heated in an oil bath at 60 °C for 6 h, and cooled to room temperature overnight. The reaction was diluted with water (35 mL) and acidified with 1 N HCl. The resulting precipitate was extracted into the organic layer with EtOAc (2 x 30 mL), washed with brine (30 mL), dried over MgSO₄, filtered, concentrated, dried from DCM / hexanes yielding 1-[4'-(5-*iso*-propoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid (32.5 mg, 86.1% yield) as a white solid. LC/MS calcd. for C₂₃H₂₄N₄O₄ (m/e) 420, obsd. 421 (M+H⁺). ¹H NMR (DMSO-d₆) δ: 12.38 (br. s., 1H), 9.43 (br. s., 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.57 - 7.74 (m, 4H), 7.46 (d, J = 8.0 Hz, 2H), 4.76 (br. s., 1H), 2.20 (s, 3H), 1.43 - 1.57 (m, 2H), 1.02 - 1.34 (m, 8H).

Example 12

1-{4'-[5-(1-Cyclopropyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid



Step 1: [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid 1-cyclopropyl-ethyl ester

In a 20 mL reaction vial, 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (300 mg, 1.06 mmol), 1-cyclopropylethanol (139 mg, 1.61 mmol) and triethylamine (218 mg, 0.3 mL, 2.15 mmol) were combined with toluene (10 mL) to give a yellow solution and to this was added diphenylphosphoryl azide (585 mg, 0.458 mL, 2.13 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 65 °C for 2.5 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc and washed with water, saturated ammonium chloride, and brine. The aqueous layers were extracted

once with EtOAc. The organic layers were combined, dried over MgSO₄, filtered, concentrated, diluted with DCM, and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes, yielding [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid 1-cyclopropyl-ethyl ester (267 mg, 68.9% yield) as a colorless waxy solid. LC/MS calcd. for C₁₅H₁₇BrN₄O₂ (m/e) 364/366, obsd. 365/367 (M+H, ES⁺).

Step 2: 1-{4'-[5-(1-Cyclopropyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (238 mg, 0.789 mmol), [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid 1-cyclopropyl-ethyl ester (240 mg, 0.657 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (80.9 mg, 0.197 mmol), tripotassium phosphate (418 mg, 1.97 mmol), and Pd(OAc)₂ (22.1 mg, 0.0986 mmol) were combined with toluene (8 mL) and water (2 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was replaced with nitrogen, sealed, heated in dry block at 80 °C for 2.5 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc and washed with water and brine. The aqueous layers were extracted with EtOAc. The organic layers were combined, dried over MgSO₄, filtered, concentrated, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 1-{4'-[5-(1-cyclopropyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (214.2 mg, 70.8% yield) as a white solid. LC/MS calcd. for C₂₆H₂₈N₄O₄ (m/e) 460, obsd. 461 (M+H, ES⁺).

Step 3: 1-{4'-[5-(1-Cyclopropyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

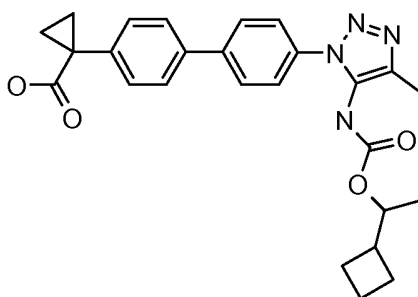
In a 250 mL round-bottomed flask, 1-{4'-[5-(1-cyclopropyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (205 mg, 0.447 mmol) was combined with THF (8 mL) and Ethanol (8 mL) to give a yellow solution. To this was dripped in NaOH (1 N, 4.5 mL, 4.5 mmol). The reaction was stirred at room temperature overnight. The reaction was diluted with water, concentrated, diluted with more water and acidified with 1 N HCl. The resulting precipitate was filtered, washed with water and hexanes and dried over house vacuum and in a desiccator yielding 1-{4'-[5-(1-

-50-

cyclopropyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-
 cyclopropanecarboxylic acid (165.4 mg, 82.9% yield) as a white solid. LC/MS calcd. for
 $C_{25}H_{26}N_4O_4$ (m/e) 446, obsd. 447 (M+H, ES⁺). ¹H NMR (DMSO-d₆) δ: 12.37 (br. s., 1H),
 9.47 (br. s., 1H), 7.88 (d, J = 8.3 Hz, 2H), 7.55 - 7.74 (m, 4H), 7.45 (d, J = 8.0 Hz, 2H), 4.12
 5 (br. s., 1H), 2.20 (s, 3H), 1.41 - 1.55 (m, 2H), 0.84 - 1.32 (m, 6H), -0.03 - 0.59 (m, 4H).

Example 13

1-{4'-[5-(1-Cyclobutyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid



Step 1: [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid 1-cyclobutyl-ethyl ester

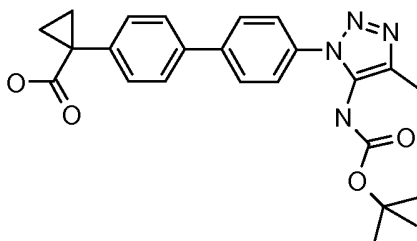
In a 20 mL reaction vial, 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid
 15 (300 mg, 1.06 mmol), 1-cyclobutylethanol (170 mg, 1.70 mmol) and triethylamine (218 mg, 0.3 mL, 2.15 mmol) were combined with toluene (10 mL) to give a yellow solution and to this was added diphenylphosphoryl azide (585 mg, 0.458 mL, 2.13 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 65 °C for 2.5 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc and washed
 20 with water, saturated ammonium chloride, and brine. The aqueous layers were extracted once with EtOAc. The organic layers were combined, dried over MgSO₄, filtered, concentrated, diluted with DCM, and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic
 25 acid 1-cyclopropyl-ethyl ester (295.2 mg, 73.2% yield) as a colorless waxy solid. LC/MS calcd. for $C_{16}H_{19}BrN_4O_2$ (m/e) 378/380, obsd. 379/381 (M+H, ES⁺).

Step 2: 1-{4'-[5-(1-Cyclobutyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (258 mg, 0.854 mmol), [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid 1-cyclobutyl-ethyl ester (270 mg, 0.712 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (87.7 mg, 0.214 mmol),
5 tripotassium phosphate (453 mg, 2.14 mmol), and Pd(OAc)₂ (24.0 mg, 0.107 mmol) were combined with toluene (8 mL) and water (2 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was purged with nitrogen, sealed, heated in dry block at 80 °C for 2.5 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc and washed with water and brine. The aqueous layers
10 were extracted with EtOAc. The organic layers were combined, dried over MgSO₄, filtered, concentrated, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 1-{4'-[5-(1-cyclobutyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (223.6 mg,
15 66.2% yield) as a white solid. LC/MS calcd. for C₂₇H₃₀N₄O₄ (m/e) 474, obsd. 475 (M+H, ES⁺).

Step 3: 1-{4'-[5-(1-Cyclobutyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

In a 250 mL round-bottomed flask, 1-{4'-[5-(1-cyclobutyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (214.5 mg,
20 0.452 mmol) was combined with THF (8 mL) and Ethanol (8 mL) to give a yellow solution. To this was dripped in NaOH (1 N, 4.5 mL, 4.5 mmol). The reaction was stirred at room temperature overnight. The reaction was diluted with water, concentrated, diluted with more water and acidified with 1 N HCl. The resulting precipitate was filtered, washed with water
25 and hexanes and dried over house vacuum and in a desiccator yielding 1-{4'-[5-(1-cyclobutyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid (174 mg, 83.6% yield) as a white solid. LC/MS calcd. for C₂₆H₂₈N₄O₄ (m/e) 460, obsd. 461 (M+H, ES⁺). ¹H NMR (DMSO-d₆) δ: 12.39 (br. s., 1H), 9.47 (br. s., 1H), 7.88 (d, J = 7.8 Hz, 2H), 7.64 (dd, J = 18.7, 8.2 Hz, 4H), 7.46 (d, J = 8.3 Hz, 2H), 4.67 (br. s., 1H), 2.36 (br. s., 1H), 2.20 (s, 3H), 1.54 - 2.02 (m, 6H), 1.43 - 1.53 (m, 2H),
30 1.17 - 1.31 (m, 2H), 1.05 (br. s., 3H).

Example 14**1-[4'-(5-*tert*-Butoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid****Step 1: [3-(4-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid *tert*-butyl ester**

In a 20 mL reaction vial, 3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (500 mg, 1.77 mmol), 2-methylpropan-2-ol (197 mg, 2.66 mmol) and triethylamine (359 mg, 0.494 mL, 3.54 mmol) were combined with toluene (10 mL) to give a yellow solution and to this was added diphenylphosphoryl azide (946 mg, 0.764 mL, 3.54 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 65 °C for 2 h, and cooled to room temperature overnight. The reaction was concentrated, diluted with DCM, and purified by flash chromatography (silica gel, 0% to 40% EtOAc in hexanes).

Appropriate fractions combined, concentrated, and dried from DCM / hexanes, yielding [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid *tert*-butyl ester (420 mg, 67.1% yield) as a white solid. LC/MS calcd. for C₁₄H₁₇BrN₄O₂ (m/e) 352/3354, obsd. 353/355 (M+H, ES⁺).

Step 2: 1-[4'-(5-*tert*-Butoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid methyl ester

In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (395 mg, 1.31 mmol), [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid *tert*-butyl ester (420 mg, 1.19 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (146 mg, 0.357 mmol), tripotassium phosphate (757 mg, 3.57 mmol), and Pd(OAc)₂ (40 mg, 0.178 mmol) were combined with toluene (10 mL) and water (2 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was purged with nitrogen, sealed, heated in dry block at 100 °C for 4 h, and cooled to room temperature overnight. The reaction was filtered, rinsed with water (5 mL) and EtOAc (60 mL). The filtrate was diluted with water (50 mL) and extracted with EtOAc. The aqueous layer was extracted again with EtOAc (40

mL). The organic layers were washed with brine, combined, dried over MgSO_4 , filtered, concentrated, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions were combined, concentrated, and dried from DCM / hexanes yielding 1-[4'-(5-*tert*-butoxycarbonylamino-4-methyl-

5 [1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid methyl ester (420 mg, 78.8% yield) as a white solid. LC/MS calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_4\text{O}_4$ (m/e) 448, obsd. 449 ($\text{M}+\text{H}$, ES^+).

Step 3: 1-[4'-(5-*tert*-Butoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid

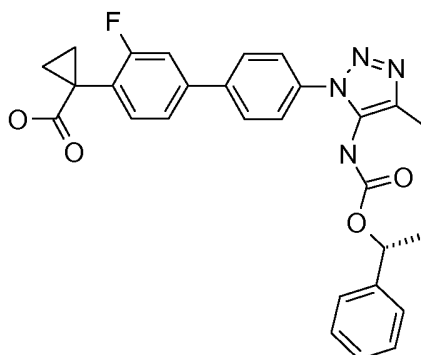
In a 8 mL vial, 1-[4'-(5-*tert*-butoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-

10 yl]-cyclopropanecarboxylic acid methyl ester (22.1 mg, 0.047 mmol) was combined with THF (4 mL) and to this was dripped in NaOH (1 N, 0.5 mL, 0.5 mmol). The reaction was stirred at room temperature for 30 min, water was added (2 mL), and then stirred overnight. The reaction was diluted with water, concentrated, diluted with more water, and acidified with 1 N HCl. The resulting precipitate was filtered, washed with water and hexanes and

15 dried over house vacuum and in a desiccator yielding 1-[4'-(5-*tert*-butoxycarbonylamino-4-methyl-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid (17.1 mg, 83.7 % yield) as a white solid. LC/MS calcd. for $\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_4$ (m/e) 434, obsd. 435 ($\text{M}+\text{H}$, ES^+). ^1H NMR ($\text{DMSO}-d_6$) δ : 12.40 (br. s., 1H), 9.24 (br. s., 1H), 7.90 (d, $J = 8.0$ Hz, 2H), 7.58 - 7.71 (m, 4H), 7.46 (d, $J = 8.3$ Hz, 2H), 2.20 (s, 3H), 1.16 - 1.55 (m, 13H).

Examples 15

1-{3-Fluoro-4'-[4-methyl-5-((*R*)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid



Step 1: 1-(4-Bromo-2-fluoro-phenyl)-cyclopropanecarbonitrile

In a 0.5 L round-bottomed flask, 2-(4-bromo-2-fluoro-phenyl)acetonitrile (10 g, 46.7 mmol) dissolved in THF (50 mL) was added drop wise under nitrogen to a slurry of NaH (60 %

dispersion in mineral, 4.11 g, 103 mmol) in DMF (100 mL). The reaction was stirred in an ice bath for 30 min. To this cooled mixture was added 1,2-dibromoethane (8.78 g, 5.71 mL, 46.7 mmol). The reaction was stirred under nitrogen in the ice bath and allowed to warm to room temperature over 3 h. The reaction was diluted with EtOAc (500 mL), filtered, and washed with water and brine. The aqueous layers were extracted with EtOAc (250 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated yielding 1-(4-bromo-2-fluoro-phenyl)cyclopropanecarbonitrile (13.7 g, 122% yield) as a red waxy / solid /oil. LC/MS calcd. for C₁₀H₇BrFN (m/e) 239/241, obsd. 240/242 (M+H, ES⁺).

Step 2: 1-(4-Bromo-2-fluoro-phenyl)-cyclopropanecarboxylic acid

In a 1 L round-bottomed flask, 1-(4-bromo-2-fluorophenyl)cyclopropanecarbonitrile (11.2 g, 46.7 mmol) and LiOH (58 g, 1.38 mol) were combined with water (230 mL) to give a yellow suspension. The mixture was heated in an oil bath at 100 °C overnight. The mixture was diluted to 1 L with water and ice and extracted with ethyl ether (3 x 300 mL). There was some white insoluble material between phases that was not included in aqueous layer. The aqueous layer was acidified with concentrated HCl (ca. 110 mL) slowly with addition of ice. A very fine precipitate formed and the milky solution was not filtered but extracted with DCM (4 x 250 ml). The organic layers were combined, dried over MgSO₄, filtered, and concentrated yielding 1-(4-bromo-2-fluorophenyl)cyclopropanecarboxylic acid (10.87 g, 89.9% yield) as a yellow solid. LC/MS calcd. for C₁₀H₈BrFO₂ (m/e) 258/260, obsd. 259/261 (M+H, ES⁺).

Step 3: 1-(4-Bromo-2-fluoro-phenyl)-cyclopropanecarboxylic acid methyl ester

In a 1 L round-bottomed flask, 1-(4-bromo-2-fluorophenyl)cyclopropanecarboxylic acid (10.8 g, 41.7 mmol) was combined with DMF (180 mL) to give a yellow solution and to this magnetically stirred solution was added K₂CO₃ (17.3 g, 125 mmol). To this was dripped in over 1 h, methyl iodide (47.3 g, 20.9 ml, 333 mmol) dissolved in DMF (20 ml). The yellow suspension was stirred at RT overnight. The reaction was concentrated, diluted with water (500 mL), and extracted with EtOAc (2 x 500 ml). The EtOAc layers were washed with water brine (250 ml), combined, dried over MgSO₄, filtered, and concentrated yielding 1-(4-bromo-2-fluoro-phenyl)-cyclopropanecarboxylic acid methyl ester (10.3 g, 90.5% yield) as light brown oil. LC/MS calcd. for C₁₁H₁₀BrFO₂ (m/e) 272/274, obsd. 273/275 (M+H, ES⁺).

Step 4: 1-[2-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester

In a 350 mL reaction vial, methyl 1-(4-bromo-2-fluoro-phenyl)-cyclopropanecarboxylate

(10.3 g, 37.7 mmol), BISPIN (11.5 g, 45.3 mmol) and potassium acetate (7.4 g, 75.4 mmol) were combined with 1,4 dioxane (77.2 mL) to give a light brown suspension. The mixture was purged with nitrogen (5 min), PdCl₂(DPPF)-DCM (1.54 g, 1.89 mmol) and was added. The vial was sealed and heated in an oil bath at 80 °C for 4 h. The reaction was filtered through celite, rinsed with DCM, concentrated, diluted with ethyl ether (500 ml), and washed with water (2 x 500 mL). The first aqueous layer was filtered to remove black solids and rinsed with ethyl ether. This filtrate was combined with the second aqueous layer and extracted with ethyl ether (500 mL). The organic layers were washed with brine (250 mL), combined, dried over MgSO₄, filtered, and concentrated as red oil. The crude material was purified by flash chromatography (silica gel, 0% to 20% EtOAc in hexanes). The appropriate fractions were combined and concentrated yielding the crude product (12.32 g) as a yellow oil.

The crude product was a mixture of starting materials and product and was therefore subjected to the same reaction conditions again. In a 350 mL reaction vial containing the crude product and 1,4 dioxane (200 mL) was added BISPIN (13.6 g, 53.6 mmol) and potassium acetate (8.77 g, 89.3 mmol) to give a light brown suspension. The mixture was purged with nitrogen (5 min), and PdCl₂(DPPF) (3.65 g, 4.47 mmol) was added. The vial was sealed, and the reaction was heated in an oil bath at 80 °C for 3.5 h. The reaction was cooled to room temperature for 5 days. The reaction was diluted with EtOAc and water, concentrated, and diluted with more EtOAc (200 mL) and water (200 ml). The resulting black mixture was inseparable. A partial amount (200 mL) of the aqueous layer (first aqueous layer) was removed from the separatory funnel, and the remaining mixture was washed with brine (2 x 200 mL, second and third aqueous / brine layers). The black mixture remaining in the separatory funnel was filtered resulting in two phases in the filtrate. This was separated, and the organic layer (first organic layer) was dried over MgSO₄. To the first aqueous and second aqueous / brine layers were added EtOAc (200 mL / each), mixed, filtered through same funnel, separated, and each organic layer was washed with the third aqueous / brine layer. The second and third organic layers were combined with the first containing MgSO₄, dried, filtered, and concentrated yielding the crude product (24 g). The material was dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 20% EtOAc in hexanes). The appropriate fractions were concentrated, and dried from DCM/Hex, yielding 1-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (6.9 g, 48.2% yield) as an oil which solidifies

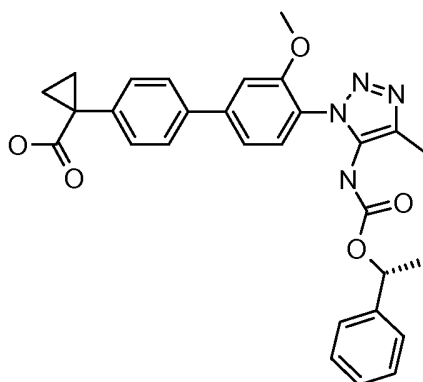
(crystallizes) as white solid upon cooling to room temperature. LC/MS calcd, for $C_{17}H_{22}BFO_4$ (m/e) 320, obsd. 321 (M+H, ES^+).

Step 5: 1-{3-Fluoro-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

5 In a 20 mL vial, 1-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (383 mg, 0.320 mmol), [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid *tert*-butyl ester (400 mg, 0.997 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (123 mg, 0.299 mmol), tripotassium phosphate (635 mg, 2.99 mmol), and $Pd(OAc)_2$ (33.6 mg, 0.150 mmol) were combined with
10 toluene (10 mL) and water (2 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was purged with nitrogen, sealed, heated in dry block at 80 °C for 4.5 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, concentrated, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50%
15 EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 1-{3-fluoro-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (380 mg, 74.1% yield) as a white solid. LC/MS calcd. for $C_{29}H_{27}FN_4O_4$ (m/e) 514, obsd. 515 (M+H, ES^+).

Step 6: 1-{3-Fluoro-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

20 In a 200 mL round-bottomed flask, 1-{3-fluoro-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (380 mg, 0.739 mmol) was combined with THF (10 mL) and MeOH (10 mL) to give a yellow solution. To this was dripped in 1 M NaOH (7.39 mL, 7.39 mmol). The
25 reaction was stirred at room temperature for 1.5 days, stored in a refrigerator for 2.5 days. The reaction was diluted with water, concentrated, diluted with more water and acidified with 1 N HCl. The resulting precipitate was filtered, washed with water and hexanes, and dried over house vacuum and in a desiccator yielding 1-{3-Fluoro-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic
30 acid (303 mg, 82% yield) as a white solid. LC/MS calcd. for $C_{28}H_{25}FN_4O_4$ (m/e) 500, obsd. 501 (M+H, ES^+). 1H NMR ($DMSO-d_6$) δ : 12.50 (br. s., 1H), 9.70 (br. s., 1H), 7.89 (d, J = 6.5 Hz, 2H), 7.43 - 7.71 (m, 5H), 6.86 - 7.42 (m, 5H), 5.70 (br. s., 1H), 2.17 (s, 3H), 1.26 - 1.64 (m, 5H), 1.16 - 1.25 (m, 2H).

Examples 16**1-{3'-Methoxy-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid****5 Step 1: 1-Azido-4-bromo-2-methoxy-benzene**

To a mixture of 4-bromo-2-methoxyphenylboronic acid (5 g, 21.7 mmol), sodium azide (2.11 g, 32.5 mmol), and copper(II) acetate (393 mg, 2.17 mmol) in a 100 mL 2-neck RB flask was added methanol (40 mL) at room temperature under nitrogen atmosphere. The resulting brown solution was stirred for 15 h at room temperature and the flask was opened to the air by removing one of the stopper. Within few minutes, it started to change the color to brown suspension and then the stopper was closed again. After 15 h at room temperature, it almost stayed the same brown color. Then, again the stopper was opened, it became slowly darkened. TLC analysis indicated the presence of a new spot. Then, the reaction mixture was heated with heat gun to complete the reaction. During this period, it turned to a light black suspension and after 1 h at ambient temperature the reaction mixture was poured into a mixture of saturated ammonium chloride and ammonium hydroxide. The organic compound was extracted into diethyl ether (2 x 100 mL) and the combined extracts were washed with brine solution and dried over anhydrous MgSO_4 . Filtration and concentration gave the crude oil which was purified using an ISCO (120 g) column chromatography eluting with hexanes. The fractions were combined and the solvent was removed under vacuum to obtain 1-azido-4-bromo-2-methoxy-benzene a light yellow oil (4.14 g, 84% yield).

Step 2: 3-(4-Bromo-2-methoxy-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid methyl ester

In a solution of 1-azido-4-bromo-2-methoxy-benzene (3.95 g, 17.3 mmol) and methyl but-2-ynoate (1.7 g, 17.3 mmol) in toluene (36 mL) was heated to 150 °C and stirred for 15 h at this temperature at which time TLC analysis indicated the presence of two new spots. During the 15 h stirring, it was slowly turned from a light yellow color solution to the dark brown

solution. Then, the heating was stopped and the toluene was removed under vacuum to obtain the dark brown oil (~8.0 g) which was purified using an ISCO (120 g) column chromatography eluting with 0-50% EA in hexanes to obtain all the spots. The desired regioisomer 3-(4-bromo-2-methoxy-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid methyl ester was isolated as dark brown viscous oil (250 mg, 4.5% yield). LC/MS calcd. for $C_{12}H_{12}BrN_3O_3$ (m/e) 326, obsd. 328 [M+H, ES⁺].

Step 3: 3-(4-Bromo-2-methoxy-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid

To a solution of methyl 1-(4-bromo-2-methoxy-phenyl)-4-methyl-1H-1,2,3-triazole-5-carboxylate (220 mg, 0.68 mmol) in THF (4 mL) was added an excess of lithium hydroxide monohydrate (283 mg, 6.75 mmol) in water (1.0 mL) at room temperature. The resulting brown solution was heated to 50 °C in an oil bath for 3 h at which time LCMS analysis indicated the absence of starting material. Then, it was cooled to room temperature and the solvent was removed under vacuum. After dilution with NaOH (~5 mL) and water (50 mL), the neutral impurities were extracted into diethyl ether (2 x 50 mL). The basic aqueous layer was neutralized with 1 N HCl and the resulting solids were collected by filtration and washed with water and hexanes. After air drying, 155 mg (74% yield) of 3-(4-bromo-2-methoxy-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid was isolated as off-white solid. LC/MS calcd. for $C_{11}H_{10}BrN_3O_3$ (m/e) 312, obsd. 314.0 [M+H, ES⁺].

Step 4: [3-(4-Bromo-2-methoxy-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester

To a suspension of 1-(4-bromo-2-methoxy-phenyl)-4-methyl-1H-1,2,3-triazole-5-carboxylic acid (152 mg, 0.49 mmol) in toluene (4 mL) in a vial was added triethylamine (49.3 mg, 67.9 µL, 0.489 mmol) at room temperature under nitrogen atmosphere. To the resulting brown solution were added diphenylphosphorylazide (134 mg, 105 µL, 0.49 mmol) followed by (R)-1-phenylethanol (59.5 mg, 58.8 µL, 0.49 mmol) at room temperature under nitrogen atmosphere. Then, the rubber septum was replaced with a cap and the brown solution was heated to 80 °C and it was stirred for 3 h at this temperature. Then, the reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The brown oil was purified using an ISCO (80 g) column chromatography eluting with 0-100% EA in hexanes. The desired fractions were combined and the solvent was removed under vacuum to obtain [3-(4-bromo-2-methoxy-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (173 mg, 82% yield) as a white solid. LC/MS calcd. for $C_{19}H_{19}BrN_4O_3$ (m/e) 431, obsd. 432.9 [M+H, ES⁺].

Step 5: 1-{3'-Methoxy-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

To a mixture of [3-(4-bromo-2-methoxy-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (100 mg, 0.23 mmol), methyl 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxylate (105 mg, 0.35 mmol), palladium(II) acetate (7.81 mg, 0.035 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (28.6 mg, 0.69 mmol), and potassium phosphate tribasic (148 mg, 0.69 mmol) were added previously degassed toluene (4.5 mL) and water (1.0 mL) at room temperature under nitrogen atmosphere. The resulting light yellow suspension was heated to 105 °C and stirred for 2 h by which time TLC analysis indicated the absence of starting material. Within 1 h, the reaction mixture was converted to a black reaction mixture. After 2 h, the reaction mixture was cooled to room temperature and poured into a mixture of water and brine solution. The organic compound was extracted into EA (2 x 50 mL) and the combined extracts were washed with brine solution and dried over anhydrous MgSO₄. Filtration and concentration gave the crude residue which was purified by using an ISCO (40 g) column chromatography eluting with 0-100% EA in hexanes. The desired fractions were combined and the solvent was removed under vacuum to isolate 1-{3'-methoxy-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (95 mg, 75% yield) as off-white solid. LC/MS calcd. for C₃₀H₃₀N₄O₅ (m/e) 526, obsd. 527.1 [M+H, ES⁺].

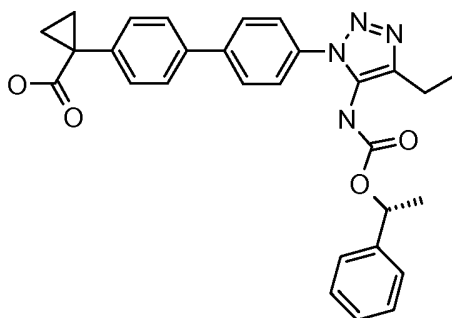
Step 6: 1-{3'-Methoxy-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

To a solution of 1-{2'-methoxy-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (87 mg, 0.17 mmol) in THF (4.5 mL) and ethanol (4.5 mL) was added an excess of 1 M sodium hydroxide (1.65 mL, 1.65 mmol) at room temperature. The resulting colorless solution was stirred for 15 h at which time LCMS analysis indicated the absence of starting material. Then, the solvent was removed under vacuum and the basic aqueous layer was diluted with water and neutralized with 1 N HCl. The resulting solids were collected by filtration and washed with water and hexanes. After air drying, 50 mg (59% yield) of 1-{3'-methoxy-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid was isolated as a white solid. LC/MS calcd. for C₂₉H₂₈N₄O₅ (m/e) 512, obsd. 513.1 [M+H, ES⁺]. ¹H NMR (DMSO-d₆) δ: 12.40 (br. s., 1H), 9.43 (br. s.,

1H), 7.70 (d, J = 8.3 Hz, 2H), 7.41 - 7.51 (m, 3H), 7.18 - 7.39 (m, 7H), 5.70 (d, J = 6.3 Hz, 1H), 3.74 (s, 3H), 2.16 (s, 3H), 1.34 - 1.56 (m, 5H), 1.16 - 1.24 (m, 2H).

Example 17

5 1-{4'-[4-Ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid



Step 1: 3-(4-Bromo-phenyl)-5-ethyl-3H-[1,2,3]triazole-4-carboxylic acid ethyl ester

To a solution of 1-azido-4-bromobenzene (5 g, 25.2 mmol) in toluene (50 mL) was added a neat 2-pentynoic acid ethyl ester (3.19 g, 25.2 mmol) in a 250 mL sealed tube and then it was kept for 2 minutes under nitrogen atmosphere. Then, the flask was sealed with a tight cap and the resulting light yellow solution was heated to 150 °C and stirred for 2 h at which time TLC analysis indicated the presence of two new spots and LCMS analysis indicated the presence of the desired mass. Then, the dark brown reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The resulting dark brown residue (8.3 g) was purified using an ISCO (330 g) column chromatography eluting with 0-50% EA in hexanes. The top spot in TLC was isolated as a desired 3-(4-bromo-phenyl)-5-ethyl-3H-[1,2,3]triazole-4-carboxylic acid ethyl ester as off-white solid (2.83 g, 34.6% yield) and the bottom spot was confirmed as a wrong regioisomer, 3-(4-bromo-phenyl)-5-ethyl-3H-[1,2,3]triazole-4-carboxylic acid ethyl ester which was isolated as a light brown oil (3.44 g, 42% yield). LC/MS calcd. for C₁₃H₁₄BrN₃O₂ (m/e) 324, obsd. 326 [M+H, ES⁺].

Step 2: 3-(4-Bromo-phenyl)-5-ethyl-3H-[1,2,3]triazole-4-carboxylic acid

To a brown solution of 3-(4-bromo-phenyl)-5-ethyl-3H-[1,2,3]triazole-4-carboxylic acid ethyl ester (2.8 g, 8.64 mmol) in THF (40 mL) was added a solution of lithium hydroxide monohydrate (1.81 g, 43.2 mmol) in water (10 mL) at room temperature. The resulting brown solution was stirred for 15 h at room temperature at which time LCMS analysis indicated the absence of starting material. Then, the solvent was removed under vacuum. After dilution with NaOH (~5 mL) and water (50 mL), the neutral impurities were extracted

into diethyl ether (100 mL) and it also removed the brown color. The basic aqueous layer was neutralized with 1 N HCl and the resulting white solids were collected by filtration and washed with water and hexanes. After air drying, 2.13 g (83% yield) of 3-(4-bromo-phenyl)-5-ethyl-3H-[1,2,3]triazole-4-carboxylic acid was isolated as off-white solid. LC/MS calcd. for $C_{11}H_{10}BrN_3O_2$ (m/e) 296, obsd. 297.7 [M+H, ES⁺].

Step 3: [3-(4-Bromo-phenyl)-5-ethyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester

To a suspension of 3-(4-bromo-phenyl)-5-ethyl-3H-[1,2,3]triazole-4-carboxylic acid (592 mg, 2.0 mmol) in toluene (10 mL) in a vial was added triethylamine (202 mg, 279 μ L, 2.0 mmol) at room temperature under nitrogen atmosphere. To the resulting brown solution were added diphenylphosphoryl azide (550 mg, 431 μ L, 2.0 mmol) followed by (R)-1-phenylethanol (244 mg, 241 μ L, 2.0 mmol) at room temperature under nitrogen atmosphere. Then, the resulting light brown solution was heated to 80 °C and stirred for 2 h at this temperature. Then, the clear light brown reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The brown oil was purified using an ISCO (80 g) column chromatography eluting with 0-100% EA in hexanes to obtain the desired [3-(4-bromo-phenyl)-5-ethyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (696 mg, 89% yield) as a white solid. LC/MS calcd. for $C_{19}H_{19}BrN_4O_2$ (m/e) 415, obsd. 417 [M+H, ES⁺].

Step 4: 1-{4'-[4-Ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

To a mixture of [3-(4-bromo-phenyl)-5-ethyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (300 mg, 0.72 mmol), methyl 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxylate (327 mg, 1.08 mmol), palladium(II) acetate (24.3 mg, 0.11 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (89.0 mg, 0.22 mmol), and potassium phosphate tribasic (460 mg, 2.17 mmol) were added previously degassed toluene (9.0 mL) and water (2.0 mL) at room temperature under nitrogen atmosphere. The resulting light yellow suspension was heated to 105 °C and stirred for 2 h by which time TLC analysis indicated the absence of starting material. Then, the reaction mixture was cooled to room temperature and poured into a mixture of water and brine solution. The organic compound was extracted into EA (2 x 50 mL) and the combined extracts were washed with brine solution and dried over anhydrous $MgSO_4$. Filtration and concentration gave the crude residue which was purified by using an ISCO (80 g) column chromatography eluting with 0-100% EA in hexanes. The desired fractions were combined

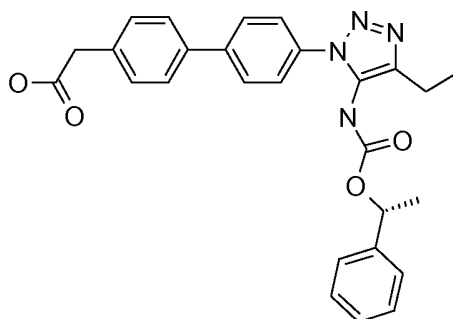
and the solvent was removed under vacuum to isolate the desired 1-{4'-[4-ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (240 mg, 65% yield). LC/MS calcd. for $C_{30}H_{30}N_4O_4$ (m/e) 510, obsd. 511.1 [M+H, ES⁺].

Step 5: 1-{4'-[4-Ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

To a solution of 1-{4'-[4-ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (234 mg, 0.46 mmol) in THF (10 mL) and ethanol (10 mL) was added an excess of 1.0 M sodium hydroxide (4.58 mL, 4.58 mmol) solution at room temperature. The resulting colorless solution was stirred for 15 h at which time LCMS analysis indicated the absence of starting material. Then, the solvent was removed under vacuum and the basic aqueous layer was diluted with water and neutralized with 1 N HCl. The resulting solids were collected by filtration and washed with water and hexanes. After air drying, 193 mg (85% yield) of 1-{4'-[4-ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid was isolated as a white solid. LC/MS calcd. for $C_{29}H_{28}N_4O_4$ (m/e) 496, obsd. 497.1 [M+H, ES⁺]. ¹H NMR (DMSO-d₆) δ: 12.40 (br. s., 1H), 9.66 (br. s., 1H), 7.83 (d, J = 6.5 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 7.3 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.34 (br. s., 5H), 5.71 (br. s., 1H), 2.56 (d, J = 7.5 Hz, 2H), 1.36 - 1.60 (m, 5H), 1.16 - 1.23 (m, 5H).

Examples 18

{4'-[4-Ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid



Step 1: {4'-[4-Ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester

To a mixture of (R)-1-phenylethyl 1-(4-bromophenyl)-4-ethyl-1H-1,2,3-triazol-5-ylcarbamate (200 mg, 0.48 mmol), ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)phenyl)acetate (210 mg, 0.72 mmol), palladium(II) acetate (16.2 mg, 0.072 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (59.3 mg, 0.144 mmol), and potassium phosphate tribasic (307 mg, 1.44 mmol) were added previously degassed toluene (4.5 mL) and water (1.0 mL) at room temperature under nitrogen atmosphere. The resulting light yellow suspension was heated to 105 °C and stirred for 1 h by which time TLC analysis indicated the absence of starting material. Then, the reaction mixture was cooled to room temperature and poured into a mixture of water and brine solution. The organic compound was extracted into EA (2 x 50 mL) and the combined extracts were washed with brine solution and dried over anhydrous MgSO₄. Filtration and concentration gave the crude residue which was purified by using an ISCO (80 g) column chromatography eluting with 0-100% EA in hexanes. The desired fractions were combined and the solvent was removed under vacuum to isolate {4'-[4-ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester (133 mg, 55% yield). LC/MS calcd. for C₂₈H₂₈N₄O₄ (m/e) 498, obsd. 499.1 [M+H, ES⁺].

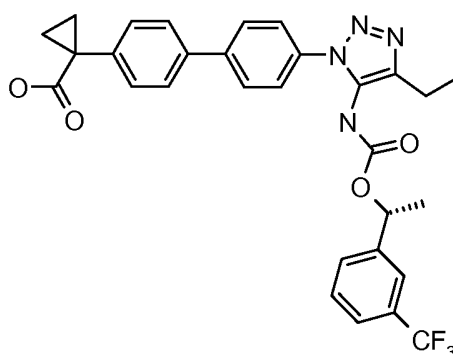
Step 2: {4'-[4-Ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid

To a solution of {4'-[4-ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester (105 mg, 0.21 mmol) in THF (5 mL) and ethanol (5.0 mL) was added an excess of 1 M sodium hydroxide (2.11 mL, 2.11 mmol) solution in water at room temperature. The resulting colorless solution was stirred for 15 h at room temperature by which time LCMS analysis indicated the absence of starting material. Then, the solvent was removed under vacuum and the basic aqueous solution was neutralized with 1 N HCl. The resulting solids were collected by filtration and washed with water and hexanes. After air drying, 74 mg (75% yield) of {4'-[4-ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid was isolated as a white solid. LC/MS calcd. for C₂₇H₂₆N₄O₄ (m/e) 470, obsd. 470.1 [M+H, ES⁺]. ¹H NMR (DMSO-d₆) δ: 12.43 (br. s., 1H), 9.16 - 9.88 (m, 1H), 7.84 (d, J = 6.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.52 - 7.64 (m, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.07 - 7.38 (m, 5H), 5.70 (br. s., 1H), 3.66 (s, 2H), 2.57 (d, J = 7.0 Hz, 2H), 1.48 (br. s., 3H), 1.20 (t, J = 7.5 Hz, 3H).

Example 19

1-(4'-{4-Ethyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid

-64-



Step 1: [3-(4-Bromo-phenyl)-5-ethyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(3-trifluoromethyl-phenyl)-ethyl ester

To a suspension of 1-(4-bromophenyl)-4-ethyl-1H-1,2,3-triazole-5-carboxylic acid (623 mg, 2.1 mmol) in toluene (10 mL) in a vial was added triethylamine (213 mg, 293 μ L, 2.1 mmol) at room temperature under nitrogen atmosphere. To the resulting brown solution were added diphenylphosphoryl azide (579 mg, 453 μ L, 2.1 mmol) and (R)-1-(3-(trifluoromethyl)phenyl)ethanol (400 mg, 2.1 mmol) at room temperature under nitrogen atmosphere. Then, the resulting light brown solution was heated to 80 $^{\circ}$ C and stirred for 2.5 h at this temperature. Then, the clear light brown reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The resulting brown oil was purified using an ISCO (80 g) column chromatography eluting with 0-100% EA in hexanes. The desired fractions were combined and the solvent was removed under vacuum to obtain [3-(4-bromo-phenyl)-5-ethyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(3-trifluoromethyl-phenyl)-ethyl ester (735 mg, 72% yield) as a white solid. LC/MS calcd. for $C_{20}H_{18}BrF_3N_4O_2$ (m/e) 483, obsd. 484.9 [M+H, ES^+].

Step 2: 1-(4'-{4-Ethyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid methyl ester

To a mixture of [3-(4-bromo-phenyl)-5-ethyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(3-trifluoromethyl-phenyl)-ethyl ester (300 mg, 0.62 mmol), methyl 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxylate (281 mg, 0.93 mmol), palladium(II) acetate (20.9 mg, 0.09 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (76.5 mg, 0.19 mmol), and potassium phosphate tribasic (395 mg, 1.86 mmol) in a vial were added freshly degassed toluene (4.5 mL) and water (1.0 mL) at room temperature under nitrogen atmosphere. Then, the cap was closed and the resulting light yellow suspension was heated to 105 $^{\circ}$ C and stirred for 1 h by which time TLC analysis indicated the absence of starting material. Then, the reaction mixture was cooled to room temperature and poured into a

mixture of water and brine solution. The organic compound was extracted into EA (2 x 50 mL) and the combined extracts were washed with brine solution and dried over anhydrous MgSO₄. Filtration and concentration gave the crude residue which was purified by using an ISCO (80 g) column chromatography eluting with 0-100% EA in hexanes. The desired fractions were combined and the solvent was removed under vacuum to isolate 1-(4'-{4-ethyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid methyl ester (245 mg, 68% yield). LC/MS calcd. for C₃₁H₂₉F₃N₄O₄ (m/e) 578, obsd. 579.4 [M+H, ES⁺].

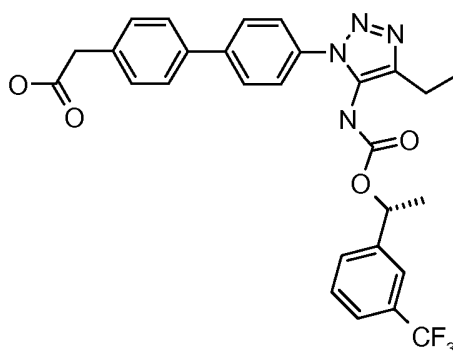
Step 3: 1-(4'-{4-Ethyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid

To a solution of 1-(4'-{4-ethyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid methyl ester (240 mg, 0.42 mmol) in THF (5 mL) and ethanol (5 mL) was added an excess of 1.0 N sodium hydroxide (4.15 mL, 4.15 mmol) solution in water at room temperature. The resulting solution was stirred for 15 h at room temperature at which time TLC analysis indicated the absence of starting material. Then, it was diluted with water and the solvent was removed under vacuum. The neutral impurities were extracted into diethyl ether (100 mL) and the basic aqueous layer was neutralized with 1.0 N HCl. The resulting precipitate was extracted into EA (2 x 45 mL) and the combined extracts were washed with brine solution. After drying and filtration, the solvent was removed under vacuum to obtain 1-(4'-{4-ethyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid (219 mg, 93.5% yield). LC/MS calcd. for C₃₀H₂₇F₃N₄O₄ (m/e) 564, obsd. 565.3 [M+H, ES⁺]. ¹H NMR (DMSO-d₆) δ: 12.24 (br. s., 1H), 9.28 - 9.93 (m, 1H), 7.82 (d, J = 6.8 Hz, 2H), 7.53 - 7.76 (m, 7H), 7.47 (d, J = 8.3 Hz, 3H), 5.80 (br. s., 1H), 2.54 - 2.64 (m, 2H), 1.37 - 1.61 (m, 5H), 1.13 - 1.23 (m, 5H).

Examples 20

{4'-[4-Ethyl-5-((R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid

-66-



Step 1: {4'-[4-Ethyl-5-((R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester

To a mixture of (R)-1-(3-(trifluoromethyl)phenyl)ethyl 1-(4-bromophenyl)-4-ethyl-1H-1,2,3-triazol-5-ylcarbamate (200 mg, 0.41 mmol), ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (120 mg, 0.41 mmol), palladium(II) acetate (13.9 mg, 0.06 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (51.0 mg, 0.12 mmol), and potassium phosphate tribasic (264 mg, 1.24 mmol) in a vial were added freshly degassed toluene (4.5 mL) and water (1.0 mL) at room temperature under nitrogen atmosphere. Then, the cap was closed and the resulting light yellow suspension was heated to 105 °C and stirred for 1 h by which time TLC analysis indicated the absence of starting material. Then, the reaction mixture was cooled to room temperature and poured into a mixture of water and brine solution. The organic compound was extracted into EA (2 x 50 mL) and the combined extracts were washed with brine solution and dried over anhydrous MgSO₄. Filtration and concentration gave the crude residue which was purified by using an ISCO (80 g) column chromatography eluting with 0-100% EA in hexanes. The desired fractions were combined and the solvent was removed under vacuum to isolate {4'-[4-ethyl-5-((R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester (194 mg, 83% yield). LC/MS calcd. for C₃₀H₂₉F₃N₄O₄ (m/e) 566, obsd. 567.4 [M+H, ES⁺].

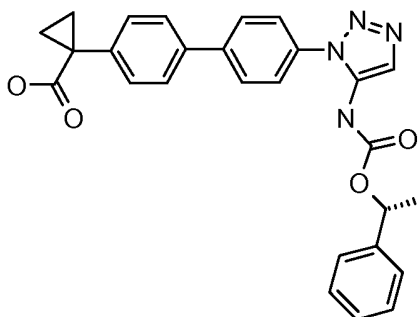
Step 2: {4'-[4-Ethyl-5-((R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid

To a solution of {4'-[4-ethyl-5-((R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester (185 mg, 0.33 mmol) in THF (5 mL) and ethanol (5 mL) was added an excess of 1.0 N sodium hydroxide (3.27 mL, 3.27 mmol) solution in water at room temperature. The resulting colorless solution was stirred for 15 h at room temperature at which time TLC analysis indicated the absence of starting material.

Then, it was diluted with water (~15 mL) and the solvent was removed under vacuum. The basic aqueous layer was neutralized with 1.0 N HCl. The resulting precipitate was extracted into EA (2 x 45 mL) and the combined extracts were washed with brine solution. After drying over anhydrous MgSO₄ and filtration, the solvent was removed under vacuum to obtain the desired acid which was dissolved in dichloromethane (~5 mL) and then diluted with hexanes. As a result, solids were formed and they were collected by filtration and washed with hexanes. After air drying, 135 mg (77% yield) of {4'-[4-ethyl-5-((R)-1-(3-trifluoromethyl-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid was isolated as a white solid. LC/MS calcd. for C₂₈H₂₅F₃N₄O₄ (m/e) 538, obsd. 539.3 [M+H, ES⁺]. ¹H NMR (DMSO-d₆) δ: 12.40 (s, 1H), 9.30 - 9.92 (m, 1H), 7.83 (d, J = 6.8 Hz, 2H), 7.53 - 7.76 (m, 7H), 7.41 (d, J = 8.0 Hz, 3H), 5.79 (d, J = 15.6 Hz, 1H), 3.66 (s, 2H), 2.55 (d, J = 7.3 Hz, 2H), 1.51 (br. s., 3H), 1.18 (t, J = 7.4 Hz, 3H).

Example 21

1-{4'-[5-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid



Step 1: 3-(4-Bromo-phenyl)-3H-[1,2,3]triazole-4-carboxylic acid methyl ester

In 350 mL reaction vial 1-azido-4-bromo-benzene (5 g, 25.2 mmol) and propionic acid methyl ester (2.12 g, 2.11 mL, 25.2 mmol) were combined with Toluene (50 mL) to give a yellow suspension. The vial was sealed and heated in an oil bath at 150 °C for 5.5 h. The reaction was filtered, solid washed with toluene and EtOAc. The filtrate was concentrated, dissolved in minimal DCM, and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 3-(4-bromo-phenyl)-3H-[1,2,3]triazole-4-carboxylic acid methyl ester (1.5 g, 21.1% yield) as a light brown solid. LC/MS calcd. for C₁₀H₈BrN₃O₂ (m/e) 281/283, obsd. 282/284 (M+H, ES⁺).

Step 2: 3-(4-Bromo-phenyl)-3H-[1,2,3]triazole-4-carboxylic acid

To 200 mL round bottom flask containing 3-(4-bromo-phenyl)-3H-[1,2,3]triazole-4-carboxylic acid methyl ester (1.0 g, 3.54 mmol) dissolved in THF (30 mL) (brown solution) was added LiOH (0.81 g, 34 mmol) in water (10 mL) with heat to partially dissolve. The solution was stirred at room temperature for 20 h. The reaction was concentrated, diluted in water (total volume, 200 mL) extracted with ethyl ether (2 x 100mL). The aqueous layer was acidified with 1 N HCl and the resulting precipitate was filtered, washed with water and hexanes, and dried over house vacuum yielding 3-(4-bromo-phenyl)-3H-[1,2,3]triazole-4-carboxylic acid (0.78 g, 81.7% yield) as a light brown solid. LC/MS calcd. for C₉H₆N₃O₂ (m/e) 267/269, obsd. 268/270 (M+H, ES⁺).

Step 3: [3-(4-Bromo-phenyl)-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester

In a 40 mL reaction vial, 3-(4-bromo-phenyl)-3H-[1,2,3]triazole-4-carboxylic acid (399 mg, 1.45 mmol), (R)-1-phenylethanol (265 mg, 0.83 mL, 2.17 mmol) and triethylamine (293 mg, 0.4 mL, 2.9 mmol) were combined with toluene (17 mL) to give a yellow solution and to this was added diphenylphosphorylazide (797 mg, 0.624 mL, 2.89 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 65 °C for 3.5 h, and cooled to room temperature overnight. The reaction was concentrated, diluted with EtOAc, washed with Water and brine, and dried over MgSO₄, filtered, concentrated, dissolved in minimal DCM, and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes).

Appropriate fractions combined, concentrated, and dried from DCM / hexanes, yielding [3-(4-bromo-phenyl)-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (408 mg, 72.8% yield) as a white solid. LC/MS calcd. for C₁₇H₁₅BrN₄O₂ (m/e) 386/388, obsd. 387/389 (M+H, ES⁺).

Step 4: 1-{4'-[5-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (93.6 mg, 0.310 mmol), [3-(4-bromo-phenyl)-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (100 mg, 0.258 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (31.8 mg, 0.0775 mmol), Pd(OAc)₂ (8.7 mg, 0.039 mmol), and tripotassium phosphate (164 mg, 0.0775 mmol) were combined with toluene (8 mL) and water (2 mL) (previously purged with nitrogen for 20 min) to give a light yellow solution. The vial's atmosphere was replaced with nitrogen, sealed, heated in a dry block at 80 °C 4 h, and cooled to room temperature overnight. The reaction was diluted

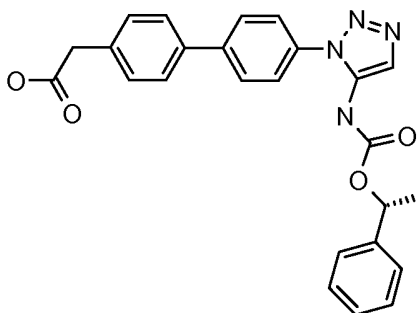
with EtOAc (70 mL) and washed with water (100 mL) and brine (50 mL). The aqueous layers were extracted with EtOAc (60 mL). The organic layers were combined, dried over MgSO₄, filtered, concentrated, dissolved in minimal DCM, and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 1-{4'-[5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (45.1 mg, 36.2% yield) as a light yellow solid. LC/MS calcd. for C₂₈H₂₆N₄O₄ (m/e) 482, obsd. 483 (M+H, ES⁺).

Step 5: 1-{4'-[5-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

In a 200 mL round-bottomed flask, 1-{4'-[5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (40 mg, 0.0829 mmol) was combined with THF (2 mL) and MeOH (2 mL) to give a yellow solution. To this was dripped in NaOH (1 M, 1 mL, 1 mmol). The reaction was stirred at room temperature overnight. The reaction was diluted with water, concentrated, diluted with more water and acidified with 1 N HCl. The resulting precipitate was filtered, washed with water and hexanes, and dried over house vacuum and in a desiccator yielding 1-{4'-[5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid (28.7 mg, 73.9% yield) as a light brown solid. LC/MS calcd. for C₂₇H₂₄N₄O₄ (m/e) 468, obsd. 469 (M+H, ES⁺). ¹H NMR (DMSO-d₆) δ: 12.38 (br. s., 1H), 10.04 (br. s., 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.82 (s, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.17 - 7.41 (m, 5H), 5.74 (d, J = 5.8 Hz, 1H), 1.34 - 1.62 (m, 5H), 1.21 (d, J = 2.5 Hz, 2H).

Example 22

{4'-[5-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid



Step 1: {4'-[5-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester

In a 20 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid ethyl ester (89.9 mg, 0.310 mmol), [3-(4-bromo-phenyl)-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (100 mg, 0.258 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (31.8 mg, 0.0775 mmol), Pd(OAc)₂ (8.7 mg, 0.039 mmol), and tripotassium phosphate (164 mg, 0.0775 mmol) were combined with toluene (7 mL) and water (2 mL) (previously purged with nitrogen for 20 min) to give a light yellow solution. The vial's atmosphere was purged with nitrogen, sealed, heated in a dry block at 80 °C for 4 h, and cooled to room temperature overnight. Additional 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid ethyl ester (89.9 mg, 0.310 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (31.8 mg, 0.0775 mmol), and Pd(OAc)₂ (8.7 mg, 0.039 mmol) were added. The vial's atmosphere was purged with nitrogen, sealed, heated in a dry block at 80 °C for 4 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc (70 mL) and washed with water (100 mL) and brine (50 mL). The aqueous layers were extracted with EtOAc (60 mL) and the organic layers were combined, dried over MgSO₄, filtered, concentrated, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding {4'-[5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester (46 mg, 37.9% yield) as a light yellow solid. LC/MS (ES) calcd. for C₂₇H₂₆N₄O₄ (m/e) 470, obsd. 471 (M+H, ES⁺).

Step 2: {4'-[5-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid

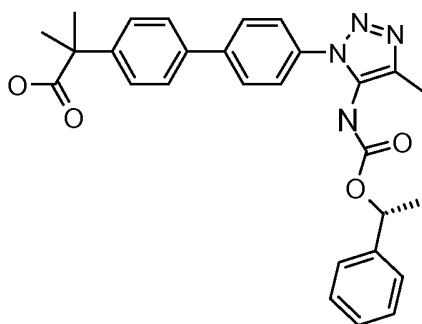
In a 200 mL round-bottomed flask, 1-{4'-[5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (41 mg, 0.087 mmol) was combined with THF (2 mL) and MeOH (2 mL) to give a yellow solution. To this was dripped in NaOH (1 M, 1 mL, 1 mmol). The reaction was stirred at room temperature overnight. The reaction was diluted with water, concentrated, diluted with more water, and acidified with 1 N HCl. The resulting precipitate was filtered, washed with water and hexanes, and dried over house vacuum and in a desiccator yielding {4'-[5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid (28.6 mg, 74.2% yield) as a yellow solid. LC/MS calcd. for C₂₅H₂₂N₄O₄ (m/e) 442, obsd. 443 (M+H, ES⁺). ¹H

NMR (DMSO- d_6) δ : 12.39 (br. s., 1H), 10.03 (br. s., 1H), 7.88 (d, J = 8.3 Hz, 2H), 7.82 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.13 - 7.39 (m, 5H), 5.74 (d, J = 5.3 Hz, 1H), 3.66 (s, 2H), 1.46 (br. s., 3H).

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Example 23

2-Methyl-2-{4'-[4-methyl-5-((R)-1-phenylethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-propionic acid



Step 1: {5-Methyl-3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-3H-[1,2,3]triazol-4-yl}-carbamic acid (R)-1-phenyl-ethyl ester

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In a 20 mL vial, (R)-1-phenylethyl 1-(4-bromophenyl)-4-methyl-1H-1,2,3-triazol-5-ylcarbamate (2.39 g, 5.96 mmol), BISPIN (1.82 g, 7.15 mmol) and potassium acetate (1.17 g, 11.9 mmol) were combined with 1,4-dioxane (59.8 mL) to give a white suspension that was purged with nitrogen for 5 min. To the mixture was added $\text{PdCl}_2(\text{DPPF})$ (0.486 g, 0.596 mmol). The vial was sealed, stirred in a dry block at 80 °C for 3.5 h, and cooled to room temperature overnight. The reaction was filtered, rinsed with EtOAc, concentrated, diluted with EtOAc (200 mL), and filtered again. The filtrate was washed with water (200 mL) and brine (100 mL). The aqueous layers were extracted with EtOAc (200 mL). The organic layers were combined, dried over MgSO_4 , filtered, concentrated, and the crude material was purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, yielding {5-methyl-3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-3H-[1,2,3]triazol-4-yl}-carbamic acid (R)-1-phenyl-ethyl ester (2.24 g, 83% yield) as a clear oil that solidifies as a white crystal upon cooling to room temperature. LC/MS calcd. for $\text{C}_{24}\text{H}_{29}\text{BN}_4\text{O}_4$ (m/e) 448, obsd. 449 ($\text{M}+\text{H}$, ES^+).

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Step 2: 2-Methyl-2-{4'-[4-methyl-5-((R)-1-phenylethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-propionic acid methyl ester

In a 20 mL vial, 2-(4-bromo-phenyl)-2-methyl-propionic acid methyl ester (130 mg, 0.506 mmol), {5-methyl-3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-3H-

[1,2,3]triazol-4-yl}-carbamic acid (R)-1-phenyl-ethyl ester (212 mg, 0.473 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (59 mg, 0.144 mmol), tripotassium phosphate (292 mg, 1.38 mmol), and Pd(OAc)₂ (17 mg, 0.075 mmol) were combined with toluene (8 mL) and water (2 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was purged with nitrogen, sealed, heated in dry block at 80 °C for 4 h, and cooled to room temperature overnight. The reaction was diluted with EtOAc, washed with water and brine, dried over MgSO₄, filtered, concentrated, dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 2-methyl-2-{4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-propionic acid methyl ester (106 mg, 45% yield) as a white solid. LC/MS calcd. for C₂₉H₃₀N₄O₄ (m/e) 498, obsd. 499 (M+H, ES⁺).

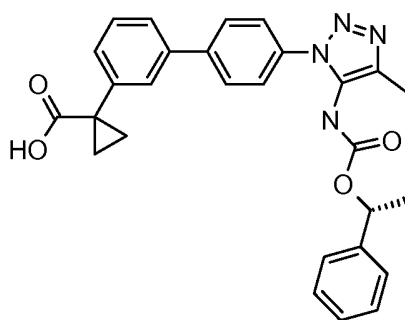
Step 3: 2-Methyl-2-{4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-propionic acid

In a 200 mL round-bottomed flask, 2-methyl-2-{4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-propionic acid methyl ester (100 mg, 0.201 mmol) was combined with THF (4 mL) and MeOH (4 mL) to give a yellow solution. To this was dripped in 1 M NaOH (2 mL, 2.0 mmol). The reaction was stirred at room temperature for 2 days and stored in a refrigerator for 1.5 days. The reaction was stirred again at room temperature for 1 day and then more 1 M NaOH (1 mL, 1 mmol) was added. The reaction was heated in a dry block at 40 °C for 6 h and then cooled to room temperature overnight. The reaction was diluted with water, concentrated, diluted with more water and acidified with 1 N HCl. The resulting precipitate was filtered, washed with water and hexanes, and dried over house vacuum and in a desiccator yielding 2-methyl-2-{4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-propionic acid (79.6 mg, 81.9 % yield) as a white solid. LC/MS calcd. for C₂₈H₂₈N₄O₄ (m/e) 484, obsd. 485 (M+H, ES⁺). ¹H NMR (DMSO-d₆) δ: 12.43 (br. s., 1H), 9.68 (br. s., 1H), 7.84 (d, J = 7.0 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.06 - 7.43 (m, 5H), 5.70 (br. s., 1H), 2.18 (s, 3H), 1.33 - 1.73 (m, 9H).

Example 24

(R)-1-(4'-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1H-1,2,3-triazol-1-yl)biphenyl-3-yl)cyclopropanecarboxylic acid

-73-



Step 1: 1-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane carboxylic acid ethyl ester

A 350 mL sealed cap vessel was charged with 1-(3-bromophenyl)cyclopropanecarboxylic acid ethyl ester (3.56 g, 13.2 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.03 g, 15.9 mmol), and potassium acetate (2.6 g, 26.5 mmol) and then 1,4-Dioxane (40 mL) was added to give a white suspension. The mixture was then nitrogen gas was bubbled through the reaction mixture for 10 minutes before the addition of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (484 mg, 0.66 mmol) at room temperature under nitrogen atmosphere. Then, the flask was sealed with a cap and the brown reaction mixture was heated in an oil bath at 80 °C for 5 h. Then, it was cooled to room temperature and poured into a solution of water (100 mL) and brine (100 mL) and the organic compound was extracted into EA (2 x 150 mL) (it was difficult to see the two layers because of the black mixture). The combined extracts were washed with brine solution and dried over anhydrous MgSO₄. Filtration and concentration gave the crude black oil (~11.11 g) which was purified using an ISCO (120 g) column chromatography eluting with 0-60% EA in hexanes. The desired fractions (20-40) were combined and the solvent was removed under vacuum to obtain 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane carboxylic acid ethyl ester as viscous oil (2.55 g, 61% yield). LC/MS calcd. for C₁₈H₂₅BO₄ (m/e) 316, obsd. 317.2 [M+H, ES⁺].

Step 2: (R)-1-(4'-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1H-1,2,3-triazol-1-yl)biphenyl-3-yl)cyclopropanecarboxylic acid ethyl ester

To a mixture of ethyl 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxylate (236 mg, 0.75 mmol), (R)-1-phenylethyl 1-(4-bromophenyl)-4-methyl-1H-1,2,3-triazol-5-ylcarbamate (200 mg, 0.5 mmol), palladium(II) acetate (16.8 mg, 0.075 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (61.4 mg, 0.15 mmol), and tripotassium phosphate (317 mg, 1.5 mmol) in a 50 mL sealed tube were added freshly degassed toluene (4.5 mL) and water (1.0 mL) at room temperature under

nitrogen atmosphere. Then, the rubber septum was replaced with a cap and the resulting light yellow suspension was heated to 110 °C with oil bath. During this period, it turned to a black suspension. Then, the reaction mixture was cooled to room temperature and poured into water and brine solution. The organic compound was extracted into EA (2 x 50 mL) and the combined extracts were washed with brine solution and dried over anhydrous MgSO₄.

Filtration and concentration gave the crude product which was purified using an ISCO (80 g) column chromatography eluting with 0-100% EA in hexanes. The desired fractions were combined and the solvent was removed under vacuum to obtain (R)-1-(4'-(4-methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-3-yl)cyclopropanecarboxylic acid ethyl ester as an amorphous solid (144 mg, 56.6% yield). LC/MS calcd. for C₃₀H₃₀N₄O₄ (m/e) 510, obsd. 511.2 [M+H, ES⁺].

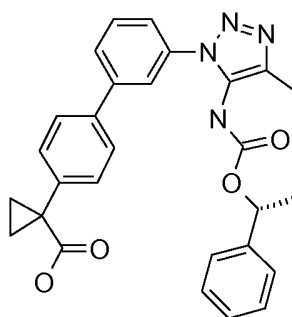
Step 3: (R)-1-(4'-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-3-yl)cyclopropanecarboxylic acid

To a solution of (R)-1-(4'-(4-methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-3-yl)cyclopropanecarboxylic acid ethyl ester (162 mg, 0.32 mmol) in ethanol (6 mL) was added an excess of 1 *N* sodium hydroxide (1.59 mL, 1.59 mmol) solution in water at room temperature. Then, the resulting cloudy solution was stirred for 20 h at which time LCMS analysis indicated the presence of still some starting material. Then, the cloudy reaction mixture was heated in an oil bath to 55 °C and stirred for 3 h at which time LCMS analysis indicated the absence of starting material. Then, it was cooled to room temperature and the solvent was removed under vacuum and the residue was diluted with water. The basic aqueous layer was neutralized with 1 *N* HCl. The resulting solids were collected by filtration and washed with water. After air drying, 130 mg (81.6% yield) of (R)-1-(4'-(4-methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-3-yl)cyclopropanecarboxylic acid was isolated as a white solid. LC/MS calcd. for C₂₈H₂₆N₄O₄ (m/e) 482, obsd. 483.1 [M+H, ES⁺]. ¹H NMR (DMSO-*d*₆) δ: 12.39 (br. s., 1H), 9.32 - 10.31 (m, 1H), 7.80 (d, *J* = 6.8 Hz, 2H), 7.70 (br. s., 2H), 7.53 - 7.64 (m, 2H), 7.39 - 7.52 (m, 4H), 7.35 (d, *J* = 7.5 Hz, 3H), 5.80 (br. s., 1H), 3.05 - 3.57 (m, 3H), 1.35 - 1.74 (m, 5H), 1.25 (br. s., 2H).

Example 25

1-{3'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

-75-



Step 1: 3-(3-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid methyl ester

In 350 mL reaction vial 1-azido-3-bromo-benzene (2.47 g, 12.5 mmol) and methyl but-2-ynoate (1.35 g, 1.37 mL, 13.7 mmol) were combined with Toluene (106 mL) to give a yellow suspension. The vial was sealed and heated in an oil bath at 150 °C accidentally for 2.5 day (4 h intended). The reaction was filtered, solid washed with toluene. The filtrate was concentrated, dissolved in minimal DCM, and purified by flash chromatography (silica gel, 0% to 30% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 3-(3-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid methyl ester (1.04 g, 28.2% yield) as a light brown solid. LC/MS calcd. for $C_{11}H_{10}BrN_3O_2$ 295/297, obsd. 296/298 (M+H, ES⁺).

Step 2: 3-(3-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid

To 250 mL round bottom flask containing 3-(3-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid methyl ester (1.0 g, 3.38 mmol) dissolved in THF (40 mL) (brown solution) was added LiOH (0.81 g, 34 mmol) in water (10 mL) with heat to partially dissolve. The solution was stirred at room temperature overnight. The reaction was concentrated, diluted in water (total volume, 200mL) extracted with ethyl ether (2 x 100 mL). The aqueous layer was acidified with 1 N HCl. The resulting precipitate was filtered, washed with water and hexanes, and dried over house vacuum and in a desiccator yielding 3-(3-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (0.913 g, 95.8% yield) as a light brown solid. LC/MS calcd. for $C_{10}H_8N_3O_2$ (m/e) 281/283, obsd. 281/284 (M+H, ES⁺).

Step 3: [3-(3-Bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester

In a 40 mL reaction vial, 3-(3-bromo-phenyl)-5-methyl-3H-[1,2,3]triazole-4-carboxylic acid (0.91 g, 3.2 mmol), (R)-1-phenylethanol (0.84 g, 0.83 mL, 6.9 mmol) and triethylamine (0.91 g, 1.3 mL, 9.0 mmol) were combined with toluene (28 mL) to give a yellow solution and to this was added diphenylphosphorylazide (2.5 g, 1.9 mL, 9.0 mmol). The vial's atmosphere was purged with nitrogen, sealed, heated in an oil bath at 65 °C for 2.5 h, and cooled to room

temperature overnight. The reaction was concentrated as yellow viscous oil, diluted with DCM, and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, dried from DCM / hexanes, yielding [3-(3-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (0.86 g, 66% yield) as a light yellow solid / gum. LC/MS calcd. for $C_{18}H_{17}BrN_4O_2$ (m/e) 400/402, obsd. 401/403 (M+H, ES^+).

Step 4: 1-{3'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

In a 40 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarboxylic acid methyl ester (356 mg, 1.18 mmol), [3-(3-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (430 mg, 1.07 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (132 mg, 0.321 mmol), and $Pd(OAc)_2$ (36.1 mg, 0.161 mmol) were combined with toluene (34 mL) (previously purged with nitrogen for 20 min) to give a light yellow solution. To this was added tripotassium phosphate (682 mg, 3.21 mmol) dissolved in water (9 mL) (previously purged with nitrogen for 20 min). The vial's atmosphere was purged with nitrogen, sealed, heated in oil bath at 100 °C accidentally for 2.5 days (intended 4 h) and cooled to room temperature in 1 h. The reaction was filtered, diluted with EtOAc (50 mL) and washed with water / brine (100/50 mL) and brine (150 mL). The aqueous layers were extracted with EtOAc (2 x 150 mL). The organic layers were combined, dried over $MgSO_4$, filtered, concentrated, dissolved in minimal DCM, and purified by flash chromatography (silica gel, 0% to 100% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding 1-{3'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (142 g, 26.7% yield) as a white solid. LC/MS calcd. for $C_{29}H_{28}N_4O_4$ (m/e) 496, obsd. 497 (M+H, ES^+).

Step 5: 1-{3'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

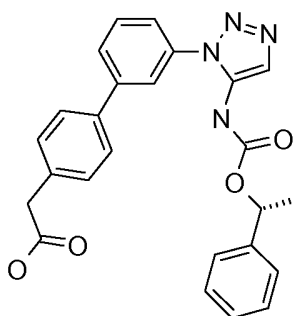
In a 100 mL round-bottomed flask, 1-{3'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (141 mg, 0.284 mmol) was combined with THF (10 mL) to give a colorless solution. To this was dripped in NaOH (1 M, 2.8 mL, 2.8 mmol). The reaction was stirred at room temperature and additional water and THF were added. After 18 h, the reaction was diluted with water, concentrated, diluted with more water and acidified with 1 N HCl. The resulting precipitate

-77-

was filtered, washed with water and hexanes, and dried over house vacuum yielding 1-{3'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid (49 mg, 35.8% yield) as a white solid. LC/MS calcd. for $C_{28}H_{26}N_4O_4$ (m/e) 482, obsd. 483 (M+H, ES^+). 1H NMR (DMSO- d_6) δ : 12.39 (br. s., 1H), 9.72 (br. s., 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.77 (s, 1H), 7.56 - 7.73 (m, 3H), 7.51 (d, J = 7.3 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.28 (br. s., 5H), 5.70 (br. s., 1H), 2.12 - 2.27 (m, 3H), 1.27 - 1.65 (m, 5H), 1.19 (d, J = 2.8 Hz, 2H).

Example 26

{3'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid



Step 1: {3'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester

In a 40 mL vial, 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid ethyl ester (311 mg, 1.07 mmol), [3-(3-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (430 mg, 1.07 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (132 mg, 0.321 mmol), and $Pd(OAc)_2$ (36.1 mg, 0.161 mmol) were combined with toluene (12 mL) (previously purged with nitrogen for 20 min) to give a light yellow solution. To this was added tripotassium phosphate (682 mg, 3.21 mmol) dissolved in water (4 mL) (previously purged with nitrogen for 20 min). The vial's atmosphere was replaced with nitrogen, sealed, heated in oil bath at 100 °C accidentally for 2.5 days (intended 4 h) and cooled to room temperature in 1 h. The reaction was filtered, diluted with EtOAc (50 mL) and washed with water / brine (100/50 mL) and brine (150 mL). The aqueous layers were extracted with EtOAc (2 x 150 mL). The organic layers were combined, dried over $MgSO_4$, filtered, concentrated, dissolved in minimal DCM, and purified by flash chromatography (silica gel, 0% to 100% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding {3'-[4-methyl-5-

-78-

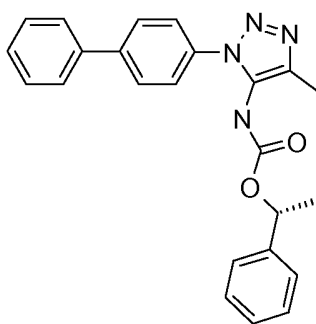
((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester (96.7 mg, 18.6% yield) as a white solid. LC/MS calcd. for $C_{28}H_{28}N_4O_4$ (m/e) 484, obsd. 485 (M+H, ES^+).

Step 2: {3'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid

In a 100 mL round-bottomed flask, {3'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid ethyl ester (90 mg, 0.186 mmol) was combined with THF (5 mL) to give a colorless solution. To this was dripped in LiOH (78 mg, 1.86 mmol) in water (1 mL) with heat to partially dissolve. The reaction was stirred at room temperature for 17 h. The reaction was diluted with water, concentrated, diluted with more water and acidified with 1 N HCl. The resulting precipitate was filtered, washed with water and hexanes, and dried over house vacuum yielding 1-{3'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid (64.7 mg, 76.3% yield) as a white solid. LC/MS calcd. for $C_{26}H_{24}N_4O_4$ (m/e) 456, obsd. 457 (M+H, ES^+). 1H NMR (DMSO- d_6) δ : 12.41 (br. s., 1H), 9.72 (br. s., 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.78 (s, 1H), 7.59 - 7.73 (m, 3H), 7.51 (d, J = 7.5 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.06 - 7.34 (m, 5H), 5.69 (br. s., 1H), 3.65 (s, 2H), 2.19 (s, 3H), 1.44 (br. s., 3H).

Example 27

(3-Biphenyl-4-yl-5-methyl-3H-[1,2,3]triazol-4-yl)-carbamic acid (R)-1-phenyl-ethyl ester



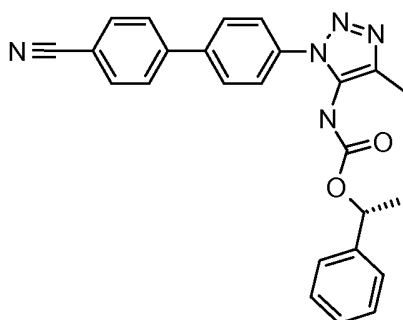
In a 20 mL vial, phenylboronic acid (6.9 mg, 0.057 mmol), [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid *tert*-butyl ester (18.9 mg, 0.0471 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (7.7 mg, 0.019 mmol), tripotassium phosphate (30 mg, 0.14 mmol), and $Pd(OAc)_2$ (2.0 mg, 0.0089 mmol) were combined with toluene (4 mL) and water (1 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was replaced with nitrogen, sealed, heated in

-79-

dry block at 100 °C for 3.5 h, and cooled to room temperature overnight. The reaction was filtered through celite, rinsed with EtOAc, concentrated, dissolved in minimal DCM, and purified by flash chromatography (silica gel, 0% to 100% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding (3-biphenyl-4-yl-5-methyl-3H-[1,2,3]triazol-4-yl)-carbamic acid (R)-1-phenyl-ethyl ester (12.4mg, 66.1% yield) as a white solid. LC/MS calcd. for C₂₄H₂₂N₄O₂ (m/e) 398, obsd. 399 (M+H, ES⁺). ¹H NMR (DMSO-d₆) δ: 9.67 (br. s., 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.76 (d, J = 7.3 Hz, 2H), 7.49 - 7.68 (m, 4H), 7.41 - 7.49 (m, 1H), 6.92 - 7.40 (m, 5H), 5.70 (br. s., 1H), 2.18 (s, 3H), 1.49 (br. s., 3H).

Example 28

[3-(4'-Cyano-biphenyl-4-yl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester



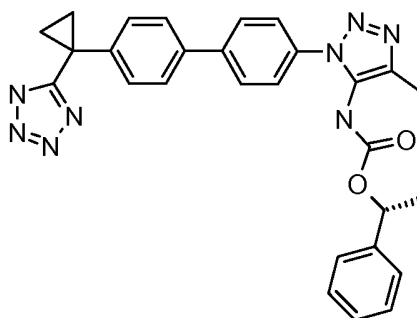
In a 20 mL vial, 4-cyanophenylboronic acid (20.1 mg, 0.137 mmol), [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid *tert*-butyl ester (50 mg, 0.125 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (15.3 mg, 0.0374 mmol), tripotassium phosphate (79.4 mg, 0.374 mmol), and Pd(OAc)₂ (4.2 mg, 0.0187 mmol) were combined with toluene (2 mL) and water (0.5 mL) (previously purged with nitrogen for 20 min) to give a light yellow suspension. The vial's atmosphere was replaced with nitrogen, sealed, heated in dry block at 100 °C for 4 h, and cooled to room temperature overnight. The reaction was filtered and rinsed with water (5 mL) and EtOAc (60 mL). The filtrate was washed with water (50 mL) and brine (50 mL). The aqueous layer was extracted with EtOAc (60 mL). The organic layer was washed with same brine. The organic layers were combined, concentrated, dissolved in minimal DCM, and purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding [3-(4'-cyano-biphenyl-4-yl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester (20 mg, 0.047 mmol, 38 % yield) as a white solid.

LC/MS calcd. for $C_{25}H_{21}N_4O_2$ (m/e) 423, obsd. 424 ($M+H$, ES^+). 1H NMR (DMSO- d_6) δ : 9.72 (br. s., 1H), 7.86 - 8.07 (m, 6H), 7.65 (d, J = 8.3 Hz, 2H), 6.80 - 7.48 (m, 5H), 5.69 (br. s., 1H), 2.18 (s, 3H), 1.48 (br. s., 3H).

5

Example 29

(R)-1-Phenyl-ethyl-1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)biphenyl-4-yl)-4-methyl-1H-1,2,3-triazol-5-ylcarbamate



Step 1: (R)-1-Phenyl-ethyl-1-(4'-(1-cyanocyclopropyl)biphenyl-4-yl)-4-methyl-1H-1,2,3-triazol-5-ylcarbamate

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To a mixture of (R)-1-phenylethyl 4-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-1,2,3-triazol-5-ylcarbamate (485 mg, 1.08 mmol), 1-(4-bromophenyl)cyclopropanecarbonitrile (360 mg, 1.62 mmol), palladium(II) acetate (36.4 mg, 0.16 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (133 mg, 0.33 mmol), and potassium phosphate tribasic (689 mg, 3.25 mmol) in a vial were added toluene (9 mL) and water (2.0 mL) at room temperature under nitrogen atmosphere. Then, the cap was closed and the resulting light brown suspension was heated to 105 °C and stirred for 3 h by which time TLC analysis indicated the presence of new spots. Then, the reaction mixture was cooled and it was diluted with water. The organic compound was extracted into EA (2 x 50 mL) and the combined extracts were washed with brine solution and dried over anhydrous $MgSO_4$. Filtration and concentration gave the crude residue which was purified by using an ISCO (80 g) column chromatography eluting with 0-100% EA in hexanes. The desired fractions were combined and the solvent was removed under vacuum to isolate (R)-1-phenylethyl-1-(4'-(1-cyanocyclopropyl)biphenyl-4-yl)-4-methyl-1H-1,2,3-triazol-5-ylcarbamate (190 mg, 38% yield) as a white solid. LC/MS calcd. for $C_{28}H_{25}N_5O_2$ (m/e) 463, obsd. 464.8 [$M+H$, ES^+].

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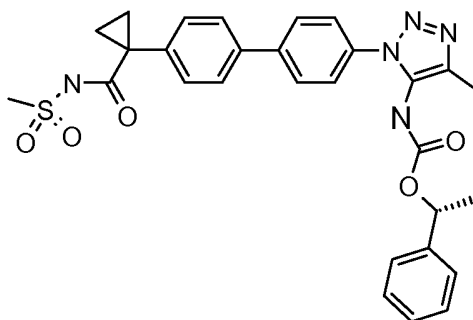
25

Step 2: (R)-1-Phenyl-ethyl-1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)biphenyl-4-yl)-4-methyl-1H-1,2,3-triazol-5-ylcarbamate

To a solution of (R)-1-phenylethyl 1-(4'-(1-cyanocyclopropyl)biphenyl-4-yl)-4-methyl-1H-1,2,3-triazol-5-ylcarbamate (50 mg, 0.11 mmol) in toluene (5 mL) were added di-*n*-butyltin oxide (5.37 mg, 0.22 mmol) and azidotrimethylsilane (12.4 mg, 14.3 μ L, 0.11 mol) at room temperature under nitrogen atmosphere. The resulting cloudy solution was heated to 100 °C and stirred for 15 h by which time LCMS and TLC analysis indicated the absence of starting material. Then, it was cooled to room temperature and poured into brine solution and EA. The two layers were separated and the aqueous layer was extracted with EA one more time. The combined extracts were washed with brine solution and dried over anhydrous MgSO₄. Filtration and concentration gave the crude product which was purified using an ISCO (40 g) column chromatography eluting with 0-100% EA in hexanes and 10% methanol in dichloromethane. The desired product came with 10% methanol in dichloromethane and the fractions were combined and the solvent was removed under vacuum to obtain (R)-1-phenylethyl-1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)biphenyl-4-yl)-4-methyl-1H-1,2,3-triazol-5-ylcarbamate as a white solid (25 mg, 46% yield). LC/MS calcd. for C₂₈H₂₆N₈O₂ (m/e) 506, obsd. 507.1 [M+H, ES⁺]. ¹H NMR (DMSO-*d*₆) δ : 16.08 (br. s., 1H), 9.20 - 9.84 (m, 1H), 7.85 (d, *J* = 7.0 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.52 - 7.65 (m, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.34 (br. s., 5H), 5.52 - 5.84 (m, 1H), 2.17 (s, 3H), 1.51 - 1.63 (m, 4H), 1.15 - 1.35 (m, 3H).

Example 30

{3-[4'-(1-Methanesulfonylaminocarbonyl-cyclopropyl)-biphenyl-4-yl]-5-methyl-3H-[1,2,3]triazol-4-yl}-carbamic acid (R)-1-phenyl-ethyl ester



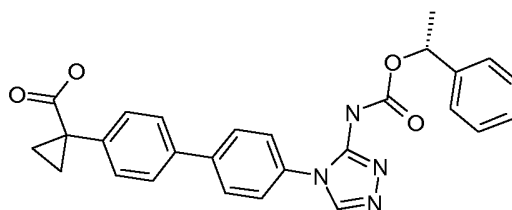
In a 50 mL round-bottomed flask, 1-{4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid (50 mg, 0.201 mmol) was combined with DCM (1 ml) and DMF (drop) under nitrogen to give a white suspension. To this was added oxalyl chloride (26.3 mg, 18.1 μ L, 0.207 mmol) drop wise in two portions with 10 min in between additions. The reaction was stirred at room temperature for 1.5 h.

-82-

The reaction was concentrated, dried from DCM / Toluene and DCM / hexanes, and dissolved in THF (1.00 ml). In a 5 mL vial, methanesulfonamide (29.6 mg, 311 μ mol) was combined with DCM (1 ml) under nitrogen to give a colorless solution. To this was added NaH (60% dispersion in mineral oil, 7.46 mg, 0.311 mmol) and the white suspension was stirred at room temperature for 1.5 h. The acyl chloride THF solution (with rinsed with THF, 1 x 1 mL) was added drop wise to the sulfonamide mixture. The reaction was stirred at room temperature for 1 day. The reaction was stored in the refrigerator for 3 days. Additional NaH (60% dispersion in mineral oil, 7.46 mg, 0.311 mmol) was added and the reaction was stirred at room temperature for 1 day. Additional NaH (60% dispersion in mineral oil, 7.46 mg, 0.311 mmol) was added and the reaction was stirred at room temperature for 1 day. The reaction was diluted with EtOAc and wash with water and brine, dried over MgSO₄, filtered, concentrated, dissolved in minimal DCM, and purified by flash chromatography (silica gel, 0% to 5% MeOH in DCM). Appropriate fractions combined, concentrated, and dried from DCM / hexanes yielding {3-[4'-(1-methanesulfonylaminocarbonyl-cyclopropyl)-biphenyl-4-yl]-5-methyl-3H-[1,2,3]triazol-4-yl}-carbamic acid (R)-1-phenyl-ethyl ester (5.6 mg, 9.7% yield) as a white solid. LC/MS calcd. for C₂₉H₂₉N₅O₅S (m/e) 559, obsd. 560 (M+H, ES⁺). ¹H NMR (DMSO-d₆) δ : 11.24 (br. s., 1H), 9.68 (br. s., 1H), 7.85 (d, J = 7.0 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 7.8 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 7.34 (br. s., 5H), 5.70 (br. s., 1H), 3.23 (s, 3H), 2.17 (s, 3H), 1.29 - 1.73 (m, 5H), 1.23 (br. s., 2H).

Example 31

1-{4'-[3-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,4]triazol-4-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid



Step 1: 1-Bromo-4-isothiocyanatobenzene

In a 250 mL round-bottomed flask, calcium carbonate (6.11 g, 61.0 mmol, Eq: 2.1) and 4-bromoaniline (5 g, 29.1 mmol) were combined with dichloromethane (25 ml) and water (25.0 ml) to give a light brown suspension. The reaction mixture was cooled to 0 °C and thiophosgene (3.68 g, 2.45 ml, 32.0 mmol, Eq: 1.1) was added dropwise over 4 min. The

reaction was stirred at 0 °C for 30 min then at 25 °C for 19 h. The reaction mixture was filtered through celite and the filter cake was washed with dichloromethane. The aqueous layer was back-extracted with dichloromethane (1 x 25 mL). The organic layers were combined, washed with H₂O (1 x 25 mL), saturated NaCl (1 x 20 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The light brown solid was dried under vacuum to afford 5.43g (87%) of the desired product. ¹H NMR (DMSO-d₆) δ ppm 7.55 - 7.74 (m, 2H), 7.28 - 7.50 (m, 2H).

Step 2: (4-Bromophenyl)-thiourea

In a 500 mL round-bottomed flask, 1-bromo-4-isothiocyanatobenzene (1.5 g, 7.01 mmol) was combined with 0.4M ammonia in THF (52.5 mL, 21.0 mmol, Eq: 3) to give a yellow solution. The reaction was stirred at 25 °C overnight. The crude reaction mixture was concentrated *in vacuo* to afford the desired product as a light brown solid. (M+H)⁺ = 230.9/233.0 (m/e).

Step 3: N-(4-Bromophenyl)-hydrazinecarboximidamide nitrate

In a 250 mL round-bottomed flask, 1-(4-bromophenyl)thiourea (1.62 g, 7.01 mmol) was combined with methanol (50 ml) to give a light brown suspension. MeI (1.09 g, 482 μl, 7.71 mmol, Eq: 1.1) was added and the reaction mixture was stirred at 25 °C for 17 h. The crude reaction mixture was concentrated *in vacuo* to yield a light brown powder. The material was used without further purification.

In a 250 mL round-bottomed flask, 1-(4-bromophenyl)-2-methyl-isothiourea hydroiodide (2.61 g, 7.00 mmol) was combined with water (10 mL) and ethanol (10.0 mL) to give a light brown solution. Hydrazine monohydrate (525 mg, 509 μL, 10.5 mmol, Eq: 1.5) was added and the reaction was stirred at 25 °C for 20 h. The crude reaction mixture was concentrated *in vacuo* to about half volume and silver nitrate (1.19 g, 7.00 mmol) was added with vigorous stirring. The gray/brown solid was filtered through Celite and the filter cake was washed twice with boiling water. The filtrate was concentrated *in vacuo* to give a thick yellow oil. The oil was dried under vacuum with slight heating to afford 2.27 g (111%) of the desired material. The product was used without further purification. (M+H)⁺ = 229.1/231.0 (m/e)

Step 4: 4-(4-Bromophenyl)-4H-[1,2,4]triazol-3-ylamine

In a 500 mL round-bottomed flask, N'-(4-bromophenyl)-hydrazinecarboximidamide nitrate (2.27 g, 7.77 mmol) and formic acid (715 mg, 596 μL, 15.5 mmol, Eq: 2) were combined to give a yellow solution. The reaction mixture was heated to 120 °C for 3.5 h. The reaction was cooled and basified with 3M NaOH. The mixture was diluted with 150 ml

dichloromethane and stirred vigorously. The insoluble solid was filtered and the phases were separated. The organic phase was dried over Na₂SO₄ and filtered. The aqueous phase was discarded. The filtered solid was combined with the dried organic phase and concentrated *in vacuo*. The residue was taken up in refluxing ethanol and filtered hot to remove a small amount of white insoluble solid. The light brown filtrate was stripped to a tan powder and dried under vacuum to afford 1.665 g (90%) of the desired material. (M+H)⁺ = 239.0/240.9 (m/e). ¹H NMR (DMSO-d₆) δ ppm 8.20 (s, 1H), 7.66 - 7.81 (m, 2H), 7.34 - 7.54 (m, 2H), 5.86 (s, 2H).

Step 5: 1-[4'-(3-Amino-[1,2,4]triazol-4-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid methyl ester

In a 20 mL sealed tube, 4-(4-bromophenyl)-4H-1,2,4-triazol-3-amine (349 mg, 1.46 mmol), 4-(1-(methoxycarbonyl)cyclopropyl)phenylboronic acid (450 mg, 2.04 mmol, Eq: 1.4) and 2M Na₂CO₃ (2.19 ml, 4.38 mmol, Eq: 3) were combined with dioxane (6 ml) to give a light yellow suspension. PdCl₂(dppf) (95.4 mg, 117 μmol, Eq: 0.08) was added and the reaction was purged with argon. The reaction mixture was sealed and heated to 100 °C for 24 h under argon. The reaction was cooled and diluted with EtOAc and water. The mixture was filtered and the filtrate was washed with water and brine. The organic layer was dried over Na₂SO₄, combined with the filtered solid and concentrated *in vacuo*. Celite was added to the residue and the mixture was triturated with refluxing methanol. The mixture was filtered and the filter cake was washed twice with refluxing methanol. The filtrate was stripped *in vacuo* and the crude material was purified by flash chromatography (silica gel, 80 g, 0% to 10% methanol in dichloromethane) to afford 257 mg (53%) of the desired product as a light brown powder. (M+H)⁺ = 335.1 (m/e). ¹H NMR (DMSO-d₆) δ ppm 8.24 (s, 1H), 7.79 - 7.86 (m, 2H), 7.62 - 7.70 (m, 2H), 7.53 - 7.60 (m, 2H), 7.41 - 7.49 (m, 2H), 5.86 (s, 2H), 3.58 (s, 3H), 1.42 - 1.61 (m, 2H), 1.16 - 1.35 (m, 2H).

Step 6: (R)-1-Phenylethyl 1H-imidazole-1-carboxylate

In a 250 mL round-bottomed flask, (R)-1-phenylethanol (2.01 g, 16.5 mmol) and carbonyl diimidazole (2.67 g, 16.5 mmol, Eq: 1.00) were combined with ethyl acetate (40 ml) to give a colorless solution. The reaction mixture was refluxed for 20 h under argon, cooled and diluted with EtOAc. The mixture was washed with H₂O (2 x 40 mL), saturated NaCl (1 x 20 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The material crystallized upon standing to afford 3.42 g (96%) of the desired product as off white needles. ¹H NMR (DMSO-d₆) δ

ppm 8.42 (s, 1H), 7.65 (dd, J = 1.8, 1.3 Hz, 1H), 7.45 - 7.54 (m, 2H), 7.22 - 7.45 (m, 3H), 7.09 (dd, J = 1.6, 0.9 Hz, 1H), 6.05 (q, J = 6.6 Hz, 1H), 1.66 (d, J = 6.6 Hz, 3H).

Step 7: 1-{4'-[3-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,4]triazol-4-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

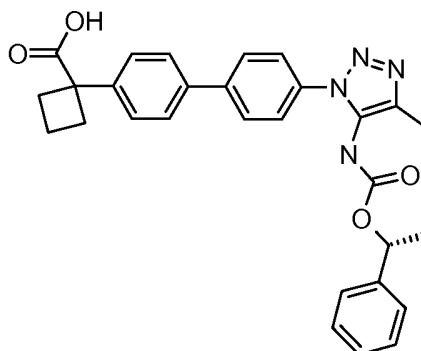
5 In a 250 round-bottomed flask, methyl 1-(4'-(3-amino-4H-1,2,4-triazol-4-yl)biphenyl-4-yl)cyclopropanecarboxylate (115 mg, 344 μ mol) was combined with THF (6 ml) to give a light brown suspension. 1M LiHMDS in THF (447 μ l, 447 μ mol, Eq: 1.3) was added and the brown solution was stirred at 25 °C under argon for 15 min. (R)-1-phenylethyl 1H-imidazole-1-carboxylate (112 mg, 516 μ mol, Eq: 1.5) was added in 1 ml THF and the
10 reaction mixture was stirred for 15 min at 25 °C. The reaction was quenched with water and diluted with 10% methanol in dichloromethane. Na₂SO₄ was added and the mixture was filtered through Celite and the brown filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 24 g, 0% to 10% methanol in dichloromethane) to afford 85 mg (51%) of the desired product as an off white solid.
15 (M+H)⁺ = 483.1 (m/e). ¹H NMR (DMSO-d₆) δ ppm 10.01 (s, 1H), 8.87 (s, 1H), 7.76 - 7.93 (m, 2H), 7.58 - 7.75 (m, 2H), 7.38 - 7.57 (m, 4H), 7.12 - 7.38 (m, 5H), 5.62 (d, J = 6.8 Hz, 1H), 3.58 (s, 3H), 1.47 - 1.60 (m, 2H), 1.34 (d, J = 5.6 Hz, 2H), 1.15 - 1.31 (m, 3H).

Step 8: 1-{4'-[3-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,4]triazol-4-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid

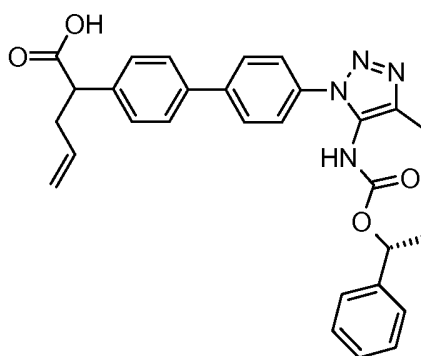
20 In a 250 mL round-bottomed flask, 1-{4'-[3-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,4]triazol-4-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester (110 mg, 228 μ mol) was combined with tetrahydrofuran (5 mL) and methanol (1 mL) to give a yellow solution. 1M LiOH (2 mL, 2.00 mmol, Eq: 8.77) was added and the reaction was stirred at 25 °C for 17 hrs. The crude reaction mixture was concentrated *in vacuo*, acidified with 1M
25 HCl and diluted with EtOAc. The phases were separated and the organic layer was washed with H₂O (1 x 15 mL), saturated NaCl (1 x 15 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 12 g, 0% to 10% methanol in dichloromethane) to afford 86 mg (80%) of the desired product as a white solid. (M+H)⁺ = 469.2 (m/e). ¹H NMR (DMSO-d₆) δ ppm 12.39 (br. s., 1H), 10.01 (br. s.,
30 1H), 8.87 (br. s., 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.39 - 7.59 (m, 4H), 7.10 - 7.39 (m, 5H), 5.62 (d, J = 6.3 Hz, 1H), 1.45 - 1.54 (m, 2H), 1.40 (br. s., 1H), 1.09 - 1.37 (m, 4H).

Examples 32 and 33

(R)-1-(4'-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-4-yl)cyclobutanecarboxylic acid (Example 32)



5 **(R)-2-{4'-[4-Methyl-5-(-1-phenylethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-pent-4-enoic acid (Example 33)**



Step 1: 1-(4-Bromophenyl)cyclobutane carboxylic acid ethyl ester and 2-(4-bromophenyl)-pent-4-enoic acid ethyl ester

10 To a solution of 2-(4-bromophenyl)acetic acid ethyl ester (5.98 g, 24.6 mmol) in DMF (60 mL) was cooled to 0 °C and then the solid sodium hydride (2.17 g, 54.4 mmol) was added in five portions in a period of 10 minutes. During the addition, it was a vigorous reaction with foaming and the reaction mixture was turned to yellow suspension. Additional 10 mL of DMF was used to wash the sodium hydride. The resulting yellow suspension was stirred for

15 20 minutes and the neat 1,3-dibromopropane (5.46 g, 2.75 mL, 27.1 mmol) was added at this temperature. After 5 minutes, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. During this period, the reaction mixture was turned to a colorless cloudy solution and it was stirred for 1 h. Then, the reaction mixture was poured into a 0.1 N HCl and the organic compound was extracted into EA (2 x 100 mL). The

20 combined extracts were washed with water and brine solution and dried over anhydrous MgSO₄. Filtration of the drying agent and concentration of the filtrate gave the crude white suspension which was purified using an ISCO (120 g) column chromatography eluting with

EA in hexanes (0-15%). Both compounds, 1-(4-bromophenyl)cyclobutane carboxylic acid ethyl ester and 2-(4-bromophenyl)-pent-4-enoic acid ethyl ester, were isolated as a mixture.

Step 2: (R)-1-(4'-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-4-yl)cyclobutanecarboxylic acid ethyl ester and (R)-2-{4'-[4-methyl-5-(1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-pent-4-enoic acid ethyl ester

To a suspension of (R)-1-phenylethyl 4-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-1,2,3-triazol-5-ylcarbamate (1.34 g, 3 mmol), 1-(4-bromophenyl)cyclobutane carboxylic acid ethyl ester and 2-(4-bromophenyl)-pent-4-enoic acid ethyl ester (1.02 g, 3.6 mmol), palladium(II) acetate (135 mg, 0.6 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (493 mg, 1.2 mmol), and potassium phosphate tribasic (1.91 g, 9.0 mmol) in a 100 mL RB flask were added toluene (18 mL) and water (4.0 mL) at room temperature under nitrogen atmosphere. Then, the resulting light brown suspension was heated to 105 °C and stirred for 3 h by which time TLC analysis indicated the absence of starting material. Then, the black reaction mixture was cooled to room temperature and diluted with water. The organic compound was extracted into EA (2 x 100 mL) and the combined extracts were washed with brine solution and dried over anhydrous MgSO₄. Filtration of the drying agent and concentration of the filtrate gave the crude residue which was purified by using an ISCO (120 g) column chromatography eluting with EA in hexanes (0-100%) to obtain (R)-1-(4'-(4-methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-4-yl)cyclobutanecarboxylic acid ethyl ester and (R)-2-{4'-[4-methyl-5-(1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-pent-4-enoic acid ethyl ester as a mixture. LC/MS calcd. for C₃₁H₃₂N₄O₄ (m/e) 524, obsd. 525.3 [M+H, ES⁺].

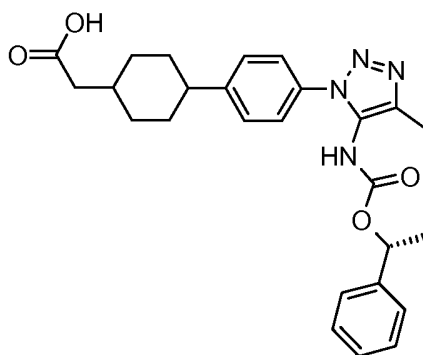
Step 3: ((R)-1-(4'-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-4-yl)cyclobutanecarboxylic acid and (R)-2-{4'-[4-methyl-5-(1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-pent-4-enoic acid

To a solution of a mixture of obtained (R)-1-(4'-(4-methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-4-yl)cyclobutanecarboxylic acid ethyl ester and (R)-2-{4'-[4-methyl-5-(1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-pent-4-enoic acid ethyl ester (120 mg, 0.229 mmol) in THF (6.0 mL) and EtOH (6.0 mL) was added an excess of 1 *N* sodium hydroxide (2.29 mL, 2.29 mmol) solution in water at room temperature. The resulting light yellow solution was stirred for 2

days at room temperature at which time TLC analysis indicated the absence of starting material. Then, the solvent was removed under vacuum and the basic aqueous layer was neutralized with 1 N HCl. The resulting white cloudy solution was extracted with EA (2 x 50 mL) and the combined extracts were washed with brine solution. Dried and removed the solvent to afford the crude mixture which was purified using DAICEL OI column (3 x 25 cm, 40% methanol and CO₂, 70 mL/min and the peaks were collected at 220 nM. Peak 1 was collected and the solvent was removed to obtain (R)-2-{4'-[4-methyl-5-(1-phenylethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-pent-4-enoic acid (12 mg, 10.5% yield, **Example 33**). ¹H NMR (CHLOROFORM-d) δ: 7.29 - 7.61 (m, 8H), 7.19 (s, 6H), 5.44 - 5.83 (m, 2H), 4.92 - 5.14 (m, 2H), 3.67 (t, J = 6.4 Hz, 1H), 2.81 (dt, J = 14.2, 7.2 Hz, 1H), 2.41 - 2.60 (m, 1H), 2.24 (s, 3H), 1.12 - 1.30 (m, 3H). And the peak 2 was collected and the solvent was removed to obtain ((R)-1-(4'-(4-methyl-5-((1-phenylethoxy)carbonylamino)-1H-1,2,3-triazol-1-yl)biphenyl-4-yl)cyclobutanecarboxylic acid (26 mg, 23% yield, **Example 32**). ¹H NMR (CHLOROFORM-d) δ: 7.29 - 7.55 (m, 8H), 7.19 (s, 6H), 5.69 (br. s., 1H), 2.78 - 2.91 (m, 2H), 2.45 - 2.59 (m, 2H), 2.24 (s, 3H), 1.99 - 2.11 (m, 1H), 1.87 (td, J = 10.0, 4.5 Hz, 1H), 1.10 - 1.35 (m, 3H). LC/MS calcd. for C₂₉H₂₈N₄O₄ (m/e) 496, obsd. 497.3 [M+H, ES⁺].

Example 34

(R)-2-(4-(4-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1H-1,2,3-triazol-1-yl)phenyl)cyclohexyl)acetic acid



Step 1: 2-(4-Idocyclohexyl)-acetic acid ethyl ester

To a mixture of ethyl 2-(4-hydroxycyclohexyl)acetate (3 g, 16.1 mmol), iodine (6.13 g, 24.2 mmol), imidazole (1.64 g, 24.2 mmol), and triphenylphosphine (6.34 g, 24.2 mmol) was added dichloromethane (100 mL) at room temperature under nitrogen atmosphere. The resulting brown suspension was stirred for 15 h at which time TLC analysis indicated the absence of starting material. Then, the solvent was removed under vacuum and most of the

residue was dissolved in EA (~500 mL) and some of the residue was not dissolved which was found to be $\text{Ph}_3\text{P}=\text{O}$ by ^1H NMR. The EA solution was washed two times with a solution of water and methanol (3:1) to remove the remaining triphenylphosphineoxide and then washed with brine solution. The organic layer was dried over anhydrous MgSO_4 , filtration, and concentration gave the crude residue which was purified using an ISCO (120 g) column chromatography eluting with EA in hexanes (0-50%). The desired fractions were combined and the solvent was removed under vacuum to obtain 2-(4-iodocyclohexyl)acetic acid ethyl ester (3.39 g, 71.1% yield) as a viscous light yellow oil. ^1H NMR of this product indicated that it contained ~30-40% of elimination side product (olefin) and it was not eparable on TLC.

Step 2: 1-[4-(4-(2-Ethoxy-2-oxoethyl)cyclohexyl)phenyl]-5-methyl-1H-1,2,3-triazole--carboxylic acid *tert*-butyl ester

In a 3-neck 50 mL RB flask, equipped with an additional funnel and a thermometer, was charged with zinc dust, 99.9% (490 mg, 7.5 mmol) at room temperature under nitrogen atmosphere. Then, the flask was purged with nitrogen under vacuum and THF (2 mL) was added to cover the zinc dust. 1,2-Dibromoethane (60.6 mg, 27.8 μL , 0.322 mmol) was added and the mixture was heated with heat gun until evolution of ethylene gas ceased. Then, the suspension was cooled to room temperature and chlorotrimethylsilane (35.0 mg, 40.8 μL , 0.322 mmol) was added and the mixture was stirred for 15 min at room temperature. Then, a solution of 2-(4-iodocyclohexyl)acetic acid ethyl ester (740 mg, 2.5 mmol) in THF (2 mL and 1 mL for washing) was added drop-wise for 5 minutes. After addition, the reaction mixture was heated to ~60 °C with oil bath and stirred for 3 h by which time TLC analysis of the hydrolyzed reaction mixture indicated the absence of starting material. Then, the heating was stopped and the excess zinc dust was allowed to settle (15 h) to give a top layer as a colorless solution.

In another 2-neck 25 mL RB flask, palladium(II) acetate (24.9 mg, 0.111 mmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (91.0 mg, 0.222 mmol) were charged and the flask was purged with nitrogen gas. Then, THF (1 mL) was added and the resulting light brown suspension was stirred for 5 min before the addition of a solution of 1-(4-bromophenyl)-4-methyl-1H-1,2,3-triazole-5-carboxylic acid *tert*-butyl ester (150 mg, 0.444 mmol) in THF (3 mL) at room temperature under nitrogen atmosphere. Then, the above prepared colorless zinc solution was added to this mixture. After the addition, it turned to a dark brown solution which was then heated to 60 °C and stirred for 8 h at which time TLC

analysis of the hydrolyzed reaction mixture indicated the absence of starting material. Then, it was cooled to room temperature and diluted with saturated ammonium chloride solution and EA. The two layers were separated and the aqueous layer was extracted with EA. The combined organic extracts were washed with brine solution and dried over anhydrous
5 MgSO₄. Filtration of the drying agent and concentration of the filtrate gave the crude light yellow residue which was purified using an ISCO (80 g) column eluting with EA in hexanes (0-60%). The desired fractions were combined and the solvent was removed under vacuum to obtain 1-[4-(4-(2-ethoxy-2-oxoethyl)cyclohexyl)phenyl]-5-methyl-1*H*-1,2,3-triazole--
10 carboxylic acid *tert*-butyl ester (55 mg, 29% yield) as a light brown oil. LC/MS calcd. for C₂₄H₃₃N₃O₄ (m/e) 427, obsd. 428.1 [M+H, ES⁺].

Step 3: 1-[4-(4-(2-Ethoxy-2-oxoethyl)cyclohexyl)phenyl]-5-methyl-1*H*-1,2,3-triazole--carboxylic acid

To a light yellow solution of 1-(4-(4-(2-ethoxy-2-oxoethyl)cyclohexyl)phenyl)-4-methyl-1*H*-1,2,3-triazole-5-carboxylic acid *tert*-butyl ester (96 mg, 0.225 mmol) in dichloromethane (5
15 mL) was added an excess of TFA (2.56 g, 1.73 mL, 22.5 mmol) at room temperature under nitrogen atmosphere. The resulting light yellow solution was stirred for 20 h at which time TLC analysis indicated the absence of starting material. Then, the solvent was removed under vacuum and the residue was azeotrophed with toluene. The residue was dried under high vacuum to obtain 1-[4-(4-(2-ethoxy-2-oxoethyl)cyclohexyl)phenyl]-5-methyl-1*H*-1,2,3-
20 triazole--carboxylic acid (85 mg, 97% yield) as a light brown solid. LC/MS calcd. for C₂₀H₂₅N₃O₄ (m/e) 371, obsd. 372.1 [M+H, ES⁺].

Step 4: (R)-2-(4-(4-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)phenyl)cyclohexyl)acetic acid ethyl ester

To a light brown solution with few solids of 1-(4-(4-(2-ethoxy-2-oxoethyl)cyclohexyl)phenyl)-4-methyl-1*H*-1,2,3-triazole-5-carboxylic acid (85 mg, 0.229
25 mmol) in toluene (5 mL) was added triethylamine (46.3 mg, 63.8 μL, 0.458 mmol) at room temperature. To the resulting solution were added diphenylphosphoryl azide (69.3 mg, 54.2 μL, 0.252 mmol) followed by (R)-1-phenylethanol (30.8 mg, 30.4 μL, 0.252 mmol) at room temperature. The resulting solution was heated with oil bath to 81 °C and stirred for 1 h at
30 which time TLC analysis indicated the presence of a new spot. Then, the reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The crude residue (~450 mg) was suspended in dichloromethane and filtered. The filtrate was loaded onto an ISCO (40 g) column chromatography eluting with EA in hexanes (0-100%). The

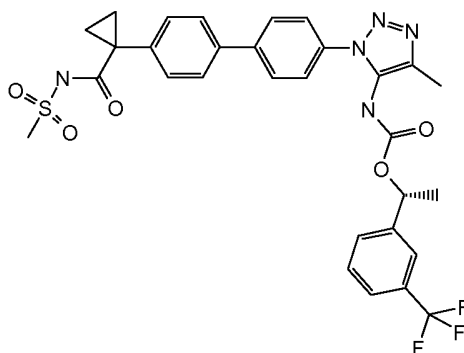
desired fractions were combined and the solvent was removed under vacuum to obtain (R)-2-(4-(4-(4-methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)phenyl)cyclohexyl)acetic acid ethyl ester (50 mg, 45% yield) as a white solid. LC/MS calcd. for C₂₈H₃₄N₄O₄ (m/e) 490, obsd. 491.3 [M+H, ES⁺].

Step 5: (R)-2-(4-(4-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)phenyl)cyclohexyl)acetic acid

To a colorless solution of (R)-2-(4-(4-(4-methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)phenyl)cyclohexyl)acetic acid ethyl ester (46 mg, 0.94 mmol) in THF (5 mL) and EtOH (5 mL) was added an excess of 1 M solution of sodium hydroxide (2.81 mL, 2.81 mmol) in water. The resulting colorless solution was stirred for 15 h at room temperature at which time LC/MS and TLC analysis indicated the absence of starting material. Then, the solvent was removed under vacuum and the basic aqueous layer was neutralized with 1 *N* HCl. The resulting white solids were collected by filtration and washed with water and hexanes. After air drying, (R)-2-(4-(4-(4-methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)phenyl)cyclohexyl)acetic acid (35 mg, 80.7% yield) was isolated as a white solid. ¹H NMR (DMSO-*d*₆) δ: 12.05 (s, 1H), 9.15 - 9.74 (m, 1H), 6.97 - 7.64 (m, 9H), 5.70 (br. s., 1H), 2.54 - 2.72 (m, 1H), 2.07 - 2.26 (m, 5H), 1.62 - 1.91 (m, 5H), 1.36 - 1.59 (m, 4H), 1.04 - 1.32 (m, 3H). LC/MS calcd. for C₂₆H₃₀N₄O₄ (m/e) 462, obsd. 463.3 [M+H, ES⁺].

Example 35

{3-[4'-(1-Methanesulfonylaminocarbonyl-cyclopropyl)-biphenyl-4-yl]-5-methyl-3*H*-[1,2,3]triazol-4-yl}-carbamic acid (R)-1-(3-trifluoromethyl-phenyl)-ethyl ester



Step 1: N-[1-(4-Bromo-phenyl)-cyclopropanecarbonyl]-methanesulfonamide

In a 100 mL round-bottomed flask, 1-(4-bromo-phenyl)-cyclopropanecarboxylic acid (4 g, 16.6 mmol) was combined with DCM (15 mL) and 3 drops of DMF to give a white suspension. To this was added drop wise a clear solution of oxalyl chloride (6.96 g, 4.8 mL,

54.8 mmol) dissolved in DCM (6 mL). After 10 min, the mixture became clear and the reaction was stirred at room temperature for 2 hr. The reaction was concentrated, dried from toluene and hexanes, and stored in a freezer overnight. In a 200 mL round-bottomed flask, NaH (60% mineral dispersion, 876 mg, 36.5 mmol) was washed with hexanes and the resulting solid was diluted with DMF (6 mL) to give a white suspension. The suspension was cooled in an ice bath and methanesulfonamide (3.16 g, 33.2 mmol) dissolved in DMF (6 mL) was added drop wise under nitrogen. After addition (5 min) the ice bath was removed and the reaction was warmed to room temperature overnight. The reaction was cooled in an ice bath, the acid chloride previous prepared and dissolved in DMF (6 mL) was added drop wise, and the reaction was warmed to room temperature overnight. The reaction was diluted with 0.2 N HCl (200 mL) and extracted with EtOAc (2 x 100 mL). The organic layers were washed with brine, combined, dried, over MgSO₄, and concentrated. The crude material was dissolved in minimal DCM and purified by flash chromatography (silica gel, 0% to 60% EtOAc in hexanes, 0.5 % AcOH). The appropriate fractions were combined, concentrated, and dried from DCM/hexanes yielding N-[1-(4-bromo-phenyl)-cyclopropanecarbonyl]-methanesulfonamide (2.74 g, 51.9 % yield), as a white solid. LC/MS calcd. for C₁₁H₁₂BrNO₃S (m/e) 317/319, obsd. 318/320 (M+H, ES⁺).

Step 2: N-{1-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarbonyl}-methanesulfonamide

In a 350 mL reaction vial containing N-[1-(4-bromo-phenyl)-cyclopropanecarbonyl]-methanesulfonamide (2.71 g, 8.52 mmol) was added bis-pinacolatodiboron (3.24 g, 12.8 mmol) and potassium acetate (2.51 g, 25.6 mmol, Eq: 3) and 1,4 dioxane (63.8 mL) to give a white suspension. The mixture was purged with nitrogen for 20 min and then PdCl₂(dppf)CH₂Cl₂ (701 mg, 859 μmol) was added. The vial was sealed and heated in an oil bath at 80 °C for 16 hr. The reaction was diluted with EtOAc (150 mL), filtered, rinsed with 0.2 M HCl (200 mL) and EtOAc (50 mL). The combined filtrate was mixed vigorously, filtered, and separated. The aqueous layer was extracted once with EtOAc (150 mL). The organic layers were washed with brine, combined, dried over MgSO₄, filtered, concentrated, and dried from DCM/hexanes as a brown solid (4 g). The crude material was supported on Celite and purified by flash chromatography (silica gel, 0 to 60 % EtOAc in hexanes, 0.5 % AcOH). The appropriate fractions were combined, concentrated, and dried from DCM/Hexanes, yielding N-{1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-

cyclopropanecarbonyl}-methanesulfonamide (2.75 g, 88.4 % yield), as a white solid. LC/MS calcd. for $C_{17}H_{24}BNO_5S$ (m/e) 365, obsd. 366 (M+H, ES^+).

Step 3: {3-[4'-(1-Methanesulfonylaminocarbonyl-cyclopropyl)-biphenyl-4-yl]-5-methyl-3H-[1,2,3]triazol-4-yl}-carbamic acid (R)-1-(3-trifluoromethyl-phenyl)-ethyl ester

In a 8 mL vial, [3-(4-bromo-phenyl)-5-methyl-3H-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-(3-trifluoromethyl-phenyl)-ethyl ester (47 mg, 100 μ mol), N-{1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropanecarbonyl}-methanesulfonamide (40.2 mg, 110 μ mol), DPPF (8.33 mg, 15.0 μ mol) and $PdCl_2(dppf)CH_2Cl_2$ (12.3 mg, 15.0 μ mol) were combined with DMF (1 mL) (previous purged with nitrogen for 20 min) to give a light brown / red solution. To this was added 2N Na_2CO_3 (200 μ L, 401 μ mol) (previous purged with nitrogen for 20 min) and a precipitate formed. The resulting red mixture was purged with nitrogen for 1 min. The vial was sealed, placed in a dry block, and heated at 80°C for 2 hr. The reaction was diluted with EtOAc (50 mL) and 0.1 N HCl (50 mL), mixed, filtered, and separated. The aqueous layer was extracted with EtOAc (50 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$, filtered, concentrated, and dried from DCM / hexanes as a yellow film (120 mg). The crude material was supported on Celite and purified by flash chromatography (silica gel, 0% to 60% EtOAc in hexanes, 0.5 % AcOH). Appropriate fractions were combined, concentrated, dried from DCM / hexanes and DCM yielding {3-[4'-(1-methanesulfonylaminocarbonyl-cyclopropyl)-biphenyl-4-yl]-5-methyl-3H-[1,2,3]triazol-4-yl}-carbamic acid (R)-1-(3-trifluoromethyl-phenyl)-ethyl ester (32 mg, 50.9 % yield) as a light yellow solid. LC/MS calcd. for $C_{30}H_{28}F_3N_5O_5S$ (m/e) 627, obsd. 628 (M+H, ES^+). 1H NMR ($DMSO-d_6$) δ : 11.23 (br. s., 1H), 9.80 (br. s., 1H), 7.85 (d, J = 6.5 Hz, 2H), 7.49 - 7.77 (m, 8H), 7.45 (d, J = 8.3 Hz, 2H), 5.68 - 5.95 (m, 1H), 3.23 (s, 3H), 2.17 (br. s., 3H), 1.44 - 1.64 (m, 4H), 1.23 (br. s., 3H).

Example 36

Calcium Flux Assay using Fluorometric Imaging Plate Reader (FLIPR)

Cell Culture Conditions: The ChemiScreen Calcium-optimized stable cell line containing the human recombinant LPA1 Lysophospholipid receptor was purchased from Chemicon International, Inc./Millipore. The cells were cultured in DMEM-high glucose supplemented with 10% fetal bovine serum, 2mM glutamine, 100U/mL penicillin/100 μ g/mL streptomycin, 1X non-essential amino acids, 10mM HEPES and 0.25mg/mL Geneticin. Cells were harvested with trypsin-EDTA and counted using ViaCount reagent. The cell suspension

volume was adjusted to 2.0×10^5 cells/mL with complete growth media. Aliquots of 50 μ L were dispensed into 384 well black/clear tissue culture treated plates (BD) and the microplates were placed in a 37°C incubator overnight. The following day plates were used in the assay.

- 5 Dye Loading and Assay: Loading Buffer (FLIPR Calcium-4, Molecular Devices) was prepared by dissolving the contents of one bottle into 100 mL Hank's Balanced Salt Solution containing 20 mM HEPES and 2.5 mM probenecid. Plates were loaded onto Biotek plate washer and growth media was removed and replaced with 20 μ L of Hank's Balanced Salt Solution containing 20 mM HEPES and 2.5 mM probenecid, followed by 25 μ L of Loading
- 10 Buffer. The plates were then incubated for 30 minutes at 37°C. During the incubation, test compounds were prepared by adding 90 μ L of HBSS/20 mM HEPES/0.1% BSA buffer to 2 μ L of serially diluted compounds. To prepare serial dilutions, 10 mM stocks of compounds were prepared in 100% DMSO. The compound dilution plate was set up as follows: well # 1 received 29 μ L of stock compound and 31 μ L DMSO; wells
- 15 2-10 received 40 μ L of DMSO; mixed and transferred 20 μ L of solution from well #1 into well #2; continued with 1:3 serial dilutions out 10 steps; transferred 2 μ L of diluted compound into duplicate wells of 384 well "assay plate" and then added the 90 μ L of buffer. After incubation, both the cell and "assay" plates were brought to the FLIPR and 20 μ L of the diluted compounds were transferred to the cell plates by the FLIPR. Compound addition
- 20 was monitored by FLIPR to detect any agonist activity of the compounds. Plates were then incubated for 30 minutes at room temperature protected from light. After the incubation, plates were returned to the FLIPR and 20 μ L of 4.5X concentrated agonist was added to the cell plates. During the assay, fluorescence readings were taken simultaneously from all 384 wells of the cell plate every 1.5 seconds. Five readings were taken to establish a stable
- 25 baseline, then 20 μ L of sample was rapidly (30 μ L /sec) and simultaneously added to each well of the cell plate. The fluorescence was continuously monitored before, during and after sample addition for a total elapsed time of 100 seconds. Responses (increase in peak fluorescence) in each well following agonist addition was determined. The initial fluorescence reading from each well, prior to ligand stimulation, was used as zero baseline
- 30 value for the data from that well. The responses were expressed as % inhibition of the buffer control. The IC_{50} value, defined as the concentration of a compound required for 50% inhibition of the buffer control, was calculated by fitting the percent inhibition data for 10 concentrations to a sigmoidal dose-response (4 parameter logistic) model using Genedata

Condoseo program [model 205, $F(x) = (A+(B-A)/(1+((C/x)^D)))]$ and the results shown in Table 1 below:

Table 1
LPA1 and LPA3 antagonist activities

Example #	LPA1 IC ₅₀ (μM) or (inhibition% @ μM)	LPA3 IC ₅₀ (μM) or (inhibition% @ μM)
1	0.025	>30
2	>30 (40% @ 30)	>30
3	>30	>30
4	>30	>30
5	0.035	>30
6	0.112	25.9 (55.2% @ 30)
7	0.174	6.86
8	>30	>30
9	0.217	>30
10	0.398	>30
11	>30	>30
12	0.134	>30
13	0.161	>30
14	0.985	>30
15	0.022	(46.3% @ 30)
16	0.245	>30
17	0.043	21.73 (63.7% @ 30)
18	1.228 (79.8% @ 30)	>30
19	0.412	4.82
20	21.23 (58.3% @ 30)	14.3 (72.5% @ 30)
21	0.036	>30 (22% @ 30)
22	>30	>30
23	0.796 (80.9% @ 30)	>30
24	>30	>30
25	>30	>30

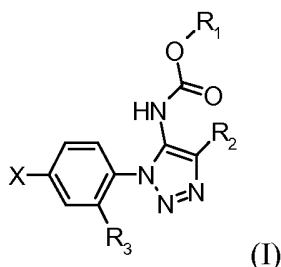
-96-

26	>30	>30
27	>30	>30
28	>30	>30
29	0.023	>30
30	0.033	>30
31	>30 (11% @ 30)	>30
32	0.174	>30
33	0.088	>30
34	9.478	>30
35	4.534	5.736

It is to be understood that the invention is not limited to the particular embodiments of the invention described above, as variations of the particular embodiments may be made and still fall within the scope of the appended claims.

Claims

1. A compound of formula (I):



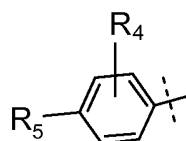
- 5 wherein:

R₁ is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or -CF₃;

R₂ is hydrogen or lower alkyl;

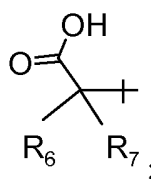
R₃ is hydrogen, fluorine or -OCH₃;

- 10 X is cycloalkyl acetic acid or



R₄ is hydrogen or halogen;

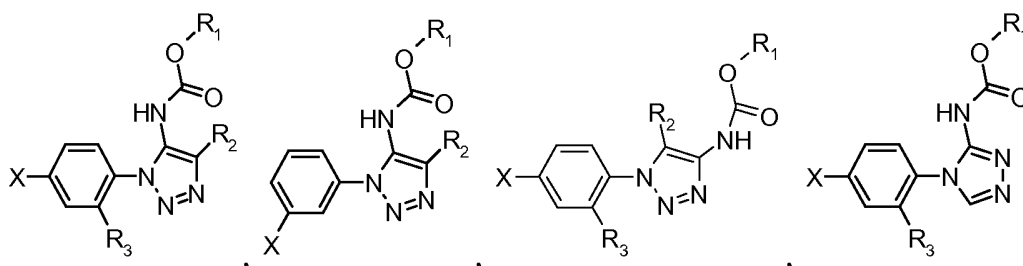
R₅ is hydrogen, cyano, tetrazole-cyclopropyl, methanesulfonylaminocarbonyl-cyclopropyl or



- 15 R₆ and R₇ are, independently of each other, hydrogen or lower alkyl; or

R₆ and R₇, together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

2. A compound of general formula (I), (Ia), (Ib) or (Ic):



-98-

(II)

(Ia)

(Ib)

(Ic)

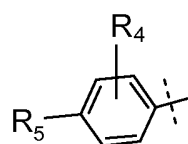
wherein:

R₁ is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or -CF₃;

5 R₂ is hydrogen or lower alkyl;

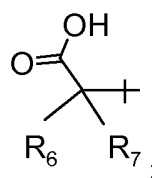
R₃ is hydrogen, fluorine or -OCH₃;

X is cycloalkyl acetic acid or



R₄ is hydrogen or halogen;

10 R₅ is hydrogen, cyano, tetrazole-cyclopropyl, methanesulfonylaminocarbonyl-cyclopropyl or

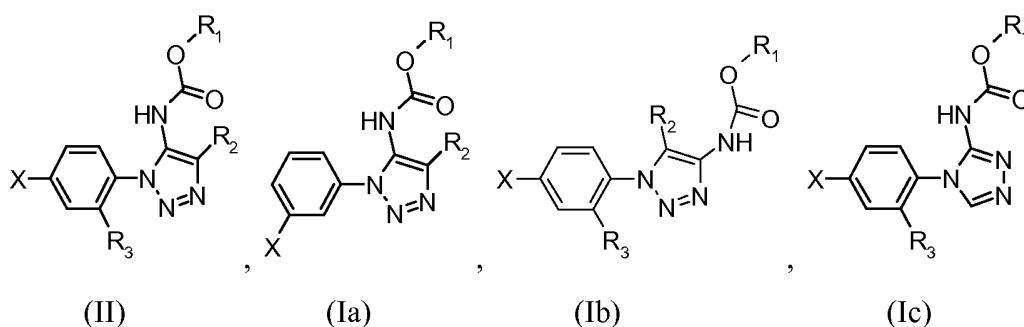


R₆ and R₇ are, independently of each other, hydrogen or lower alkyl; or

R₆ and R₇, together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

15

3. A compound of formula (I), (Ia), (Ib) or (Ic):



wherein:

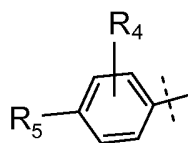
20 R₁ is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or -CF₃;

R₂ is hydrogen or lower alkyl;

R₃ is hydrogen, fluorine or -OCH₃;

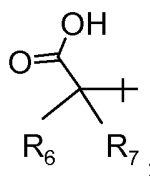
X is cycloalkyl acetic acid or

-99-



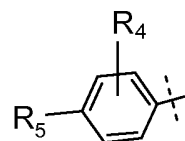
R₄ is hydrogen or halogen;

R₅ is hydrogen, cyano, tetrazole-cyclopropyl, methanesulfonylaminocarbonyl-cyclopropyl or



- 5 R₆ and R₇ are, independently of each other, hydrogen, lower alkyl or lower alkenyl; or
 R₆ and R₇, together with the carbon to which they are attached, form a cycloalkyl group,
 or a pharmaceutically acceptable salt thereof.
- 10 4. The compound according to any of claims 1 to 3, wherein R₁ is unsubstituted lower alkyl.
5. The compound according to any of claims 1 to 4, wherein R₁ is dimethylpropyl, butyl or
 isopropyl.
- 15 6. The compound according to any of claims 1 to 3, wherein R₁ is lower alkyl substituted with
 cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or -CF₃.
7. The compound according to claim 6, wherein R₁ is -CH(CH₃)-phenyl, -CH(CH₃)-
 fluorophenyl, -CH(CH₃)-trifluoromethylphenyl, ethyl-cyclopropyl or ethyl-cyclobutyl.
- 20 8. The compound according to any of claims 1 to 7, wherein R₂ is lower alkyl.
9. The compound according to any of claims 1 to 8, wherein R₂ is methyl.
- 25 10. The compound according to any of claims 1 to 9, wherein R₃ is hydrogen.
11. The compound according to any of claims 1 to 10, wherein X is cyclohexyl acetic acid.

-100-

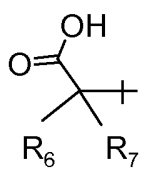


12. The compound according to any of claims 1 to 10, wherein X is

13. The compound according to claim 12, wherein R₄ is hydrogen or fluorine.

5 14. The compound according to claim 12, wherein R₅ is hydrogen, cyano, tetrazole-cyclopropyl or methanesulfonylaminocarbonyl-cyclopropyl.

15. The compound according to claim 12, wherein R₅ is

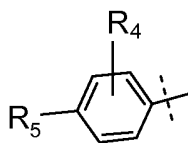


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16. The compound according to claim 12, wherein R₆ and R₇ are, independently of each other, hydrogen or methyl.

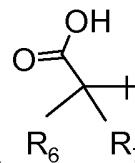
17. The compound according to claim 12, wherein R₆ and R₇, together with the carbon to which
15 they are attached, form a cyclopropyl group.

18. The compound according to claim 1 wherein R₁ is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cycloalkyl or unsubstituted phenyl; R₂ is hydrogen or lower alkyl; R₃ is hydrogen, fluorine or -OCH₃; X is cycloalkyl acetic acid or



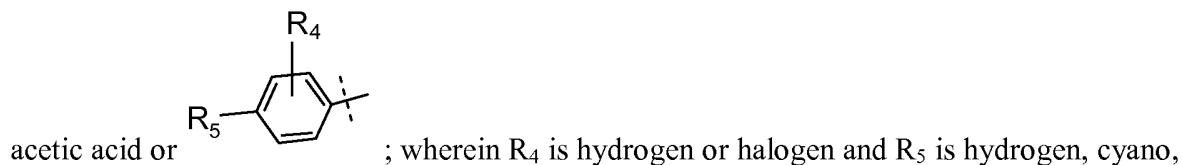
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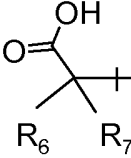
; wherein R₄ is hydrogen or halogen and R₅ is hydrogen, cyano, tetrazole-



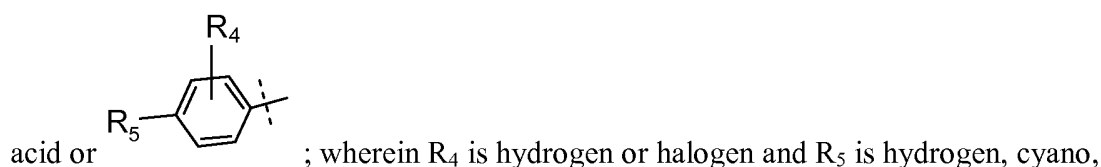
cyclopropyl, methanesulfonylaminocarbonyl-cyclopropyl or R₆ and R₇; wherein R₆ and R₇ are, independently of each other, hydrogen or lower alkyl; or R₆ and R₇, together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

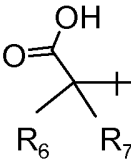
19. The compound according to 1 wherein R_1 is lower alkyl being substituted with unsubstituted phenyl; R_2 is hydrogen or lower alkyl; R_3 is hydrogen, fluorine or $-OCH_3$; X is cycloalkyl



- 5 tetrazole-cyclopropyl, methanesulfonylaminocarbonyl-cyclopropyl or  ; wherein R_6 and R_7 are, independently of each other, hydrogen or lower alkyl; or R_6 and R_7 , together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

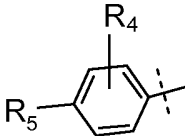
- 10 20. The compound according to claim 1 wherein R_1 is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or $-CF_3$; R_2 is ethyl; R_3 is hydrogen, fluorine or $-OCH_3$; X is cycloalkyl acetic

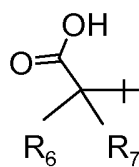


- 15 tetrazole-cyclopropyl, methanesulfonylaminocarbonyl-cyclopropyl or  ; wherein R_6 and R_7 are, independently of each other, hydrogen or lower alkyl; or R_6 and R_7 , together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

- 20 21. The compound according to claim 1 wherein R_1 is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or $-CF_3$; R_2 is hydrogen or lower alkyl; R_3 is hydrogen, fluorine or $-OCH_3$; X

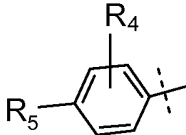
-102-

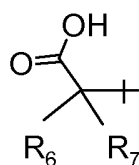
is cycloalkyl acetic acid or ; wherein R₄ is hydrogen or halogen and R₅ is



R₆ R₇; wherein R₆ and R₇, together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

- 5 22. The compound according to claim 1 wherein R₁ is lower alkyl being substituted with unsubstituted phenyl; R₂ is hydrogen or lower alkyl; R₃ is hydrogen, fluorine or –OCH₃; X is

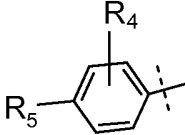
cycloalkyl acetic acid or ; wherein R₄ is hydrogen or halogen and R₅ is



R₆ R₇; wherein R₆ and R₇, together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

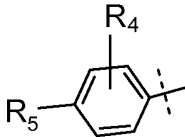
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23. The compound according to claim 1 wherein R₁ is lower alkyl or indanyl, said lower alkyl being unsubstituted or substituted with cycloalkyl, unsubstituted phenyl or phenyl substituted with halogen or –CF₃; R₂ is hydrogen or lower alkyl; R₃ is hydrogen, fluorine or –OCH₃; X

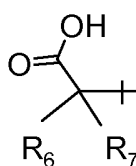
is cycloalkyl acetic acid or ; wherein R₄ is hydrogen or halogen and R₅ is

- 15 methanesulfonylaminocarbonyl-cyclopropyl, or a pharmaceutically acceptable salt thereof.

24. The compound of formula (Ia) according to claims 2 or 3 wherein R₁ is lower alkyl being

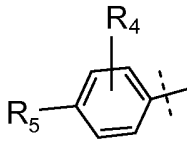
substituted with unsubstituted phenyl; R₂ is lower alkyl; X is ; wherein R₄ is

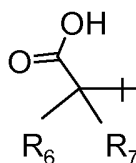
-103-



hydrogen and R_5 is R_6 and R_7 ; R_6 and R_7 are hydrogen or R_6 and R_7 , together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

- 5 25. The compound of formula (Ib) according to claims 2 or 3 wherein R_1 is lower alkyl being

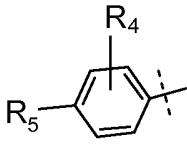
substituted with unsubstituted phenyl; R_2 is lower alkyl; R_3 is hydrogen; X is  ;

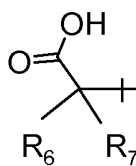


wherein R_4 is hydrogen and R_5 is R_6 and R_7 ; wherein R_6 and R_7 are hydrogen or R_6 and R_7 , together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

10

26. The compound of formula (Ic) according to claims 2 or 3 wherein R_1 is lower alkyl being

substituted with unsubstituted phenyl; R_3 is hydrogen; X is  ; wherein R_4 is



hydrogen and R_5 is R_6 and R_7 ; wherein R_6 and R_7 , together with the carbon to which they are attached, form a cycloalkyl group, or a pharmaceutically acceptable salt thereof.

15

27. The compound according to claim 1, wherein said compound is:

1-{4'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

{4'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid;

20

1-{4'-[5-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

{4'-[5-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid;

5 1-(4'-{5-[(R)-1-(2-Fluoro-phenyl)-ethoxycarbonylamino]-4-methyl-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid;

1-(4'-{4-Methyl-5-[(R)-1-(2-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid;

10 1-(4'-{4-Methyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid;

1-{4'-[5-((R)-Indan-1-yloxy carbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

1-{4'-[5-((R)-1,2-Dimethyl-propoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

15 1-{4'-[5-((R)-*sec*-Butoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

1-[4'-(5-*iso*-Propoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

20 1-{4'-[5-(1-Cyclopropyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

1-{4'-[5-(1-Cyclobutyl-ethoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

1-[4'-(5-*tert*-Butoxycarbonylamino)-4-methyl-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

25 1-{3-Fluoro-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

1-{3'-Methoxy-4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

30 1-{4'-[4-Ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

{4'-[4-Ethyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid;

1-(4'-{4-Ethyl-5-[(R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino]-[1,2,3]triazol-1-yl}-biphenyl-4-yl)-cyclopropanecarboxylic acid;

{4'-[4-Ethyl-5-((R)-1-(3-trifluoromethyl-phenyl)-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid;

5 1-{4'-[5-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

{4'-[5-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid;

2-Methyl-2-{4'-[4-methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-propionic acid;

10 (R)-1-(4'-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-3-yl)cyclopropanecarboxylic acid;

1-{3'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

15 {3'-[4-Methyl-5-((R)-1-phenyl-ethoxycarbonylamino)-[1,2,3]triazol-1-yl]-biphenyl-4-yl}-acetic acid;

(3-Biphenyl-4-yl-5-methyl-3*H*-[1,2,3]triazol-4-yl)-carbamic acid (R)-1-phenyl-ethyl ester;

[3-(4'-Cyano-biphenyl-4-yl)-5-methyl-3*H*-[1,2,3]triazol-4-yl]-carbamic acid (R)-1-phenyl-ethyl ester;

(R)-1-Phenyl-ethyl-1-(4'-(1-(1*H*-tetrazol-5-yl)cyclopropyl)biphenyl-4-yl)-4-methyl-1*H*-

20 1,2,3-triazol-5-ylcarbamate;

{3-[4'-(1-Methanesulfonylaminocarbonyl-cyclopropyl)-biphenyl-4-yl]-5-methyl-3*H*-[1,2,3]triazol-4-yl}-carbamic acid (R)-1-phenyl-ethyl ester;

1-{4'-[3-((R)-1-Phenyl-ethoxycarbonylamino)-[1,2,4]triazol-4-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

25 (R)-1-(4'-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-yl)biphenyl-4-yl)cyclobutanecarboxylic acid;

(R)-2-{4'-[4-Methyl-5-((1-phenylethoxycarbonylamino)-[1,2,3]triazol-1-yl)-biphenyl-4-yl]-pent-4-enoic acid;

(R)-2-(4-(4-(4-Methyl-5-((1-phenylethoxy)carbonylamino)-1*H*-1,2,3-triazol-1-

30 yl)phenyl)cyclohexyl)acetic acid; or

{3-[4'-(1-Methanesulfonylaminocarbonyl-cyclopropyl)-biphenyl-4-yl]-5-methyl-3*H*-[1,2,3]triazol-4-yl}-carbamic acid (R)-1-(3-trifluoromethyl-phenyl)-ethyl ester.

28. A compound according to any one of claims 1 to 27 for use as a therapeutically active substance.

29. A pharmaceutical composition, comprising a therapeutically effective amount of a compound
5 in accordance with any one of claims 1 to 27 and a therapeutically inert carrier.

30. The use of a compound according to any one of claims 1 to 27 for the treatment or prophylaxis of pulmonary fibrosis.

10 31. The use of a compound according to any one of claims 1 to 27 for the preparation of a medicament for the treatment or prophylaxis of pulmonary fibrosis.

32. A compound according to any one of claims 1 to 27 for the treatment or prophylaxis of pulmonary fibrosis.

15

33. A method for the treatment or prophylaxis of pulmonary fibrosis, which method comprises the step of administering an effective amount of a compound as defined in any one of claims 1 to 27 to a patient in need thereof.

20 34. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/062463

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	C07D249/06	C07D249/14
	A61K31/4192	A61K31/4196
	A61P29/00	
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
EPO-Internal, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/078593 A2 (AMIRA PHARMACEUTICALS INC [US]; SEIDERS THOMAS JON [US]; WANG BOWEI [U] 14 June 2012 (2012-06-14) paragraphs [00223] - [00227], [00256]; claims 1,4,6,9-15; examples 1-4 -----	1-34
A	WO 2011/159550 A2 (AMIDRA PHARMACEUTICALS INC [US]; BRITAIN JASON EDWARD [US]; SEIDERS T) 22 December 2011 (2011-12-22) claims 1,6,11,15-23 -----	1-34
A	WO 2011/159633 A1 (AMIRA PHARMACEUTICALS INC [US]; SEIDERS THOMAS JON [US]; HUTCHINSON JO) 22 December 2011 (2011-12-22) paragraphs [0094] - [00102], [00110], [00116]; claims 5,7,15,18,19,27,28,30 ----- -/-	1-34
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
Date of the actual completion of the international search		Date of mailing of the international search report
20 August 2013		02/09/2013
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Hass, Christian

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/062463

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SWANEY J S ET AL: "Pharmacokinetic and pharmacodynamic characterization of an oral lysophosphatidic acid type 1 receptor-selective antagonist", JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, US, vol. 336, no. 3, 2011, pages 693-700, XP009156147, ISSN: 0022-3565 page 693, abstract; page 694, figure 1; page 700, left-hand column, lines 3-10 -----	1-34
A	JS SWANEY ET AL: "A novel, orally active LPA1 receptor antagonist inhibits lung fibrosis in the mouse bleomycin model", BRITISH JOURNAL OF PHARMACOLOGY, vol. 160, no. 7, 2010, pages 1699-1713, XP55018263, ISSN: 0007-1188, DOI: 10.1111/j.1476-5381.2010.00828.x page 1699, abstract; page 1702, figure 1 A -----	1-34
X,P	WO 2013/025733 A1 (INTERMUNE INC [US]; BUCKMAN BRAD O [US]; NICHOLAS JOHN B [US]; EMAYAN) 21 February 2013 (2013-02-21) page 99, 100, compound T.M. 1; page 148, three compounds of the last but one row; last row, first compound from the left; page 390, compound 158; page 392, compounds 159 and 160; paragraphs [0053], [0081], [0085], [0086]; claims 1,2,52,199-207 -----	1-3, 6-10,12, 13, 15-19, 21,22, 24,26, 28-34
X,P	WO 2012/138648 A1 (IRM LLC [US]; NOVARTIS AG [CH]; TELLEW JOHN EDWARD [US]; WANG XIA [US]) 11 October 2012 (2012-10-11) page 148, compound 35; claims 1,13,15-20 ----- -/--	1-3,6, 12,13, 15,16, 28-34

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/062463

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	YIMIN QIAN ET AL: "Discovery of Highly Selective and Orally Active Lysophosphatidic Acid Receptor-1 Antagonists with Potent Activity on Human Lung Fibroblasts", JOURNAL OF MEDICINAL CHEMISTRY, vol. 55, no. 17, 13 September 2012 (2012-09-13), pages 7920-7939, XP002711399, DOI: 10.1021/JM301022V page 7920, abstract; page 7921, figure 1, formula 2; scheme 3, compounds 2, 22-30; scheme 4, compound 33; table 3 -----	1-10, 12-23, 26,28, 32,34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/062463

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012078593 A2	14-06-2012	AU 2011338561 A1 CA 2820817 A1 WO 2012078593 A2	25-07-2013 14-06-2012 14-06-2012

WO 2011159550 A2	22-12-2011	NONE	

WO 2011159633 A1	22-12-2011	NONE	

WO 2013025733 A1	21-02-2013	TW 201315717 A US 2013072449 A1 WO 2013025733 A1	16-04-2013 21-03-2013 21-02-2013

WO 2012138648 A1	11-10-2012	NONE	



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(30) 优先权数据

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A61K 31/4196(2006.01)

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A61P 37/00(2006.01)

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(74) 专利代理机构 中科专利商标代理有限责任

公司 11021

代理人 贺卫国 柳春琦

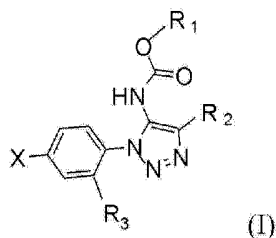
权利要求书7页 说明书68页

(54) 发明名称

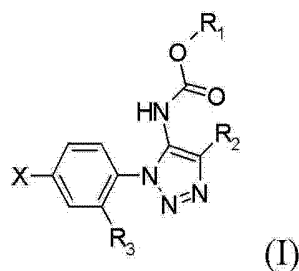
作为 LPAR 拮抗剂的 N-芳基三唑化合物

(57) 摘要

本文提供的是式 (I) 的化合物, 及其药用盐, 其中的取代基如说明书中所公开的那些。这些化合物, 以及含有它们的药物组合物, 可用于炎症疾病和病症, 例如肺纤维化的治疗。



1. 式 (I) 的化合物：



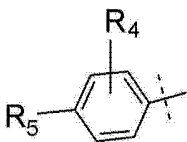
其中：

R₁ 是低级烷基或茺满基, 所述低级烷基是未被取代的或被以下基团取代的: 环烷基, 未被取代的苯基或被卤素或 -CF₃ 取代的苯基;

R₂ 是氢或低级烷基;

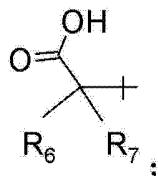
R₃ 是氢、氟或 -OCH₃;

X 是环烷基乙酸或者



R₄ 是氢或卤素;

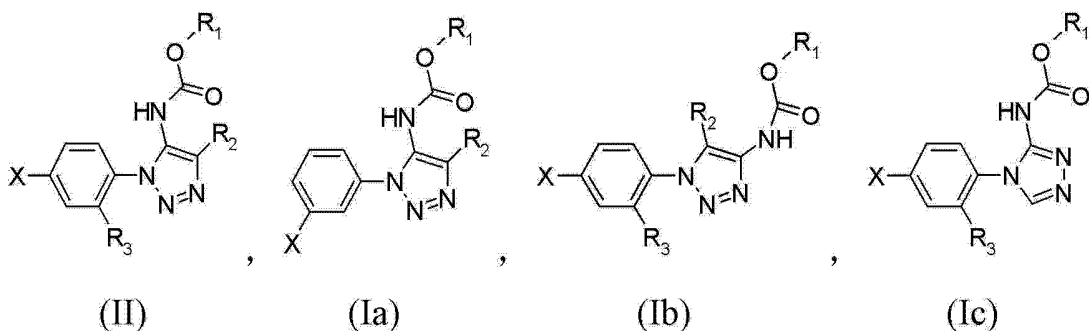
R₅ 是氢、氰基、四唑-环丙基、甲磺酰氨基羰基-环丙基或



R₆ 和 R₇ 彼此独立地为氢或低级烷基; 或者

R₆ 和 R₇ 与它们所连接的碳一起形成环烷基, 或其药用盐。

2. 通式 (I)、(Ia)、(Ib) 或 (Ic) 的化合物：



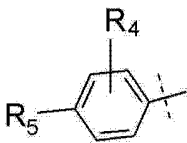
其中：

R₁ 是低级烷基或茺满基, 所述低级烷基是未被取代的或被以下基团取代的: 环烷基, 未被取代的苯基或被卤素或 -CF₃ 取代的苯基;

R₂ 是氢或低级烷基;

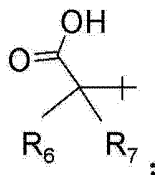
R_3 是氢、氟或 $-OCH_3$;

X 是环烷基乙酸或



R_4 是氢或卤素 ;

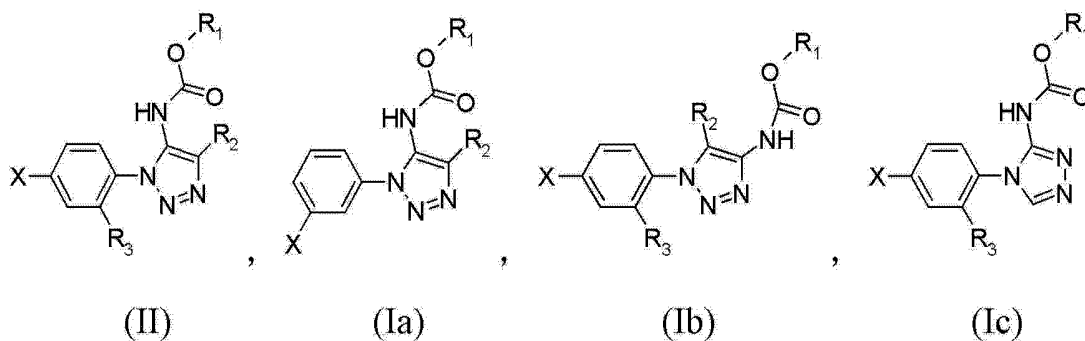
R_5 是氢、氰基、四唑 - 环丙基、甲磺酰氨基羰基 - 环丙基或



R_6 和 R_7 彼此独立地为氢或低级烷基 ; 或者

R_6 和 R_7 与它们所连接的碳一起形成环烷基, 或其药用盐。

3. 式 (I)、(Ia)、(Ib) 或 (Ic) 的化合物 :



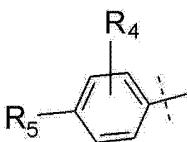
其中 :

R_1 是低级烷基或苄基, 所述低级烷基是未被取代的或被以下基团取代的 : 环烷基, 未被取代的苯基或被卤素或 $-CF_3$ 取代的苯基 ;

R_2 是氢或低级烷基 ;

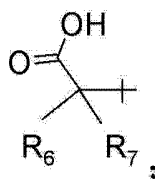
R_3 是氢、氟或 $-OCH_3$;

X 是环烷基乙酸或者



R_4 是氢或卤素 ;

R_5 是氢、氰基、四唑 - 环丙基、甲磺酰氨基羰基 - 环丙基或者



R_6 和 R_7 彼此独立地为氢,低级烷基或低级烯基;或者
 R_6 和 R_7 与它们所连接的碳一起形成环烷基,
 或其药用盐。

4. 根据权利要求 1 至 3 中的任一项所述的化合物,其中 R_1 是未被取代的低级烷基。

5. 根据权利要求 1 至 4 中的任一项所述的化合物,其中 R_1 是二甲基丙基、丁基或异丙基。

6. 根据权利要求 1 至 3 中的任一项所述的化合物,其中 R_1 是被环烷基、未被取代的苯基或被卤素或 $-\text{CF}_3$ 取代的苯基取代的低级烷基。

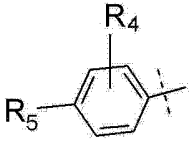
7. 根据权利要求 6 所述的化合物,其中 R_1 是 $-\text{CH}(\text{CH}_3)-$ 苯基、 $-\text{CH}(\text{CH}_3)-$ 氟苯基、 $-\text{CH}(\text{CH}_3)-$ 三氟甲基苯基、乙基-环丙基或乙基-环丁基。

8. 根据权利要求 1 至 7 中的任一项所述的化合物,其中 R_2 是低级烷基。

9. 根据权利要求 1 至 8 中的任一项所述的化合物,其中 R_2 是甲基。

10. 根据权利要求 1 至 9 中的任一项所述的化合物,其中 R_3 是氢。

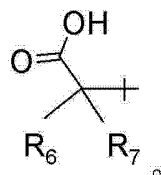
11. 根据权利要求 1 至 10 中的任一项所述的化合物,其中 X 是环己基乙酸。

12. 根据权利要求 1 至 10 中的任一项所述的化合物,其中 X 是 。

13. 根据权利要求 12 所述的化合物,其中 R_4 是氢或氟。

14. 根据权利要求 12 所述的化合物,其中 R_5 是氢、氰基、四唑-环丙基或甲磺酰氨基羰基-环丙基。

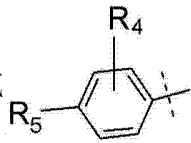
15. 根据权利要求 12 所述的化合物,其中 R_5 是

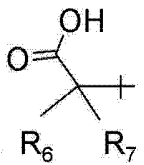


16. 根据权利要求 12 所述的化合物,其中 R_6 和 R_7 彼此独立地为氢或甲基。

17. 根据权利要求 12 所述的化合物,其中 R_6 和 R_7 与它们所连接的碳一起形成环丙基。

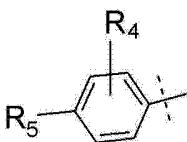
18. 根据权利要求 1 所述的化合物,其中 R_1 是低级烷基或茚满基,所述低级烷基是未被取代的或被环烷基或未被取代的苯基取代的; R_2 是氢或低级烷基; R_3 是氢、氟或 $-\text{OCH}_3$;X 是

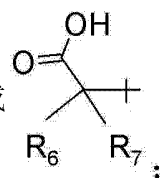
环烷基乙酸或 ; 其中 R_4 是氢或卤素并且 R_5 是氢、氰基、四唑-环丙基、甲磺酰

氨基羰基-环丙基或 ; 其中 R_6 和 R_7 彼此独立地为氢或低级烷基;或 R_6 和 R_7 与它

们所连接的碳一起形成环烷基,或其药用盐。

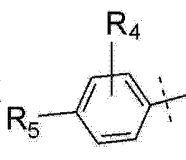
19. 根据权利要求 1 所述的化合物, 其中 R_1 是被未被取代的苯基取代的低级烷基; R_2 是

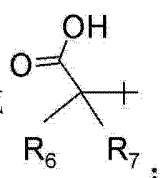
氢或低级烷基; R_3 是氢、氟或 $-OCH_3$; X 是环烷基乙酸或  其中 R_4 是氢或卤素

并且 R_5 是氢、氰基、四唑-环丙基、甲磺酰氨基羰基-环丙基或  其中 R_6 和 R_7 彼

此独立地为氢或低级烷基; 或 R_6 和 R_7 与它们所连接的碳一起形成环烷基, 或其药用盐。

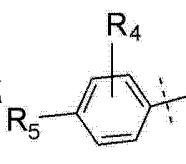
20. 根据权利要求 1 所述的化合物, 其中 R_1 是低级烷基或茚满基, 所述低级烷基是未被取代的或被以下基团取代的: 环烷基, 未被取代的苯基或被卤素或 $-CF_3$ 取代的苯基; R_2 是乙

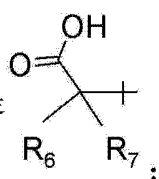
基; R_3 是氢、氟或 $-OCH_3$; X 是环烷基乙酸或  其中 R_4 是氢或卤素并且 R_5 是氢、

氰基、四唑-环丙基、甲磺酰氨基羰基-环丙基或  其中 R_6 和 R_7 彼此独立地为氢

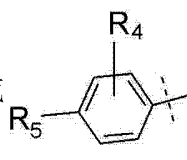
或低级烷基; 或 R_6 和 R_7 与它们所连接的碳一起形成环烷基, 或其药用盐。

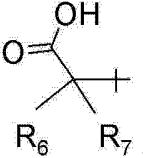
21. 根据权利要求 1 所述的化合物, 其中 R_1 是低级烷基或茚满基, 所述低级烷基是未被取代的或被以下基团取代的: 环烷基, 未被取代的苯基或被卤素或 $-CF_3$ 取代的苯基; R_2 是氢

或低级烷基; R_3 是氢、氟或 $-OCH_3$; X 是环烷基乙酸或  其中 R_4 是氢或卤素并

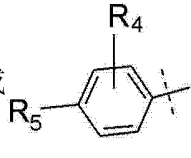
且 R_5 是  其中 R_6 和 R_7 与它们所连接的碳一起形成环烷基, 或其药用盐。

22. 根据权利要求 1 所述的化合物, 其中 R_1 是被未被取代的苯基取代的低级烷基; R_2 是

氢或低级烷基; R_3 是氢、氟或 $-OCH_3$; X 是环烷基乙酸或  其中 R_4 是氢或卤素

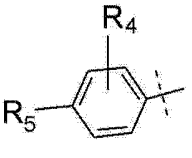
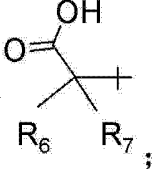
并且 R_5 是  其中 R_6 和 R_7 与它们所连接的碳一起形成环烷基,或其药用盐。

23. 根据权利要求 1 所述的化合物,其中 R_1 是低级烷基或茛满基,所述低级烷基是未被取代的或被以下基团取代的:环烷基,未被取代的苯基或被卤素或 $-\text{CF}_3$ 取代的苯基; R_2 是氢

或低级烷基; R_3 是氢、氟或 $-\text{OCH}_3$;X 是环烷基乙酸或  其中 R_4 是氢或卤素并

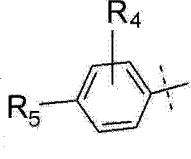
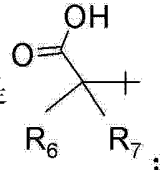
且 R_5 是甲磺酰氨基羰基-环丙基,或其药用盐。

24. 根据权利要求 2 或 3 所述的式 (Ia) 的化合物,其中 R_1 是被未被取代的苯基取代的

低级烷基; R_2 是低级烷基;X 是  其中 R_4 是氢并且 R_5 是  R_6 和 R_7 是

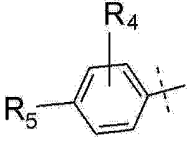
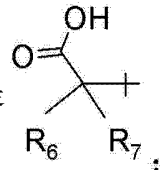
氢或者 R_6 和 R_7 与它们所连接的碳一起形成环烷基,或其药用盐。

25. 根据权利要求 2 或 3 所述的式 (Ib) 的化合物,其中 R_1 是被未被取代的苯基取代的

低级烷基; R_2 是低级烷基; R_3 是氢;X 是  其中 R_4 是氢并且 R_5 是  R_6 和 R_7 ;

其中 R_6 和 R_7 是氢或者 R_6 和 R_7 与它们所连接的碳一起形成环烷基,或其药用盐。

26. 根据权利要求 2 或 3 所述的式 (Ic) 的化合物,其中 R_1 是被未被取代的苯基取代的

低级烷基; R_3 是氢;X 是  其中 R_4 是氢并且 R_5 是  其中 R_6 和 R_7 与

它们所连接的碳一起形成环烷基,或其药用盐。

27. 根据权利要求 1 所述的化合物,其中所述化合物是:

1-{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸;

1-{4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

{4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸;

1-(4'-{5-[(R)-1-(2-氟-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸;

1-(4'-{4-甲基-5-[(R)-1-(2-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸;

1-(4'-{4-甲基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸;

1-{4'-[5-((R)-茚满-1-基氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

1-{4'-[5-((R)-1,2-二甲基-丙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

1-{4'-[5-((R)-仲丁氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

1-[4'-{(5-异丙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基}-联苯-4-基]-环丙烷甲酸;

1-{4'-[5-(1-环丙基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

1-{4'-[5-(1-环丁基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

1-[4'-{(5-叔丁氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基}-联苯-4-基]-环丙烷甲酸;

1-{3-氟-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

1-{3'-甲氧基-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

1-{4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

{4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸;

1-(4'-{4-乙基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸;

{4'-[4-乙基-5-((R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸;

1-{4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

{4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸;

2-甲基-2-{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-丙酸;

(R)-1-(4'-{(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)联

苯-3-基)环丙烷甲酸;

1-{3'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

{3'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸;

(3-联苯-4-基-5-甲基-3H-[1,2,3]三唑-4-基)-氨基甲酸(R)-1-苯基-乙酯;

[3-(4'-氰基-联苯-4-基)-5-甲基-3H-[1,2,3]三唑-4-基)-氨基甲酸(R)-1-苯基-乙酯;

(R)-1-苯基-乙基-1-(4'-(1-(1H-四唑-5-基)环丙基)联苯-4-基)-4-甲基-1H-1,2,3-三唑-5-基氨基甲酸酯;

{3-[4'-(1-甲磺酰氨基羰基-环丙基)-联苯-4-基]-5-甲基-3H-[1,2,3]三唑-4-基}-氨基甲酸(R)-1-苯基-乙酯;

1-{4'-[3-((R)-1-苯基-乙氧基羰基氨基)-[1,2,4]三唑-4-基]-联苯-4-基}-环丙烷甲酸;

(R)-1-(4'-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)联苯-4-基)环丁烷甲酸;

(R)-2-{4'-[4-甲基-5-((1-苯基乙氧基羰基氨基)-[1,2,3]三唑-1-基)-联苯-4-基]-戊-4-烯酸};

(R)-2-(4-(4-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)苯基)环己基)乙酸;或者

{3-[4'-(1-甲磺酰氨基羰基-环丙基)-联苯-4-基]-5-甲基-3H-[1,2,3]三唑-4-基}-氨基甲酸(R)-1-(3-三氟甲基-苯基)-乙酯。

28. 根据权利要求1至27中的任一项所述的化合物,所述化合物用作治疗活性物质。

29. 一种药物组合物,所述药物组合物包含治疗有效量的根据权利要求1至27中的任一项所述的化合物和治疗惰性载体。

30. 根据权利要求1至27中的任一项所述的化合物用于肺纤维化的治疗或预防的用途。

31. 根据权利要求1至27中的任一项所述的化合物用于制备药物的用途,所述药物用于肺纤维化的治疗或预防。

32. 根据权利要求1至27中的任一项所述的化合物,所述化合物用于肺纤维化的治疗或预防。

33. 一种用于治疗或预防肺纤维化的方法,所述方法包括将有效量的如权利要求1至27中的任一项所述的化合物向需要其的患者给药的步骤。

34. 如上所述的本发明。

作为 LPAR 拮抗剂的 N-芳基三唑化合物

[0001] 本发明涉及可用于治疗和 / 或预防哺乳动物中的炎症疾病或病症的有机化合物, 并且特别是 N-芳基三唑化合物, 它们的制造, 含有它们的药物组合物和它们作为溶血磷脂酸 (LPA) 拮抗剂的用途。

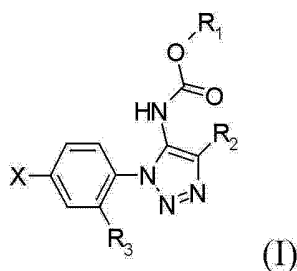
[0002] LPA 是生物活性磷酸脂质家族, 其通过与 LPA 受体, 一种 G-蛋白质 - 结合受体 (GPCR) 家族相互作用发挥如生长因子调节剂的功能。该脂质家族具有通过酯键连接至甘油的长链饱和的 (如 C18 : 0 或 C16 : 0) 或不饱和的 (C18 : 1 或 C20 : 4) 碳链。在生物学系统中, LPA 通过膜磷脂质的脱酯化由多步酶路径产生。贡献于 LPA 合成的酶包括溶血磷脂酶 D (lysoPLD)、自分泌运动因子 (ATX)、磷脂酶 A1 (PLA1)、磷脂酶 A2 (PLA2) 和酰基甘油激酶 (AGK) (British J. of Pharmacology 2012, 165, 829-844)。

[0003] 至少有六种 LPA 受体被识别 (LPAR1-6)。LPA 信号传导对很多不同的细胞类型施加宽范围的生物学响应, 其可以导致细胞生长、细胞增殖、细胞迁移和细胞收缩。LPA 路径的增量调节与多种疾病相关, 包括癌症, 过敏性气管炎, 以及肾、肺和肝的纤维化。因此, 靶向 LPA 受体或 LPA 代谢酶可以对医学上重要的疾病的治疗提供新的方式, 所述医学上重要的疾病包括神经精神病学疾病、神经性疼痛、不育、心血管疾病、炎症、纤维化和癌症 (Annu. Rev. Pharmacol. Toxicol. 2010, 50, 157-186 ; J. Biochem. 2011, 150, 223-232)。

[0004] 纤维化是导致细胞外基质 (ECM) 的过度积累的不受控组织愈合过程的结果。最近报道, LPA1 受体在特发性肺纤维化 (IPF) 患者中过度表达。敲除 LPA1 受体的小鼠被保护不受博来霉素诱导的肺纤维化影响 (Nature Medicine 2008, 14, 45-54)。因此, 拮抗 LPA1 受体可用于治疗纤维化, 如肾纤维化, 肺纤维化, 动脉纤维化和系统性硬化症。

[0005] 在本发明的一个实施方案中, 所提供的是通式 (I) 的化合物 :

[0006]

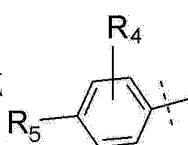


[0007] 其中 :

[0008] R_1 是低级烷基或苄基, 所述低级烷基是未被取代的或被以下基团取代的 : 环烷基, 未被取代的苯基或被卤素或 $-CF_3$ 取代的苯基 ;

[0009] R_2 是氢或低级烷基 ;

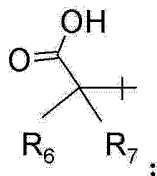
[0010] R_3 是氢、氟或 $-OCH_3$;

[0011] X 是环烷基乙酸或 

[0012] R_4 是氢或卤素 ;

[0013] R_5 是氢、氰基、四唑-环丙基、甲磺酰氨基羰基-环丙基或者

[0014]



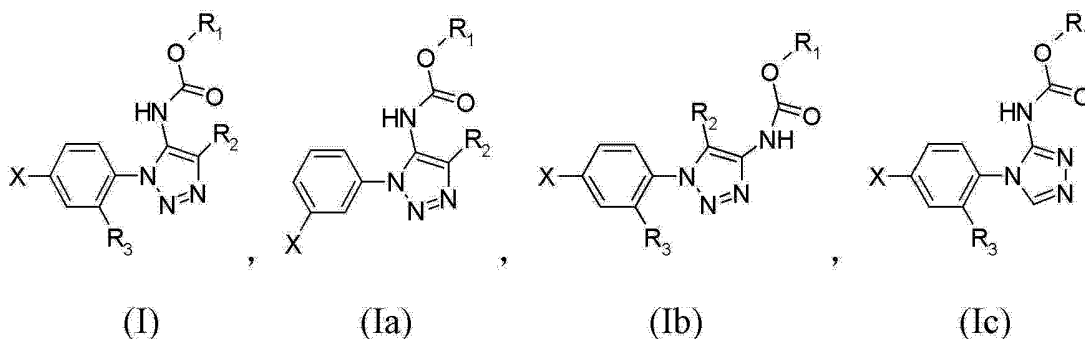
[0015] R_6 和 R_7 彼此独立地为氢或低级烷基；或者

[0016] R_6 和 R_7 与它们所连接的碳一起形成环烷基，

[0017] 或其药用盐。

[0018] 在本发明的另一个实施方案中，所提供的是通式 (I)、(Ia)、(Ib) 或 (Ic) 的化合物：

[0019]



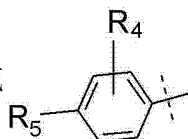
[0020] 其中：

[0021] R_1 是低级烷基或茚满基，所述低级烷基是未被取代的或被以下基团取代的：环烷基，未被取代的苯基或被卤素或 $-CF_3$ 取代的苯基；

[0022] R_2 是氢或低级烷基；

[0023] R_3 是氢、氟或 $-OCH_3$ ；

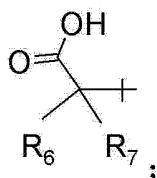
[0024] X 是环烷基乙酸或



[0025] R_4 是氢或卤素；

[0026] R_5 是氢、氰基、四唑-环丙基、甲磺酰氨基羰基-环丙基或者

[0027]



[0028] R_6 和 R_7 彼此独立地为氢或低级烷基；或者

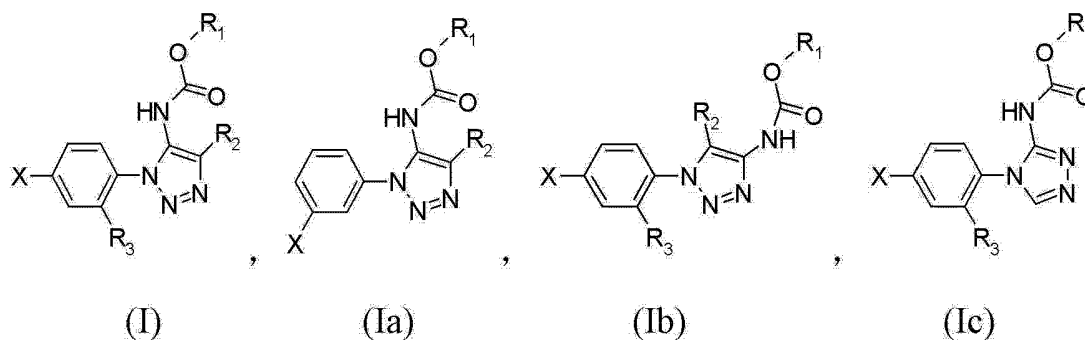
[0029] R_6 和 R_7 与它们所连接的碳一起形成环烷基，

[0030] 或其药用盐。

[0031] 在本发明的另一个实施方案中，所提供的是通式 (I)、(Ia)、(Ib) 或 (Ic) 的化合物：

物：

[0032]



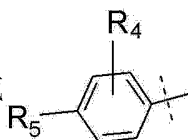
[0033] 其中：

[0034] R_1 是低级烷基或茚满基，所述低级烷基是未被取代的或被以下基团取代的：环烷基，未被取代的苯基或被卤素或 $-CF_3$ 取代的苯基；

[0035] R_2 是氢或低级烷基；

[0036] R_3 是氢、氟或 $-OCH_3$ ；

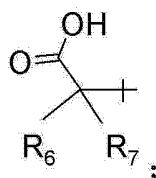
[0037] X 是环烷基乙酸或



[0038] R_4 是氢或卤素；

[0039] R_5 是氢、氰基、四唑-环丙基、甲磺酰氨基羰基-环丙基或者

[0040]



[0041] R_6 和 R_7 彼此独立地为氢、低级烷基或低级烯基；或者

[0042] R_6 和 R_7 与它们所连接的碳一起形成环烷基，

[0043] 或其药用盐。

[0044] 在本发明的另外的实施方案中，所提供的是一种药物组合物，所述药物组合物包含治疗有效量的根据式 (I) 的化合物和治疗惰性载体。

[0045] 在本发明的再另外的实施方案中，所提供的是一种治疗或预防肺纤维化的方法，所述方法包括将治疗有效量的根据式 (I) 的化合物向需要其的患者给药的步骤。

[0046] 下面引用或依赖的所有文献通过引用明确地结合至本文中。

[0047] 除非另外提及，如本文所使用的以下说明，术语“烷基”，单独或与其他基团组合，是指一个至二十个碳原子，优选一个至十六个碳原子，更优选一个至十个碳原子的支链的或直链的单价饱和脂族烃基团。

[0048] 术语“低级烷基”，单独或与其他基团组合，是指一个至九个碳原子，优选一个至六个碳原子，更优选一个至四个碳原子的支链的或直链的烷基基团。该术语的进一步的实例是如甲基、乙基、正丙基、异丙基、正丁基、仲丁基、异丁基、叔丁基、正戊基、3-甲基-丁基、

正己基、2-乙基丁基等的基团。

[0049] 术语“环烷基”是指三个至十个，优选三个至六个碳原子的、单价的单或多碳环基团。该术语的进一步的实例是如环丙基、环丁基、环戊基、环己基、环庚基、降冰片基、金刚烷基等的基团。在一个优选的实施方案中，“环烷基”部分可以任选地被一个、两个、三个或四个取代基取代，应明白所述取代基不进而被进一步取代。除非另外地具体指出，每个取代基可以独立地为，烷基、烷氧基、卤素、氨基、羟基或氧 ($O =$)。环烷基部分的实例包括，但是不限于，任选地取代的环丙基、任选地取代的环丁基、任选地取代的环戊基、任选地取代的环戊烯基、任选地取代的环己基、任选地取代的亚环己基、任选地取代的环庚基等或本文具体地示例的那些。

[0050] 术语“杂环烷基”是指单或多环烷基环，其中一个、两个或三个碳环原子被杂原子如 N、O 或 S 替代。杂环烷基的实例包括，但是不限于，吗啉基、硫代吗啉基、哌嗪基、哌啶基、吡咯烷基、四氢吡喃基、四氢呋喃基、1,3-二氧己环基等。杂环烷基可以是未被取代的或被取代的，并且可以在合适的地方通过它们的碳框架或通过它们的一个或多个杂原子连接，应明白所述取代基不进而被进一步取代。

[0051] 术语“芳基”是指具有至少一个芳族环的 6 至 12 个碳原子的芳族单或多碳环基团。这种基团的实例包括，但是不限于，苯基、萘基、1,2,3,4-四氢萘、1,2-二氢萘、茛满基、1H-茛基等。

[0052] 术语“杂芳基”是指具有至少一个含有选自 N、O 和 S 的一个、两个或三个环杂原子、余下的环原子是 C 的芳族环的 5 至 12 个原子的芳族单或多环基团。这种基团的实例包括，但是不限于，吡啶、噻唑和吡喃基。

[0053] 上述烷基、低级烷基、芳基和杂芳基可以独立地被一个、两个或三个取代基取代，应明白所述取代基不进而被进一步取代。取代基可以包括，例如，卤素、低级烷基、 $-CF_3$ 、 $-SO_2CH_3$ 、烷氧基、 $-C(O)CH_3$ 、 $-OH$ 、 $-SCH_3$ 和 $-CH_2CH_2OH$ 。

[0054] 如本文所使用的，术语“烷氧基”意指烷基 $-O-$ ；并且“烷酰基”意指烷基 $-CO-$ 。烷氧基取代基或含有烷氧基的取代基可以被，例如，一个或多个烷基取代，应明白所述取代基不进而被进一步取代。

[0055] 如本文所使用的，术语“卤素”意指氟、氯、溴或碘基团，优选氟、氯或溴基团，并且更优选氟或氯基团。

[0056] 式 I 的化合物可以具有一个或多个不对称碳原子并且可以以光学纯对映体、对映体的混合物如外消旋物、光学纯非对映异构体、非对映异构体的混合物、非对映异构体外消旋物或非对映异构体外消旋物的混合物的形式存在。光学活性形式可以例如通过外消旋物的拆分，通过不对称合成或不对称色谱（具有用手性吸附剂或洗脱剂的色谱）获得。本发明包括所有的这些形式。

[0057] 如本文所使用的，术语“药用盐”意指式 (I) 的化合物的任何药用盐。盐可以由药用无毒酸和碱包括无机和有机酸和碱制备。这种酸包括，例如，乙酸、苯磺酸、安息香酸、樟脑磺酸、柠檬酸、乙烯磺酸、二氯乙酸、甲酸、富马酸、葡糖酸、谷氨酸、马尿酸、氢溴酸、盐酸、羟乙磺酸、乳酸、马来酸、苹果酸、扁桃酸、甲磺酸、粘酸、硝酸、草酸、扑酸、泛酸、磷酸、琥珀酸、硫酸、酒石酸、草酸、对甲苯磺酸等。特别优选的是富马酸、盐酸、氢溴酸、磷酸、琥珀酸、硫酸和甲磺酸。药用碱盐包括碱金属（例如钠、钾）、碱土金属（例如钙、镁）和铝盐。

[0058] 在本发明的方法的实施中,将有效量的本发明的任一种化合物或本发明的任何化合物的组合或其药用盐经由本领域中已知的任何通常的和可接受的方法或单独地或组合地给药。因此可以将化合物或组合物经口(例如,口腔)、舌下、肠胃外(例如,肌肉内、静脉内或皮下)、经直肠(例如,通过栓剂或洗液)、经皮(例如,皮肤电穿孔)或通过吸入(例如,通过气雾剂),并且以固体、液体或气体剂量,包括片剂和悬浮液给药。给药可以任意用连续治疗以单一单位的药物剂型或以单一剂量治疗进行。治疗组合物还可以以与亲脂性盐如扑酸结合的油乳浊液或分散液的形式,或以生物可降解持续释放组合物的形式用于皮下或肌肉内给药。

[0059] 用于本文的组合物的制备的可用的药物载体可以是固体、液体或气体。因此,组合物可以采取以下形式:片剂、丸剂、胶囊、栓剂、粉末、肠衣或其他被保护的制剂(例如结合在离子交换树脂上或包裹在脂质-蛋白质泡囊中)、缓释剂、溶液、悬浮液、酏剂、气雾剂等。载体可以选自多种油包括源自石油、动物、植物或合成有机物的那些,例如,花生油、大豆油、矿物油、芝麻油等。水、盐水、葡萄糖水溶液和二醇是优选的液体载体,特别是(当与血液等渗透压时)用于注射液。例如,用于静脉内给药的制剂包括通过将一种或多种固体活性组分溶解在水中以制备水溶液,并且将溶液灭菌而制备的一种或多种活性组分的无菌水溶液。合适的药物赋形剂包括淀粉、纤维素、滑石、葡萄糖、乳糖、滑石、明胶、麦芽、大米、面粉、白垩、二氧化硅、硬脂酸镁、硬脂酸钠、甘油单硬脂酸酯、氯化钠、脱脂奶粉、甘油、丙二醇、水、乙醇等。该组合物可以经受传统的药物添加剂如防腐剂、稳定剂、湿润剂或乳化剂、用于调节渗透压的盐、缓冲剂等。合适的药物载体和它们的制剂由 E. W. Martin 描述在 Remington's Pharmaceutical Sciences 中。这种组合物将,在任何情况下,含有有效量的活性化合物以及合适的载体,以便制备合适的药物剂型用于向受体的适当给药。

[0060] 本发明的化合物的剂量依赖于多种因素,例如,给药的方式、对象的年龄和体重,以及所要治疗的对象的情况,并且最终将由主治医师或兽医确定。如通过主治医师或兽医确定的活性化合物的这种量在本文中,以及在权利要求书,称为“治疗有效量”。例如,本发明的化合物的剂量典型地在每天约 1 至约 1000mg 的范围内。优选地,治疗有效量为每天约 1mg 至约 500mg 的量。

[0061] 在本发明的一个实施方案中,所提供的是式 (I) 的化合物,其中 R_1 是二甲基丙基、丁基或异丙基。

[0062] 在本发明的另一个实施方案中,所提供的是式 (I) 的化合物,其中 R_1 是被环烷基,未被取代的苯基或被卤素或 $-CF_3$ 取代的苯基取代的低级烷基。

[0063] 在本发明的另一个实施方案中,所提供的是式 (I) 的化合物,其中 R_1 是 $-CH(CH_3)-$ 苯基、 $-CH(CH_3)-$ 氟苯基、 $-CH(CH_3)-$ 三氟甲基苯基、乙基-环丙基或乙基-环丁基。

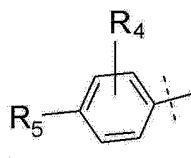
[0064] 在本发明的另一个实施方案中,所提供的是式 (I) 的化合物,其中 R_2 是低级烷基。

[0065] 在本发明的另一个实施方案中,所提供的是式 (I) 的化合物,其中 R_2 是甲基。

[0066] 在本发明的另一个实施方案中,所提供的是式 (I) 的化合物,其中 R_3 是氢。

[0067] 在本发明的另一个实施方案中,所提供的是式 (I) 的化合物,其中 X 是环己基乙酸。

[0068] 在本发明的另一个实施方案中,所提供的是式 (I) 的化合物,其中 X 是

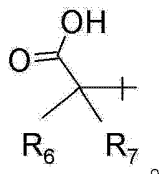


[0069] 在本发明的另一个实施方案中,所提供的是式 (I) 的化合物,其中 R₄ 是氢或氟。

[0070] 在本发明的另一个实施方案中,所提供的是式 (I) 的化合物,其中 R₅ 是氢、氰基、四唑-环丙基或甲磺酰氨基羰基-环丙基。

[0071] 在本发明的另一个实施方案中,所提供的是式 (I) 的化合物,其中 R₅ 是

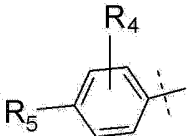
[0072]

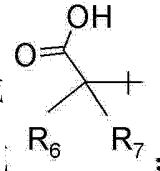


[0073] 在本发明的另一个实施方案中,所提供的是式 (I) 的化合物,其中 R₆ 和 R₇ 彼此独立地为氢或甲基。

[0074] 在本发明的另一个实施方案中,所提供的是式 (I) 的化合物,其中 R₆ 和 R₇ 与它们所连接的碳一起形成环丙基。

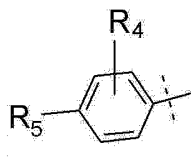
[0075] 在本发明的另一个实施方案中,所提供的是通式 (I) 的化合物,其中 R₁ 是低级烷基或茚满基,所述低级烷基是未被取代的,或是被环烷基或未被取代的苯基取代的;R₂ 是氢

或低级烷基;R₃ 是氢、氟或 -OCH₃;X 是环烷基乙酸或  其中 R₄ 是氢或卤素并

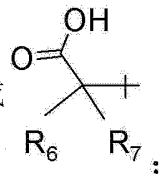
且 R₅ 是氢、氰基、四唑-环丙基、甲磺酰氨基羰基-环丙基或  其中 R₆ 和 R₇ 彼此

独立地为氢或低级烷基;或 R₆ 和 R₇ 与它们所连接的碳一起形成环烷基,或其药用盐。

[0076] 在本发明的另一个实施方案中,所提供的是通式 (I) 的化合物,其中 R₁ 是被未被取代的苯基取代的低级烷基;R₂ 是氢或低级烷基;R₃ 是氢、氟或 -OCH₃;X 是环烷基乙酸或

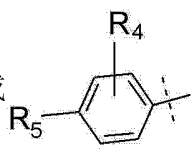


其中 R₄ 是氢或卤素并且 R₅ 是氢、氰基、四唑-环丙基、甲磺酰氨基羰基-环

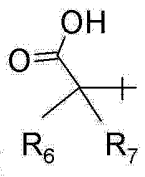
丙基或  其中 R₆ 和 R₇ 彼此独立地为氢或低级烷基;或者 R₆ 和 R₇ 与它们所连接的

碳一起形成环烷基,或其药用盐。

[0077] 在本发明的另一个实施方案中,所提供的是通式 (I) 的化合物其中 R_1 是低级烷基或茚满基,所述低级烷基是未被取代的或被以下基团取代的:环烷基,未被取代的苯基或被

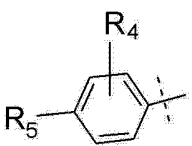
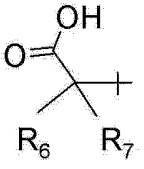
卤素或 $-CF_3$ 取代的苯基; R_2 是乙基; R_3 是氢、氟或 $-OCH_3$;X 是环烷基乙酸或  ;

其中 R_4 是氢或卤素并且 R_5 是氢、氰基、四唑-环丙基、甲磺酰氨基羰基-环丙基或

 其中 R_6 和 R_7 彼此独立地为氢或低级烷基;或者 R_6 和 R_7 与它们所连接的碳一起

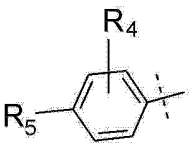
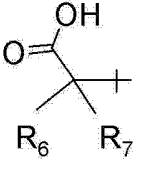
形成环烷基,或其药用盐。

[0078] 在本发明的另一个实施方案中,所提供的是通式 (I) 的化合物其中 R_1 是低级烷基或茚满基,所述低级烷基是未被取代的或被以下基团取代的:环烷基,未被取代的苯基或被卤素或 $-CF_3$ 取代的苯基; R_2 是氢或低级烷基; R_3 是氢、氟或 $-OCH_3$;X 是环烷基乙酸或

 其中 R_4 是氢或卤素并且 R_5 是  其中 R_6 和 R_7 与它们所连接的碳

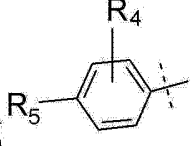
一起形成环烷基,或其药用盐。

[0079] 在本发明的另一个实施方案中,所提供的是通式 (I) 的化合物其中 R_1 是被未被取代的苯基取代的低级烷基; R_2 是氢或低级烷基; R_3 是氢、氟或 $-OCH_3$;X 是环烷基乙酸或

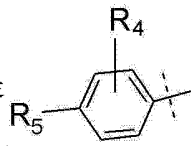
 其中 R_4 是氢或卤素并且 R_5 是  其中 R_6 和 R_7 与它们所连接的碳

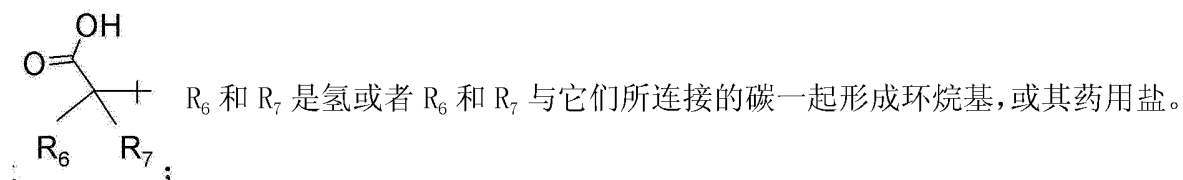
一起形成环烷基,或其药用盐。

[0080] 在本发明的另一个实施方案中,所提供的是通式 (I) 的化合物其中 R_1 是低级烷基或茚满基,所述低级烷基是未被取代的或被以下基团取代的:环烷基,未被取代的苯基或被卤素或 $-CF_3$ 取代的苯基; R_2 是氢或低级烷基; R_3 是氢、氟或 $-OCH_3$;X 是环烷基乙酸或

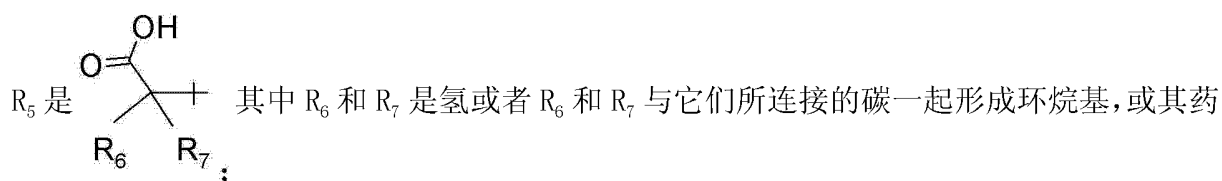
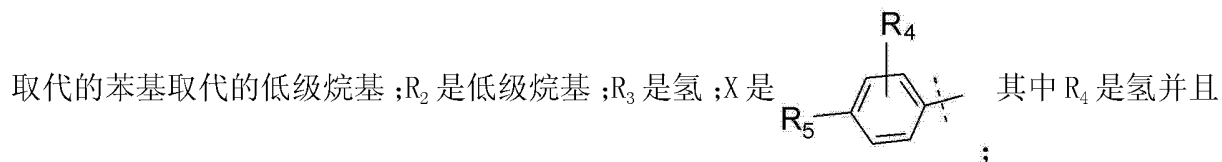
 其中 R_4 是氢或卤素并且 R_5 是甲磺酰氨基羰基-环丙基,或其药用盐。

[0081] 在本发明的另一个实施方案中,所提供的是通式 (Ia) 的化合物,其中 R_1 是被未

被取代的苯基取代的低级烷基; R_2 是低级烷基;X 是  其中 R_4 是氢并且 R_5 是

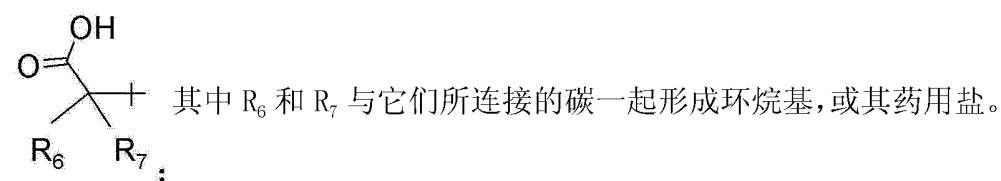
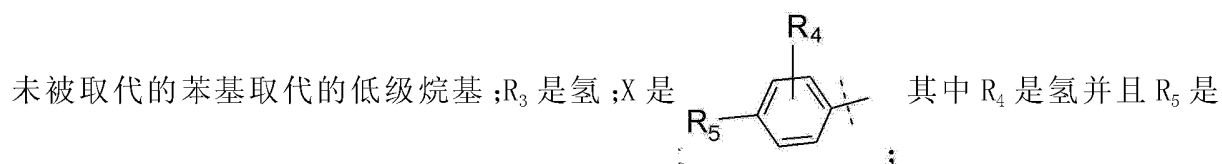


[0082] 在本发明的另一个实施方案中,所提供的是通式 (Ib) 的化合物,其中 R_1 是被未被



用盐。

[0083] 在本发明的另一个实施方案中,所提供的是通式 (Ic) 的化合物,其中 R_1 是被



[0084] 特别的式 (I) 的化合物包括以下各项:

[0085] 1-{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

[0086] {4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸;

[0087] 1-{4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸;

[0088] {4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸;

[0089] 1-(4'-[5-[(R)-1-(2-氟-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基)-环丙烷甲酸;

[0090] 1-(4'-[4-甲基-5-[(R)-1-(2-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基]-联苯-4-基)-环丙烷甲酸;

[0091] 1-(4'-[4-甲基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基]-联苯-4-基)-环丙烷甲酸;

- [0092] 1-{4' -[5-((R)-茚满-1-基氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸；
- [0093] 1-{4' -[5-((R)-1,2-二甲基-丙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸；
- [0094] 1-{4' -[5-((R)-仲丁氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸；
- [0095] 1-[4' -(5-异丙氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸；
- [0096] 1-{4' -[5-(1-环丙基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸；
- [0097] 1-{4' -[5-(1-环丁基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸；
- [0098] 1-[4' -(5-叔丁氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸；
- [0099] 1-{3-氟-4' -[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸；
- [0100] 1-{3'-甲氧基-4' -[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸；
- [0101] 1-{4' -[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸；
- [0102] {4' -[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸；
- [0103] 1-(4' -[4-乙基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基]-联苯-4-基)-环丙烷甲酸；
- [0104] {4' -[4-乙基-5-((R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸；
- [0105] 1-{4' -[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸；
- [0106] {4' -[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸；
- [0107] 2-甲基-2-{4' -[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-丙酸；
- [0108] (R)-1-(4' -(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)联苯-3-基)环丙烷甲酸；
- [0109] 1-{3' -[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸；
- [0110] {3' -[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸；
- [0111] (3-联苯-4-基-5-甲基-3H-[1,2,3]三唑-4-基)-氨基甲酸 (R)-1-苯基-乙

酯；

[0112] [3-(4'-氰基-联苯-4-基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-苯基-乙酯；

[0113] (R)-1-苯基-乙基-1-(4'-(1-(1H-四唑-5-基)环丙基)联苯-4-基)-4-甲基-1H-1,2,3-三唑-5-基氨基甲酸酯；

[0114] {3-[4'-(1-甲磺酰氨基羰基-环丙基)-联苯-4-基]-5-甲基-3H-[1,2,3]三唑-4-基}-氨基甲酸(R)-1-苯基-乙酯；

[0115] 1-{4'-[3-((R)-1-苯基-乙氧基羰基氨基)-[1,2,4]三唑-4-基]-联苯-4-基}-环丙烷甲酸；

[0116] (R)-1-(4'-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)联苯-4-基)环丁烷甲酸；

[0117] (R)-2-{4'-[4-甲基-5-((1-苯基乙氧基羰基氨基)-[1,2,3]三唑-1-基)-联苯-4-基]-戊-4-烯酸；

[0118] (R)-2-(4-(4-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)苯基)环己基)乙酸；或者

[0119] {3-[4'-(1-甲磺酰氨基羰基-环丙基)-联苯-4-基]-5-甲基-3H-[1,2,3]三唑-4-基}-氨基甲酸(R)-1-(3-三氟甲基-苯基)-乙酯。

[0120] 在本发明的另一个实施方案中，所提供的是用于作为治疗活性物质使用的式(I)的化合物。

[0121] 在本发明的另一个实施方案中，所提供的是一种药物组合物，所述药物组合物包含治疗有效量的式(I)的化合物和治疗惰性载体。

[0122] 在本发明的另一个实施方案中，所提供的是根据式(I)的化合物用于治疗或预防肺纤维化的用途。

[0123] 在本发明的另一个实施方案中，所提供的是根据式(I)的化合物用于制备药物的用途，所述药物用于肺纤维化的治疗或预防。

[0124] 在本发明的另一个实施方案中，所提供的是根据式(I)的化合物，所述式(I)的化合物用于肺纤维化的治疗或预防。

[0125] 在本发明的另一个实施方案中，所提供的是根据下面的方法制备的根据式(I)的化合物。

[0126] 在本发明的另一个实施方案中，所提供的是一种治疗或预防肺纤维化的方法，所述方法包括将治疗有效量的式(I)的化合物向需要其的患者给药的步骤。

[0127] 在本发明的另一个实施方案中，所提供的是如上所述的本发明。

[0128] 将明白的是，本发明中通式I的化合物可以在官能团处衍生以提供能够在体内转化回母体化合物的衍生物。能够在体内产生通式I的母体化合物的生理学可接受且易代谢的衍生物也在本发明的范围内。

[0129] 本发明的化合物可以用可商购的原材料开始制备，或采用本领域技术人员已知的一般合成技术和程序制备。化学品可以购自如下公司，例如Aldrich、Argonaut Technologies、VWR、Lancaster、Princeton、Alfa、Oakwood、TCI、Fluorochem、Apollo、Matrix、Maybridge或Meinoah。色谱耗材和设备可以购自如下公司，例如AnaLogix, Inc,

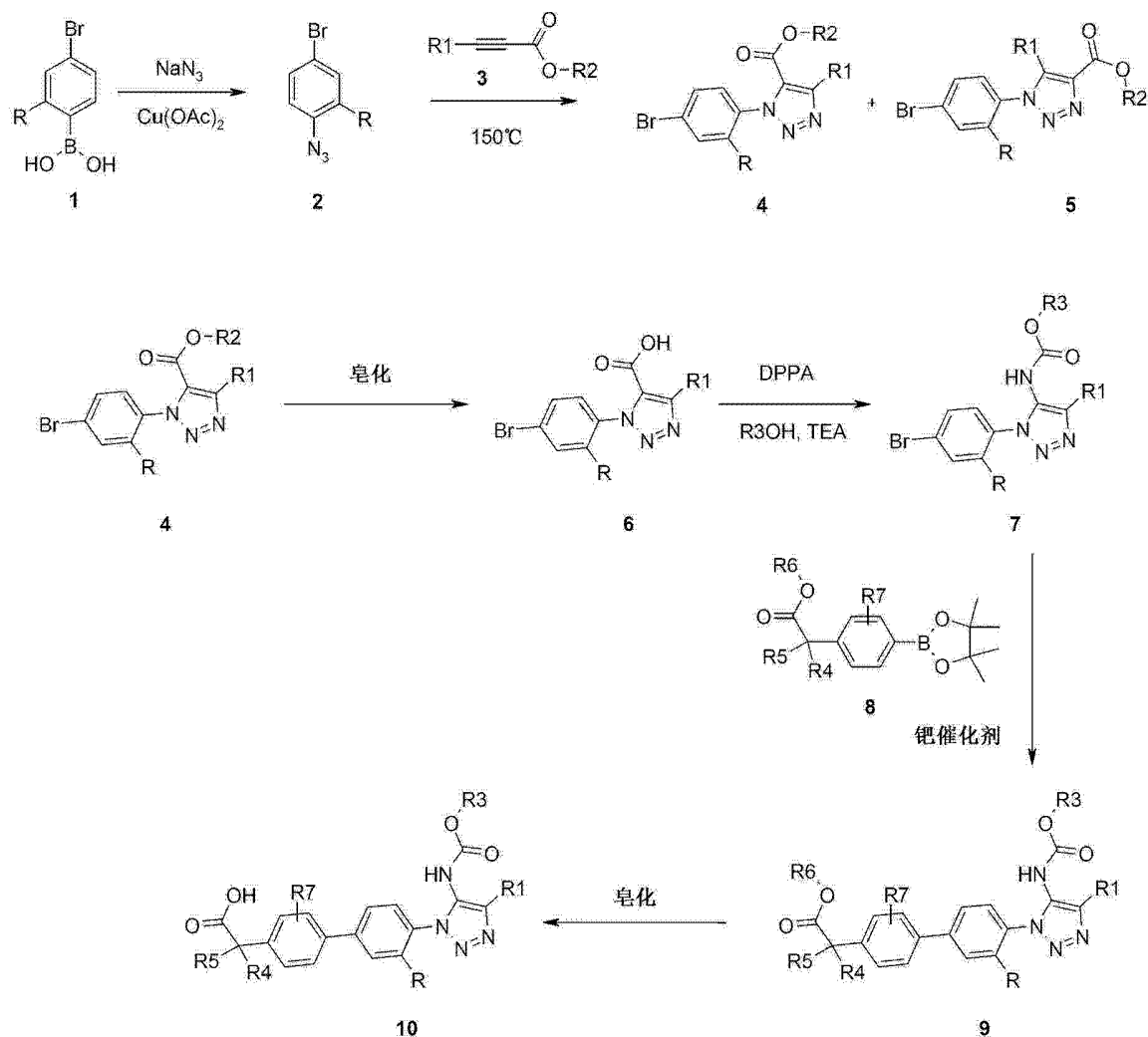
Burlington, WI ;Biotage AB, Charlottesville, VA ;Analytical Sales and Services, Inc., Pompton Plains, NJ ;Teledyne Isco, Lincoln, NE ;VWR International, Bridgeport, NJ ;Varian Inc., Palo Alto, CA, 以及 Multigram II Mettler Toledo Instrument Newark, DE。Biotage、ISCO 和 Analogix 柱是标准色谱中使用的预填充硅胶柱。最终的化合物和中间体使用 MDL ISIS Draw 应用软件中的 AutoNom2000 部件命名。

[0130] 本发明还针对治疗有效量的式 I 的化合物与用于治疗炎症性或过敏性病症和疾病的其他药物或活性剂的组合或联合给药。在一个实施方案中, 本发明涉及一种用于治疗和 / 或预防这种病症或疾病的方法, 所述方法包括将治疗有效量的式 I 的化合物和另一种药物或活性剂 (如另一种抗炎或抗过敏药物或试剂) 同时地、相继地或分别地给药至人类或动物。这些其他的药物或活性剂可以具有相同的、相似的或完全不同的作用模式。合适的其他药物或活性剂可以包括, 但是不限于: β 2- 肾上腺素能激动剂如沙丁胺醇 (albuterol) 或沙美特罗 (salmeterol); 皮质类固醇如地塞米松 (dexamethasone) 或氟替卡松 (fluticasone); 抗组胺药如氯雷他定 (loratidine); 白三烯拮抗剂如孟鲁司特 (montelukast) 或扎鲁司特 (zafirlukast); 抗 IgE 抗体治疗药如奥马佐单抗 (omalizumab); 抗感染药如夫西地酸 (fusidic acid) (特别是用于治疗特应性皮炎); 抗真菌如克霉唑 (clotrimazole) (特别是用于治疗特应性皮炎); 免疫抑制剂如他罗利姆 (tacrolimus) 和吡美莫司 (pimecrolimus); 作用于其他受体如 DP 拮抗剂的 PGD₂ 的其他拮抗剂; 4 型磷酸二酯酶的抑制剂如西洛司特 (cilomilast); 调节细胞因子产生的药物如 TNF- α 转化酶 (TACE) 的抑制剂; 调节 Th2 细胞因子 IL-4 和 IL-5 的活性的药物如阻断单克隆抗体和可溶受体; PPAR- γ 激动剂如罗格列酮 (rosiglitazone); 和 5- 脂肪氧合酶抑制剂如齐留通 (zileuton)。

[0131] 本发明的化合物可以通过任何传统的方式制备。用于合成这些化合物的合适的方法提供在实施例 1 中。通常, 式 I 的化合物可以根据下面所示方案制备。例如, 本发明的特定化合物可以使用方案 1 中列出的方案制备。

[0132] 方案 1

[0133]



[0134] 式 10 的本发明的化合物可以根据方案 1 制备。用 4- 溴苯基硼酸 1 开始, 偶联反应可以用叠氮化钠在乙酸铜的存在下进行以在质子溶剂如甲醇中在室温提供叠氮化物中间体 2。当反应混合物开放至大气时可以获得最好的产率。该叠氮化物中间体在冷条件下稳定, 但理想的是应当将其立即在环加成反应中使用。

[0135] 叠氮化物中间体 2 与炔酯 3 之间关键的 3+2 环加成反应可以在甲苯中在较高的温度, 优选在 150°C 进行 2-15h。反应时间可以依赖于炔酯的 R_1 基团, 其可以为氢、低级烷基, 优选甲基和乙基。两种三唑区域异构体 4 和 5 的比例依赖于 R_1 基团, 并且当 R_1 基团是甲基或乙基时, 该比例通常应当为 1 : 1.2, 并且当 R_1 是氢时, 该比例应当为 1 : 4, 错误的同分异构体可能支配性地形成。如果反应在铜催化剂的存在下进行可以降低反应温度。

[0136] 两种区域异构体可以分别转化为最终的化合物。酯 4 至相应的酸 6 的水解可以在碱如氢氧化锂的存在下在惰性溶剂如四氢呋喃和水中在室温在数小时内完成。

[0137] 酸 6 可以使用 Curtius 重排条件如二苯基磷酰基叠氮化物 (DPPA) 和碱如三乙胺在醇 R_3OH 的存在下在惰性溶剂如甲苯中在 $65-80^\circ\text{C}$ 在数小时内转化为氨基甲酸酯 7。 R_3 可以是简单的烷基、环烷基或芳基 - 取代的烷基。

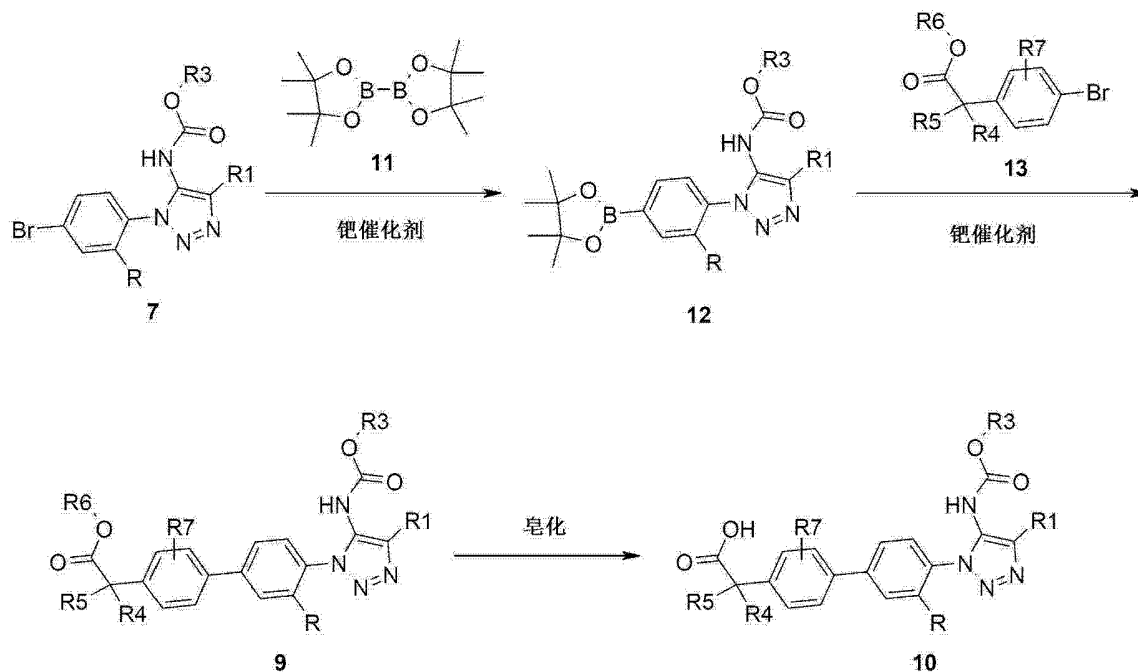
[0138] 化合物 7 与 8 之间的交联反应提供二芳基中间体 9, 这可以在钯催化剂如乙酸钯 (II) 和膦配体如 2- 二环己基膦基 -2', 6'- 二甲氧基联苯 (S-Phos) 的存在下在碱如磷酸三钾的存在下在溶剂例如甲苯和水的混合物中完成。该反应可以在更高的温度, 优选在

100-105℃进行数小时。

[0139] 本发明的最终的化合物 10 可以通过酯 9 在碱如氢氧化锂或氢氧化钠的存在下在惰性溶剂如四氢呋喃、乙醇和水中在室温在数小时内水解获得。

[0140] 方案 2

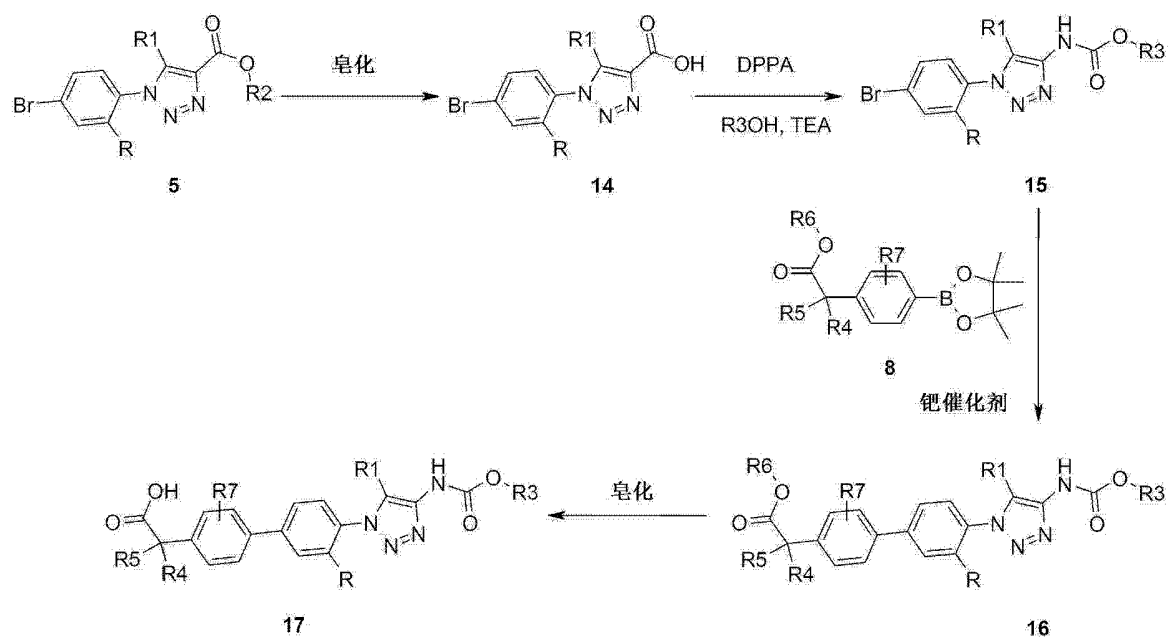
[0141]



[0142] 备选地,如方案 2 中所述,溴中间体 7 可以使用双频哪醇二硼 11 在钯催化剂如 1, 1'-双(二苯基膦基)二茂铁二氯化钯(II)的存在下在合适的碱如乙酸钾的存在下转化为相应的频哪醇硼化物中间体 12。用于该反应的优选的溶剂可以是 1,4-二噁烷在 80℃持续数小时。频哪醇合硼烷中间体 12 之后与溴中间体如 13 在钯介导的偶联条件下经历交叉偶联反应以提供化合物 9,其之后在用常规的水解条件处理之后可以给出最终的化合物 10。

[0143] 方案 3

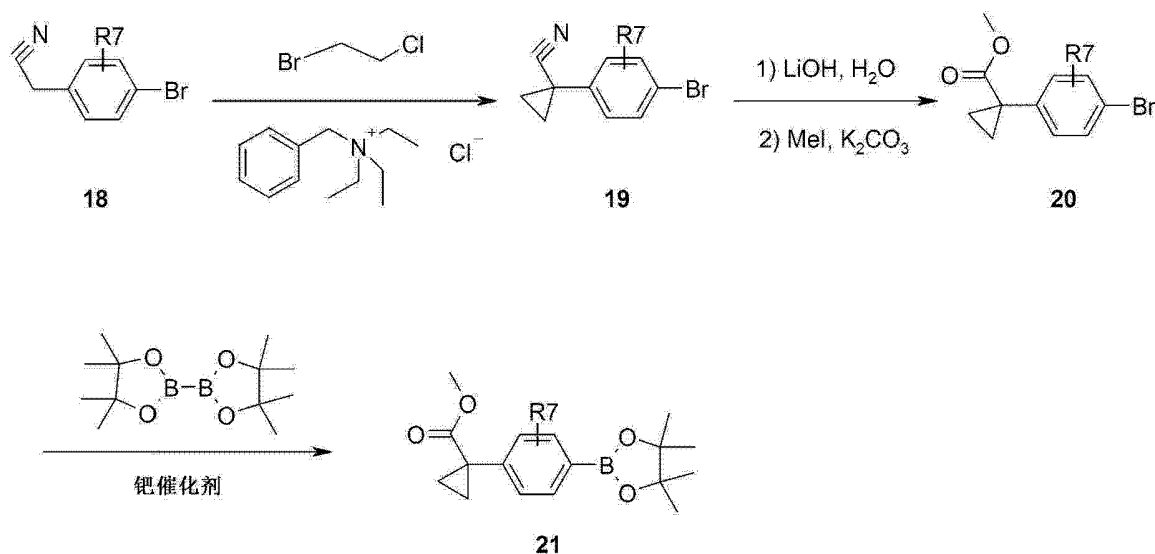
[0144]



[0145] 方案3描述了在如上所述相同的反应条件之后其他区域异构体5至相应的最终的化合物17的转化。

[0146] 方案4

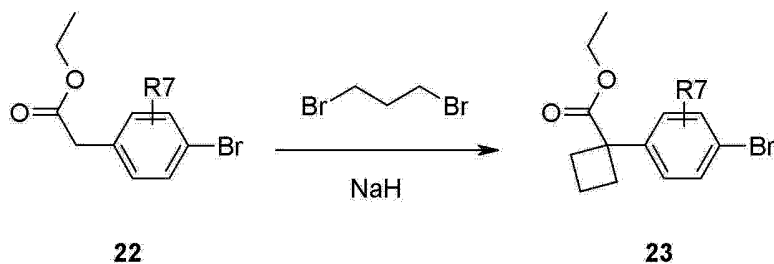
[0147]



[0148] 方案4描述了不可商购的取代的芳基硼化物中间体的合成。4-溴苯基乙腈18可以通过用1-溴-2-氯乙烷和氢氧化钠在相转移催化剂如苄基三乙基氯化铵的存在下在50℃处理数小时转化为化合物19。之后,可以将19的氰基水解为相应的酸,其可以用甲基碘在碱如碳酸钾的存在下处理以获得化合物20。溴中间体20可以与双频哪醇合二硼使用钯介导的反应条件反应以形成硼化物中间体21。

[0149] 方案5

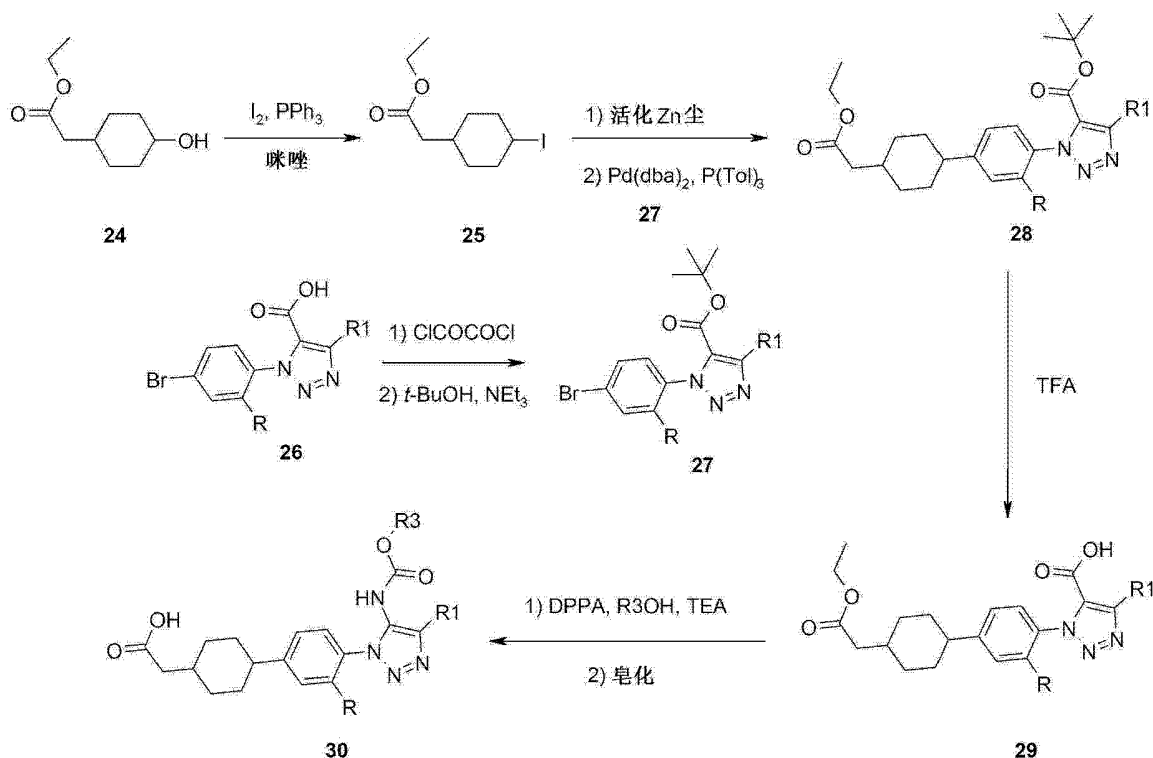
[0150]



[0151] 如方案 5 中所示,1-(4-溴苯基)环丁烷或环戊烷甲酸酯中间体如 23 可以由 2-(4-溴苯基)乙酸乙酯 22 和 1,3-二溴丙烷或 1,4-二溴丁烷在强碱如氢化钠的存在下在质子溶剂如 DMF 中在 0℃至室温在数小时内制备。

[0152] 方案 6

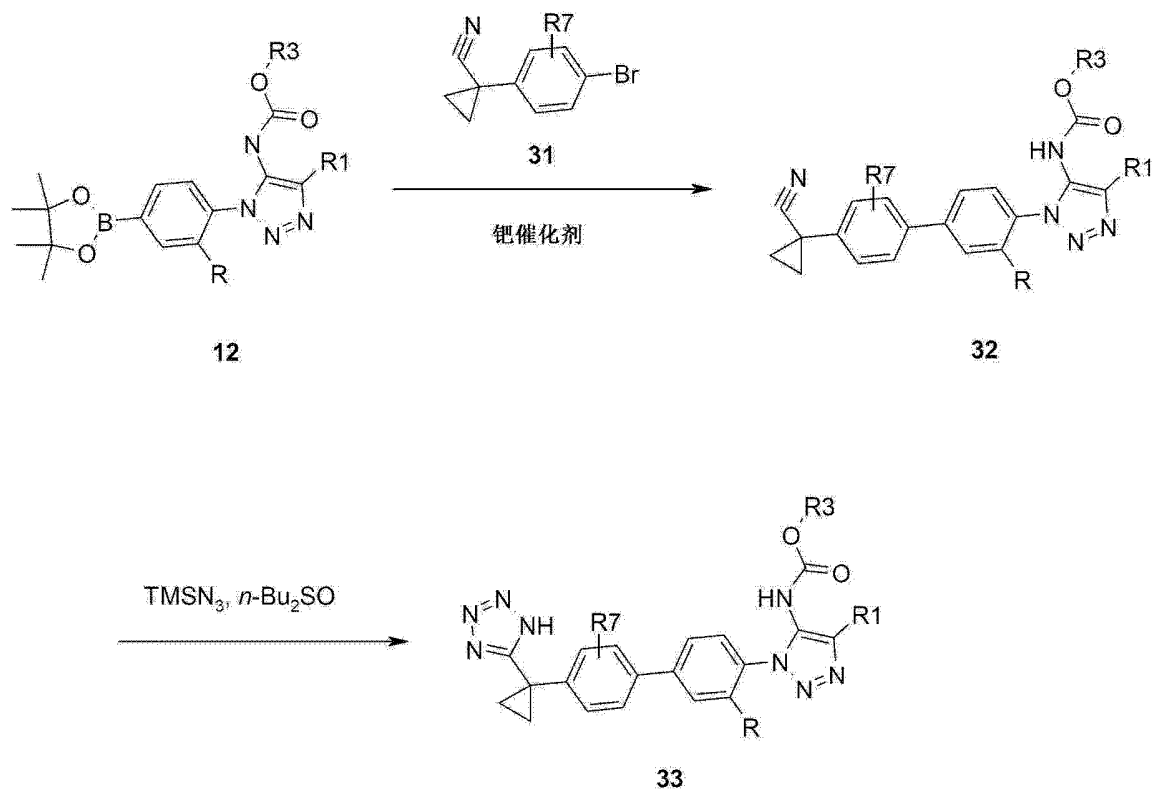
[0153]



[0154] 式 30 的本发明的化合物可以根据方案 6 制备。所需的 2-(4-碘环己基)乙酸乙酯 25 可以由 2-(4-羟基环己基)乙酸乙酯 24 使用碘和三苯基膦在咪唑的存在下在二氯甲烷中制备。之后,2-(4-碘环己基)乙酸乙酯 25 可以与活性锌尘在无水 THF 中在 60℃反应数小时以给出锌中间体,其可以与溴中间体 27 在 $\text{Pd}(\text{dba})_3$ 和三邻甲苯基膦的存在下在无水 THF 中在 60℃经历交叉偶联反应以提供偶联产物 28。28 的叔丁酯可以在 TFA 的存在下水解为酸 29。之后,Curtius 重排和皂化条件描述在方案 1 中以获得化合物 30。

[0155] 方案 7

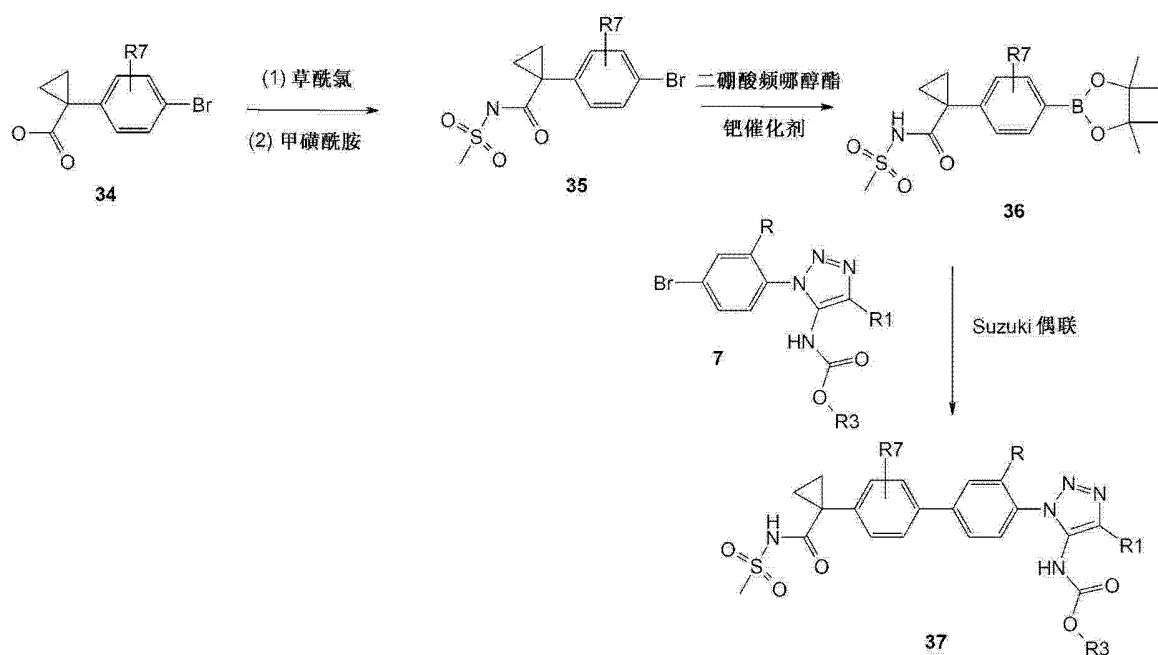
[0156]



[0157] 式 33 的本发明的化合物可以根据方案 7 制备。频哪醇硼化物中间体 12 可以与溴中间体 31 在钯催化剂如乙酸钯 (II) 和膦配体如 2-二环己基膦基-2',6'-二甲氧基联苯 (S-phos) 的存在下在混合溶剂体系如甲苯和水中在 105℃ 反应以给出化合物 32。化合物 32 可以使用叠氮基三甲基硅烷和二-正丁基氧化锡在甲苯中在 100℃ 在数小时内转化为所感兴趣的 33 的化合物。

[0158] 方案 8

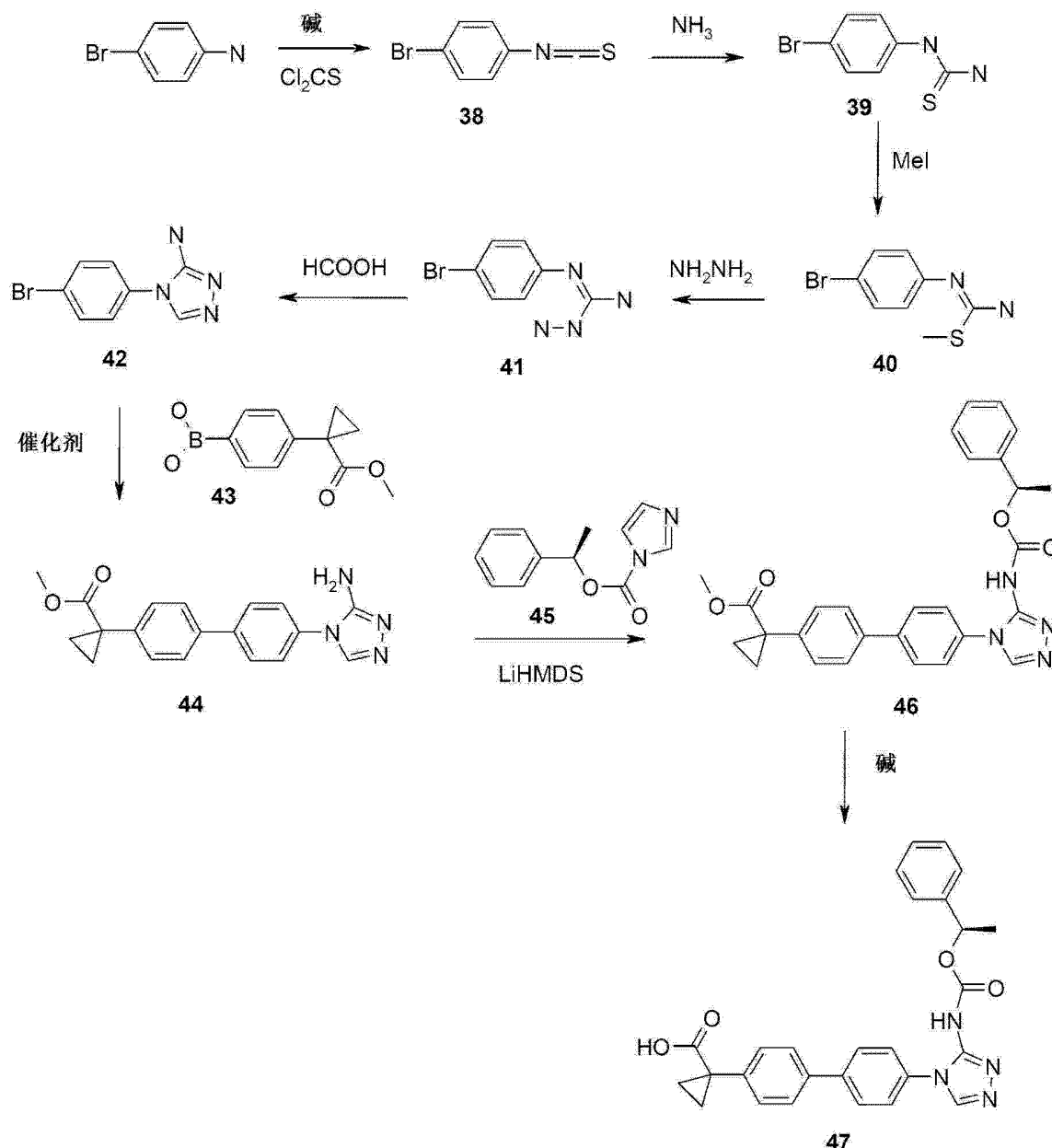
[0159]



[0160] 方案 8 描述了酰基甲基磺酰胺和它们所得到的最终的化合物的合成。酸 34 可以转化为酰氯,其可以与甲磺酰胺在碱,如氢氧化钠的存在下反应以给出 N- 酰基磺酰胺 35。芳基硼化物中间体 36 可以由芳基溴 35 制备。最终的与化合物 7 的交叉偶联步骤可以在钯催化剂,如 $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ 、DPPF 配体和碱如碳酸钠的存在下在溶剂,例如 DMF 和水的混合物中完成。该反应可以在更高的温度,优选在 85°C 进行数小时以产生最终的化合物 37。

[0161] 方案 9

[0162]



[0163] N-芳基-1,2,4-三唑衍生物 47 的化合物可以根据方案 9 制备。4-溴苯胺可以与二氯硫化碳在碱性条件下反应以提供异硫氰酸酯 38,其可以通过与氨反应转化为硫脲 39。硫脲的甲基化可以在甲基碘的存在下实现以提供中间体 40,其可以通过与肼反应转化为 1N-氨基-2N-芳基胍 41。氨基胍 41 用甲酸的处理可以导致关键的 4N-芳基-4H-3-氨基-1,2,3-三唑 42。在 Suzuki 偶联条件下,42 可以在钯催化剂的存在下与硼酸 43 偶联

以提供化合物 44。化合物 44 可以首先通过双(六甲基二甲硅烷基)氨基化锂脱质子化,并且之后与咪唑氨基甲酸酯 45 反应以提供关键的氨基甲酸酯 46。咪唑氨基甲酸酯 45 可以由相应的苯基乙醇和羰基二咪唑(CDI)制备。在碱性条件下,46 的水解可以导致 4N-芳基-4H-1,2,3-三唑衍生物 47。该化学类中的其他类似物可以使用方案 9 中所述的相同的方法制备。

实施例

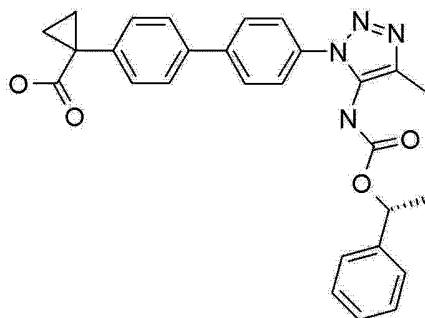
[0164] 虽然本文描写并叙述了某些示例性实施方案,本发明的化合物可以使用合适的原材料根据本文一般性描述的方法和/或通过本领域技术人员可得的方法制备。

[0165] 缩写的定义: DPPA:二苯基磷酰基叠氮; DPPF:1,1'-双(二苯基膦基)二茂铁; S-Phos:二环己基(2',6'-二甲氧基[1,1'-联苯]-2-基)-膦; DBA:二亚苄基丙酮; DCM:二氯甲烷; DMF:二甲基甲酰胺; EA:乙酸乙酯; ACN:乙腈; LiHMDS:双(三甲基甲硅烷基)氨基化锂; TEA:三乙胺; THF:四氢呋喃; TLC:薄层色谱

[0166] 实施例 1

[0167] 1-{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0168]



[0169] 步骤 1:1-叠氮基-4-溴-苯

[0170] 在 350mL 反应小瓶中,将 4-溴-苯基硼酸(21.17g,105mmol)、叠氮化钠(10.3g,158mmol)和乙酸铜(II)(1.91g,10.5mmol)与 MeOH(200mL)合并以给出棕色悬浮液。将反应物在室温搅拌过夜,对大气开放,23 小时。将反应物浓缩,用乙醚/己烷(380/20mL,第一有机层)稀释并用水(100mL,第一水性层)和饱和 NH₄Cl/浓 NH₄OH(200/300mL,第二水性层)洗涤。向第一水性层加入饱和 NH₄Cl 和浓 NH₄OH(60/40mL)并将所得到的有机层分离,用第二水性层洗涤,并且与第一有机层合并。将第一水性层用醚(300mL)第二次萃取并将有机层用第二水性层洗涤。将有机层合并,在 MgSO₄上干燥并储存在冰箱中过夜。将粗材料升温至室温,过滤、浓缩至红色/黄色油,溶解在己烷(20mL)中并通过硅胶(120g Redisep)提纯并用己烷洗脱,获得 1-叠氮基-4-溴-苯(19.5g,93.4%产率),为黄色油。LC/MS: C₆H₄BrN₃(m/e) 计算值 197/199,实测值 170/172(M-N₂+H, ES⁺)。

[0171] 步骤 2:3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸甲酯

[0172] 在 350mL 反应小瓶中,将 1-叠氮基-4-溴-苯(10g,50.5mmol)和丁-2-炔酸甲酯(5.45g,5.56mL,55.5mmol)与甲苯(106mL)合并以给出黄色悬浮液。将小瓶密封并在油浴中在 150℃加热 4.5h。冷却并储存在室温 6 天。将反应物过滤并将固体用甲苯

和 EtOAc (3x15mL) 洗涤。将滤液浓缩, 溶解在最少 DCM 中, 并且通过快速色谱 (硅胶, 己烷中 0% 至 50% EtOAc) 提纯。将合适的级分合并、浓缩, 并且由 DCM/ 己烷干燥以给出 3-(4- 溴 - 苯基) -5- 甲基 -3H-[1,2,3] 三唑 -4- 甲酸甲酯 (4.5g, 30.1% 产率), 为浅棕色固体。LC/MS : $C_{11}H_{10}BrN_3O_2$ (m/e) 计算值 295/297, 实测值 296/298 (M+H, ES⁺)。

[0173] 步骤 3 : 3-(4- 溴 - 苯基) -5- 甲基 -3H-[1,2,3] 三唑 -4- 甲酸

[0174] 向含有溶解在 THF (200mL) 中的 3-(4- 溴 - 苯基) -5- 甲基 -3H-[1,2,3] 三唑 -4- 甲酸甲酯 (4.5g, 11.5mmol) (棕色溶液) 的 1L 圆底烧瓶加入大部分溶解在水 (75mL, 加热) 中的 LiOH (2.77g, 115mmol)。将溶液在室温搅拌 16h。将反应物浓缩, 稀释在水中 (总体积, 400mL), 用乙醚 (2x100mL) 萃取。将水性层用 1N HCl 酸化, 并将所得到的沉淀物过滤, 用水和己烷洗涤, 并且在室内真空 (house vacuum) 中干燥。将白色固体部分地溶解在 DCM 和 ACN 中, 转移至圆底烧瓶, 并且干燥以提供 3-(4- 溴 - 苯基) -5- 甲基 -3H-[1,2,3] 三唑 -4- 甲酸 (3.6g, 110% 产率), 为灰白色固体。LC/MS : $C_{10}H_8N_3O_2$ (m/e) 计算值 281/283, 实测值 281/284 (M+H, ES⁺)。

[0175] 步骤 4 : [3-(4- 溴 - 苯基) -5- 甲基 -3H-[1,2,3] 三唑 -4- 基] - 氨基甲酸 (R) -1- 苯基 - 乙酯

[0176] 在 350mL 反应小瓶中, 将 3-(4- 溴 - 苯基) -5- 甲基 -3H-[1,2,3] 三唑 -4- 甲酸 (3.6g, 12.8mmol)、(R) -1- 苯基乙醇 (3.04g, 3mL, 24.9mmol) 和三乙胺 (3.27g, 4.5mL, 32.3mmol) 与甲苯 (100mL) 合并以给出黄色溶液, 并且向其加入叠氮化磷酸二苯酯 (8.94g, 7mL, 32.5mmol)。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 65°C 加热 2h, 并且冷却至室温过夜。将反应物浓缩, 为黄色粘性油, 用 DCM 稀释, 并且通过快速色谱 (硅胶, 己烷中 0-50% EtOAc) 提纯。将合适的级分合并, 浓缩, 由 DCM/ 己烷干燥, 以获得 [3-(4- 溴 - 苯基) -5- 甲基 -3H-[1,2,3] 三唑 -4- 基] - 氨基甲酸 (R) -1- 苯基 - 乙酯 (4.07g, 79.5% 产率), 为白色固体。LC/MS : $C_{18}H_{17}BrN_4O_2$ (m/e) 计算值 400/402, 实测值 401/403 (M+H, ES⁺)。

[0177] 步骤 5 : 1-(4- 溴 - 苯基) - 环丙烷甲腈

[0178] 在 1L 圆底烧瓶中, 将 2-(4- 溴苯基) 乙腈 (59.57g, 304mmol) (在 60°C 半熔化以转移)、1- 溴 -2- 氯乙烷 (65.4g, 456mmol) 和氯化 N- 苄基 -N, N- 三乙基乙胺鎓氯化物 (5.54g, 24.3mmol) 合并, 在油浴中在 50°C 加热以给出浅棕色溶液。向其滴加刚制备的 NaOH (72.9g, 1.82mol) 在 72mL 的水中的溶液 (未完全溶解)。将 NaOH 烧瓶和加液漏斗用水冲洗并且将洗涤物一样加入。将该反应物在油浴中在 50°C 在具有冷凝器的情况下搅拌过夜, 22 小时。将反应物冷却, 用水稀释 (500mL), 用 DCM (2x300mL) 萃取。将有机层用水 (2x300mL), 1N HCl (2x300mL) 和盐水 (300mL) 洗涤, 在 $MgSO_4$ 上干燥、过滤、浓缩, 并且干燥产生 1-(4- 溴 - 苯基) 环丙烷甲腈 (66.8g, 99% 产率), 为黄色固体。LC/MS : $C_{10}H_8BrN$ (m/e) 计算值 221/223, 实测值 222/224 (M+H, ES⁺), 263/265 (M+ACN+H, ES⁺)。

[0179] 步骤 6 : 1-(4- 溴 - 苯基) - 环丙烷甲酸

[0180] 在 2L 圆底烧瓶中, 将 1-(4- 溴 - 苯基) 环丙烷甲腈 (66.8g, 301mmol) 与部分地溶解在水 (1.1L) 中的 LiOH (144g, 6.02mol) 合并以给出红色悬浮液, 并且在油浴中在加热回流下搅拌 7 小时。将反应物冷却至室温经过周末。将灰白色 / 灰色混合物用水 (~ 1L) 稀释并用 EtOAc (2x400mL) 萃取, 保持固体在水性层中。将水性层用浓 HCl 酸化至 pH ~ 3 并且将所得到的沉淀物过滤并用己烷 (4x 总计 0.9L) 洗涤, 产生 1-(4- 溴 - 苯基) 环丙烷

甲酸 (73.3g, 101% 产率), 为灰白色固体。LC/MS: $C_{10}H_9BrO_2$ (m/e) 计算值 240/242, 实测值 241/243 (M+H, ES⁺), 239/241 (M-H, ES⁻)。

[0181] 步骤 7: 1-(4-溴-苯基)-环丙烷甲酸甲酯

[0182] 在 2L 圆底烧瓶中, 将 1-(4-溴-苯基) 环丙烷甲酸 (73.6g, 305mmol) 与 DMF (0.5L) 合并以给出浅棕色 / 红色溶液, 并且向该磁力搅拌下的溶液加入 K_2CO_3 (127g, 916mmol)。在约 10 分钟之后, 形成白色沉淀物并且溶液变得不能搅拌。将该物质转移至 3L 三颈烧瓶中, 用 DMF (1L) 稀释并且磁力搅拌。在 1h 内向其滴入溶解在 DMF (0.1L) 中的甲基碘 (217g, 95.4mL, 1.53mol)。将白色悬浮物在室温搅拌过夜。将反应分为两份, 并且将每一份部分地浓缩 (移除 ~ 300mL 体积), 用水 (1L) 稀释, 并且用 EtOAc (2x500mL) 萃取。将每个 EtOAc 层用水 (500mL) 和盐水 (250mL) 洗涤, 合并, 在 $MgSO_4$ 上干燥, 过滤, 浓缩, (与另一半合并), 浓缩产生 1-(4-溴苯基)-环丙烷甲酸甲酯 (73.3g, 94.1% 产率), 为浅棕色油。LC/MS: $C_{11}H_{11}BrO_2$ (m/e) 计算值 254/256, 实测值 255/257 (M+H, ES⁺)。

[0183] 步骤 8: 1-[4-(4,4,5,5-四甲基-[1,3,2] 二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯

[0184] 在 350mL 反应小瓶中, 将 1-(4-溴苯基)-环丙烷甲酸甲酯 (20g, 78.4mmol), BISPIN (23.9g, 94.1mmol) 和乙酸钾 (15.4g, 157mmol) 与 1,4-二噁烷 (150mL) 合并以给出浅棕色悬浮液。将混合物用氮吹扫 5 分钟, 加入 $PdCl_2(dppf)$ (3.2g, 3.92mmol) 并将小瓶密封并在油浴中在 80℃ 加热 4 小时。将反应物通过硅藻土 (冲洗 / DCM) 过滤、浓缩、乙醚 (500mL) 稀释, 用水 (2x500mL) 和盐水 (250mL) 洗涤。水性层具有黑色固体, 并且将其过滤并将固体用乙醚洗涤。将该滤液用乙醚 (500mL) 萃取并用相同的盐水洗涤。将乙醚层合并, 在 $MgSO_4$ 上干燥, 过滤, 并且浓缩为红色油。将粗材料通过快速色谱 (硅胶, 己烷中 0% 至 20% EtOAc) 提纯。将合适的级分合并、浓缩、由 DCM 干燥以提供 1-[4-(4,4,5,5-四甲基-[1,3,2] 二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯 (20.83g, 87.9% 产率), 为白色至白色 / 非常淡的黄色固体。LC/MS: $C_{17}H_{23}BO_4$ (m/e) 计算值 302, 实测值 303 (M+H, ES⁺)。

[0185] 步骤 9: 1-{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯

[0186] 在 350mL 小瓶中, 将 1-[4-(4,4,5,5-四甲基-[1,3,2] 二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯 (2.49g, 8.22mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3] 三唑-4-基]-氨基甲酸 (R)-1-苯基-乙酯 (3.0g, 7.48mmol)、2-二环己膦基-2',6'-二甲氧基联苯 (SPhos) (921mg, 2.24mmol) 和乙酸钯 (II) (252mg, 1.12mmol) 与甲苯 (120mL) (之前用氮吹扫 20 分钟) 合并以给出浅黄色溶液。向其加入溶解在水 (30.0mL) 中的磷酸三钾 (4.76g, 22.4mmol) (之前用氮吹扫 20 分钟)。将小瓶的气氛用氮替代, 密封, 在油浴中在 100℃ 加热 4h, 并且冷却至室温过夜。将反应物用 EtOAc (50mL) 和水 (100mL) 稀释并过滤和用水 (30mL) 和 EtOAc (50mL) 冲洗。将滤液通过加入盐水 (50mL) 分离并且将有机层用盐水 (150mL) 洗涤。将水性层用 EtOAc (2x150mL) 萃取, 并且将每个有机层用相同的盐水洗涤。将有机层合并, 在 $MgSO_4$ 上干燥、过滤、浓缩、溶解在最少 DCM 中并通过快速色谱 (硅胶, 己烷中 0% 至 50% EtOAc) 提纯。将合适的级分合并、浓缩, 并且由 DCM/ 己烷干燥, 以获得 1-{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (2.65g, 71.4% 产率), 为白色固体。LC/MS: $C_{29}H_{28}N_4O_4$ (m/e) 计

算值 496, 实测值 497 (M+H, ES⁺)。

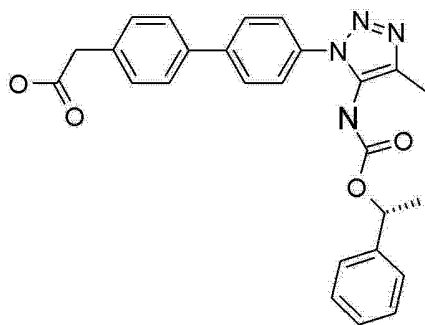
[0187] 步骤 10 : 1-{4' -[4- 甲基 -5-((R)-1- 苯基 - 乙氧基羰基氨基) -[1,2,3] 三唑 -1- 基] - 联苯 -4- 基} - 环丙烷甲酸

[0188] 在 1L 圆底烧瓶中, 将 1-{4' -[4- 甲基 -5-((R)-1- 苯基 - 乙氧基羰基氨基) -[1,2,3] 三唑 -1- 基] - 联苯 -4- 基} - 环丙烷甲酸甲酯 (2.65g, 5.34mmol) 与 THF (50mL) 合并以给出黄色溶液。向其滴入溶解在水 (12.5mL, 加热以部分地溶解) 中的 LiOH (1.28g, 53.4mmol)。将反应烧瓶密封并在油浴中在 60°C 加热 5h。将反应物冷却至室温过夜。将反应物用水稀释 (100mL)、浓缩、用更多水稀释 (500mL) 并用 1N HCl 酸化。将所得到的沉淀物过滤, 用水和己烷洗涤并在室内真空下并在干燥器中干燥。将粗产物 (2.8g), 为白色固体, 由热 ACN 研磨并且由 EtOAc, EtOH/ 水, 以及 IPA/ 水再结晶。这些尝试提纯是不成功的并且将所得到的固体 (2.0g) 通过快速反相色谱 (C18Silicycle 120g, 60mL 分钟 20-100% ACN/H₂O 20 分钟) 提纯。将合适的级分合并、浓缩、用水稀释, 并且将所得到的沉淀物过滤并用水和己烷洗涤产生 1.65g 的白色固体。将固体由 ACN 结晶以给出 1-{4' -[4- 甲基 -5-((R)-1- 苯基 - 乙氧基羰基氨基) -[1,2,3] 三唑 -1- 基] - 联苯 -4- 基} - 环丙烷甲酸 (1.48g, 57.5% 产率), 为白色固体。LC/MS : C₂₈H₂₆N₄O₄ (m/e) 计算值 482, 实测值 483 (M+H, ES⁺)。¹H NMR (DMSO-d₆) δ : 12.40 (br. s., 1H), 9.69 (br. s., 1H), 7.83 (d, J = 7.0Hz, 2H), 7.67 (d, J = 8.3Hz, 2H), 7.58 (d, J = 8.0Hz, 2H), 7.47 (d, J = 8.5Hz, 2H), 7.00-7.42 (m, 5H), 5.71 (br. s., 1H), 2.18 (s, 3H), 1.29-1.69 (m, 5H), 1.13-1.26 (m, 2H)。

[0189] 实施例 2

[0190] {4' -[4- 甲基 -5-((R)-1- 苯基 - 乙氧基羰基氨基) -[1,2,3] 三唑 -1- 基] - 联苯 -4- 基} - 乙酸

[0191]



[0192] 步骤 1 : [4-(4,4,5,5- 四甲基 -[1,3,2] 二氧杂硼杂环戊烷 -2- 基) - 苯基] - 乙酸乙酯

[0193] 在 350mL 反应小瓶中, 将 2-(4- 溴苯基) 乙酸乙酯 (25g, 103mmol)、BISPIN (31.3g, 123mmol) 和乙酸钾 (20.2g, 206mmol) 与 1,4-二噁烷 (190mL) 合并以给出白色悬浮物。将混合物用氮吹扫 5 分钟, 加入 PdCl₂(dppf) (4.2g, 5.14mmol) 并将小瓶密封并在油浴中在 80°C 加热 3h。将反应物过滤, 用乙醚冲洗, 浓缩, 用水稀释 (500mL) 并用乙醚 (2x300mL) 萃取, 并且将有机层用盐水 (250mL) 洗涤。将乙醚层合并, 在 MgSO₄ 上干燥, 过滤, 并且浓缩, 为红色油。将粗材料通过快速色谱 (硅胶, 己烷中 0% 至 20% EtOAc) 提纯。将合适的级分合并, 浓缩, 由 DCM 干燥以获得 [4-(4,4,5,5- 四甲基 -[1,3,2] 二氧杂硼杂环戊烷 -2- 基) - 苯基] - 乙酸乙酯 (25.14g, 84.2% 产率), 为白色固体 / 油。LC/MS : C₁₆H₂₃BO₄ (m/e) 计算值 290,

实测值 291 (M+H, ES⁺)。

[0194] 步骤 2: {4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯

[0195] 在 20mL 小瓶中, 将 [4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-乙酸乙酯 (79.5mg, 0.274mmol)、[1-(4-溴-苯基)-5-甲基-1H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-1-苯基-乙酯 (100mg, 0.249mmol)、磷酸三钾 (159mg, 0.748mmol)、2-二环己膦基-2',6'-二甲氧基联苯 (SPhos) (30.7mg, 0.0748mmol) 和乙酸钪 (II) (8.4mg, 0.037mmol) 与甲苯 (2mL) 和水 (0.5mL) 合并 (之前用氮吹扫 20 分钟) 以给出浅黄色悬浮液。将小瓶的气氛用氮替代, 密封, 在干燥区中在 100℃ 加热 6h, 并且冷却至室温过夜。将反应物用 EtOAc (50mL) 稀释并用水 (50mL) 和盐水洗涤。将水性层用 EtOAc (50mL) 萃取。将有机层合并, 在 MgSO₄ 上干燥, 过滤, 浓缩, 溶解在最少 DCM 中并通过快速色谱提纯 (硅胶, 己烷中 0% 至 60% EtOAc)。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥以获得 {4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯 (40mg, 0.0826mmol, 33.1% 产率), 为无色蜡状固体。LC/MS: C₂₈H₂₈N₄O₄ (m/e) 计算值 484, 实测值 485 (M+H, ES⁺)。

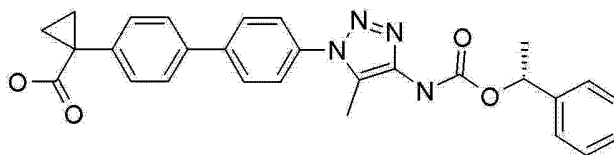
[0196] 步骤 3: {4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸

[0197] 在 200mL 圆底烧瓶中, 将 {4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯 (34mg, 0.0702mmol) 与 THF (2mL) 合并以给出黄色溶液。向其滴入溶解在水 (0.5mL, 加热以部分地溶解) 中的 LiOH (16.8mg, 0.702mmol)。将反应烧瓶密封并在油浴中在 60℃ 加热 11h。将反应物冷却至室温, 用水稀释, 并且用 1N HCl 酸化。将所得到的沉淀物过滤, 用水以及己烷洗涤, 并且在室内真空中干燥, 产生 1-{4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸 (40mg, 62.4% 产率), 为灰白色固体。LC/MS: C₂₆H₂₄N₄O₄ (me) 计算值 456, 实测值 457 (M+H, ES⁺)。¹H NMR (DMSO-d₆) δ: 12.42 (br. s., 1H), 9.19-9.80 (m, 1H), 7.83 (d, J = 6.5Hz, 2H), 7.69 (d, J = 8.0Hz, 2H), 7.57 (d, J = 7.3Hz, 2H), 7.08-7.47 (m, 7H), 5.69 (br. s., 1H), 3.65 (s, 2H), 2.16 (s, 3H), 1.13-1.64 (m, 3H)

[0198] 实施例 3

[0199] 1-{4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0200]



[0201] 步骤 1: 1-(4-溴-苯基)-5-甲基-1H-[1,2,3]三唑-4-甲酸甲酯

[0202] 在 20mL 反应小瓶中, 将 1-叠氮基-4-溴-苯 (1.647g, 8.32mmol) 和丁-2-炔酸甲酯 (0.816g, 0.8mL, 8.32mmol) 与甲苯 (15mL) 合并以给出黄色溶液。将小瓶的气氛用氮吹扫, 将小瓶密封, 并且在 150℃ 微波 1h。将反应中所得到的固体过滤, 并且用甲苯洗涤产

生 1-(4-溴-苯基)-5-甲基-1H-[1,2,3] 三唑-4-甲酸甲酯 (0.33g, 1.11mmol, 13.3% 产率)。将滤液浓缩, 转移至带甲苯 (10mL) 的反应小瓶, 加入丁-2-炔酸甲酯 (816mg, 0.8mL, 8.32mmol), 并且与上面相同地进行反应。将具有最小量固体的反应物负载在硅胶上并通过快速色谱提纯 (硅胶, 己烷中 0% 至 40% EtOAc)。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 1-(4-溴-苯基)-5-甲基-1H-[1,2,3] 三唑-4-甲酸甲酯 (0.87g, 35.3% 产率), 为浅棕色固体。将来自反应的沉淀物与从柱分离的产物合并。LC/MS: $C_{11}H_{10}BrN_3O_2$ (m/e) 计算值 295/297, 实测值 296/298 (M+H, ES⁺)。

[0203] 步骤 2: 1-(4-溴-苯基)-5-甲基-1H-[1,2,3] 三唑-4-甲酸

[0204] 向含有溶解在 THF (30mL) (棕色溶液) 中的 1-(4-溴-苯基)-5-甲基-1H-[1,2,3] 三唑-4-甲酸甲酯 (0.87g, 2.9mmol) 的 500mL 圆底烧瓶中加入大部分溶解在水 (7mL, 加热) 中的 LiOH (0.71g, 30mmol)。将溶液在室温搅拌过夜。将反应物浓缩, 稀释在水 (总体积, 100mL) 中, 并且用乙醚 (2x100mL) 萃取。将水性层用 1N HCl 酸化。将所得到的沉淀物过滤, 用水和己烷洗涤, 并且在室内真空中并且冻干干燥以获得 1-(4-溴-苯基)-5-甲基-1H-[1,2,3] 三唑-4-甲酸 (3.6g, 110% 产率), 为棕色固体。LC/MS: $C_{10}H_8N_3O_2$ (m/e) 计算值 281/283, 实测值 281/284 (M+H, ES⁺)。

[0205] 步骤 3: [1-(4-溴-苯基)-5-甲基-1H-[1,2,3] 三唑-4-基]-氨基甲酸 (R)-1-苯基-乙酯

[0206] 在 20mL 反应小瓶中, 将 1-(4-溴-苯基)-5-甲基-1H-[1,2,3] 三唑-4-甲酸 (0.67g, 2.38mmol)、(R)-1-苯基乙醇 (0.29g, 0.29mL, 2.4mmol) 和三乙胺 (0.24g, 0.33mL, 2.4mmol) 与甲苯 (100mL) 合并以给出黄色溶液, 并且向其加入二苯基磷酰基叠氮化物 (0.65g, 0.5mL, 2.4mmol)。将小瓶的气氛用氮吹扫, 密封, 在干燥区中在 80°C 加热 4h, 并且冷却至室温过夜。将反应物用 EtOAc (100mL) 稀释并用水 (100mL) 和盐水 (50mL) 洗涤。将水性层用 EtOAc (100mL) 萃取。将有机层合并, 在 $MgSO_4$ 上干燥, 过滤, 浓缩, 溶解在最少 DCM 中, 并且通过快速色谱 (硅胶, 己烷中 0% 至 25% EtOAc) 提纯。将合适的级分合并, 浓缩, 由 DCM/己烷干燥, 以给出 [1-(4-溴-苯基)-5-甲基-1H-[1,2,3] 三唑-4-基]-氨基甲酸 (R)-1-苯基-乙酯 (0.507g, 53.2% 产率), 为灰白色固体。LC/MS: $C_{18}H_{17}BrN_4O_2$ (m/e) 计算值 400/402, 实测值 401/403 (M+H, ES⁺)。

[0207] 步骤 4: 1-{4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯

[0208] 在 20mL 小瓶中, 将 1-[4-(4,4,5,5-四甲基-[1,3,2] 二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯 (75.3mg, 0.249mmol)、[1-(4-溴-苯基)-5-甲基-1H-[1,2,3] 三唑-4-基]-氨基甲酸 (R)-1-苯基-乙酯 (100mg, 0.249mmol)、磷酸三钾 (159mg, 0.748mmol), 2-二环己膦基-2',6'-二甲氧基联苯 (SPhos) (30.7mg, 0.0748mmol) 和 $Pd(OAc)_2$ (8.4mg, 0.037mmol) 与甲苯 (2mL) 和水 (0.5mL) 合并 (之前用氮吹扫 20 分钟) 以给出浅黄色溶液。将小瓶的气氛用氮吹扫, 密封, 在干燥区中在 100°C 加热 5h, 并且冷却至室温过夜。将反应物用 EtOAc (50mL) 稀释并用水 (50mL) 和盐水洗涤。将水性层用 EtOAc (50mL) 萃取。将有机层合并, 在 $MgSO_4$ 上干燥, 过滤, 浓缩, 溶解在最少 DCM 中并通过快速色谱提纯 (硅胶, 己烷中 0% 至 100% EtOAc)。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥以给出 1-{4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]

三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (74mg, 59.8% 产率), 为白色固体。LC/MS: $C_{29}H_{28}N_4O_4$ (m/e) 计算值 496, 实测值 497 (M+H, ES⁺)。

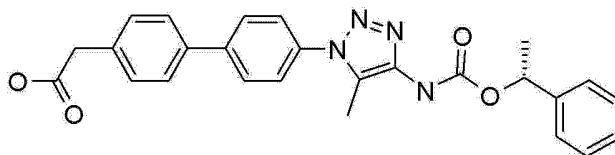
[0209] 步骤 5: 1-[4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基]-环丙烷甲酸

[0210] 在 200mL 圆底烧瓶中, 将 1-[4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基]-环丙烷甲酸甲酯 (66mg, 0.133mmol) 与 THF (3mL) 合并以给出黄色溶液。向其滴入水 (1mL) 中的 LiOH (31.8mg, 1.334mmol), 用加热部分溶解。将反应烧瓶密封并在油浴中在 60℃ 加热 11h。将反应物冷却至室温用水稀释并用 1N HCl 酸化。将所得到的沉淀物过滤, 用水、乙醚和己烷洗涤并在室内真空中干燥, 产生 1-[4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基]-环丙烷甲酸 (40mg, 62.4% 产率), 为灰白色固体。LC/MS: $C_{28}H_{26}N_4O_4$ (m/e) 计算值 482, 实测值 483 (M+H, ES⁺)。¹H NMR (DMSO-d₆) δ : 12.39 (br. s., 1H), 9.59 (br. s., 1H), 7.89 (d, J = 8.5Hz, 2H), 7.69 (dd, J = 8.3, 5.3Hz, 4H), 7.28-7.49 (m, 7H), 5.79 (q, J = 6.5Hz, 1H), 2.21 (s, 3H), 1.43-1.63 (m, 5H), 1.14-1.25 (m, 2H)。

[0211] 实施例 4

[0212] {4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸

[0213]



[0214] 步骤 1: {4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸甲酯

[0215] 在 20mL 小瓶中, 将 [4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-乙酸乙酯 (86.8mg, 0.299mmol)、[1-(4-溴-苯基)-5-甲基-1H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-1-苯基-乙酯 (100mg, 0.249mmol)、磷酸三钾 (159mg, 0.748mmol)、2-二环己膦基-2',6'-二甲氧基联苯 (SPhos) (30.7mg, 0.0748mmol) 和 Pd(OAc)₂ (8.4mg, 0.037mmol) 与甲苯 (2mL) 和水 (0.5mL) (之前用氮吹扫 20 分钟) 合并以给出浅黄色溶液。将小瓶的气氛用氮吹扫, 密封, 在干燥区中在 100℃ 加热 16h, 并且冷却至室温过夜。将反应物通过硅藻土过滤, 浓缩, 溶解在 DCM/EtOAc/MeOH 中, 负载在硅胶上并通过快速色谱提纯 (硅胶, 己烷中 0% 至 40% EtOAc)。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥以给出 {4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸甲酯 (56.6mg, 54.3% 产率), 为白色固体。LC/MS: $C_{28}H_{28}N_4O_4$ (m/e) 计算值 484, 实测值 485 (M+H, ES⁺)。

[0216] 步骤 2: {4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸

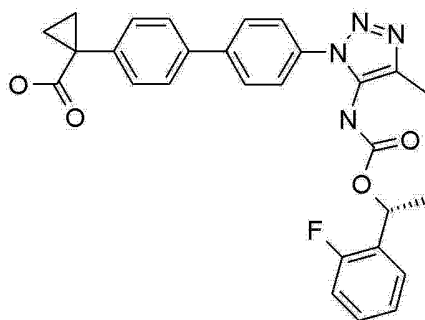
[0217] 在 200mL 圆底烧瓶中, 将 {4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸甲酯 (59mg, 0.122mmol) 与 THF (3mL) 合并以给出黄

色溶液。向其滴入水 (1mL) 中的 LiOH (29.2mg, 1.22mmol), 加热以部分地溶解。将反应烧瓶密封, 在油浴中在 60℃ 加热 3.5h, 并且冷却至室温过夜。将反应物用水稀释并用 1N HCl 酸化。将所得到的沉淀物用 EtOAc (2x75mL) 萃取。将有机层用盐水 (50mL) 洗涤, 合并, 在 MgSO₄ 上干燥, 过滤, 浓缩, 并且由 DCM/ 己烷干燥, 产生 {4'-[5-甲基-4-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸 (50mg, 90% 产率), 为灰白色固体。LC/MS: C₂₆H₂₄N₄O₄ (m/e) 计算值 456, 实测值 457 (M+H, ES⁺)。¹H NMR (DMSO-d₆) δ: 12.44 (br. s., 1H), 9.62 (br. s., 1H), 7.95 (d, J = 8.5Hz, 2H), 7.76 (t, J = 8.0Hz, 4H), 7.22-7.59 (m, 7H), 5.85 (q, J = 6.5Hz, 1H), 3.71 (s, 2H), 2.27 (s, 3H), 1.60 (d, J = 6.0Hz, 3H)。

[0218] 实施例 5

[0219] 1-(4'-[5-[(R)-1-(2-氟-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基)-环丙烷甲酸

[0220]



[0221] 步骤 1: [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-1-(2-氟-苯基)-乙酯

[0222] 在 20mL 反应小瓶中, 将 3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸 100mg, 0.354mmol、(R)-1-(2-氟苯基)乙醇 (49.6mg, 49 μL, 0.354mmol) 和三乙胺 (35.8mg, 49.3 μL, 0.354mmol) 与甲苯 (2.5mL) 合并以给出黄色悬浮液并且向其加入二苯基磷酰基叠氮化物 (97.4mg, 76.3 μL, 0.354mmol)。将小瓶的气氛用氮吹扫, 密封, 在油浴上在 80℃ 加热 4h, 并且冷却至室温过夜。加入另外的试剂, (R)-1-(2-氟苯基)乙醇 (24.8mg, 24.5 μL, 0.177mmol)、三乙胺 (72.6mg, 100 μL, 0.717mmol) 和二苯基磷酰基叠氮化物 (97.4mg, 76.3 μL, 0.354mmol)。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 80℃ 加热 2h, 并且冷却至室温。将反应物负载在硅藻土上并通过快速色谱提纯 (硅胶, 12g Redisep, 20mL/分钟, 己烷中 0% 至 40% EtOAc)。将合适的级分合并, 浓缩, 由 DCM/ 己烷干燥, 以获得 [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-1-(2-氟-苯基)-乙酯 (95.7mg, 64.4% 产率), 为固体。LC/MS: C₁₈H₁₆BrFN₄O₂ (m/e) 计算值 418/420, 实测值 419/421 (M+H, ES⁺)。

[0223] 步骤 2: 1-(4'-[5-[(R)-1-(2-氟-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基)-环丙烷甲酸甲酯

[0224] 在 20mL 小瓶中, 将 1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯 (74.4mg, 0.246mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-1-(2-氟-苯基)-乙酯 (86mg, 0.205mmol)、磷酸三钾 (131mg, 0.615mmol)、2-二环己膦基-2',6'-二甲氧基联苯 (SPhos) (25.3mg,

0.0615mmol) 和 $\text{Pd}(\text{OAc})_2$ (6.91mg, 0.0308mmol) 与甲苯 (2mL) 和水 (0.5mL) (之前用氮吹扫 20 分钟) 合并以给出浅黄色悬浮液。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 100℃ 加热 4h, 并且冷却至室温过夜。将反应物用 EtOAc (8mL) 稀释, 通过硅藻土过滤, 用 EtOAc (2x6mL) 冲洗, 干燥, 溶解在最少 DCM 中, 并且通过快速色谱 (硅胶, 己烷中 0% 至 50% EtOAc) 提纯。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 1-(4'-{5-[(R)-1-(2-氟-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸甲酯 (47.8mg, 45.3% 产率), 为白色固体。LC/MS: $\text{C}_{29}\text{H}_{27}\text{FN}_4\text{O}_4$ (m/e) 计算值 514, 实测值 515 (M+H, ES⁺)。

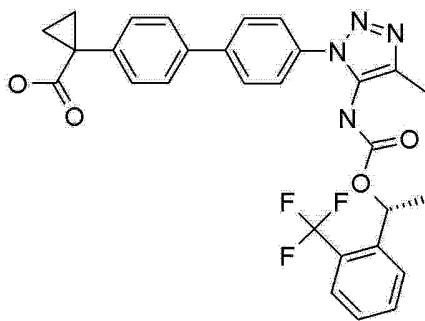
[0225] 步骤 3: 1-(4'-{5-[(R)-1-(2-氟-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸

[0226] 在 20mL 圆底烧瓶中, 将 1-(4'-{5-[(R)-1-(2-氟-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸甲酯 (42mg, 0.0816mmol) 与 THF (2mL) 合并以给出黄色溶液。向其滴入水 (0.5mL) 中的 LiOH (34.3mg, 0.816mmol), 加热以部分地溶解。将小瓶密封, 在油浴中在 60℃ 加热 11h, 并且冷却至室温过夜。将反应物用水稀释 (35mL) 并用 1N HCl 酸化。将所得到的沉淀物过滤, 用水和己烷洗涤, 并且在室内真空下并在干燥器中干燥, 以制造 1-(4'-{5-[(R)-1-(2-氟-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸 (44mg, 108% 产率), 为白色固体。LC/MS: $\text{C}_{28}\text{H}_{25}\text{FN}_4\text{O}_4$ (m/e) 计算值 500, 实测值 501 (M+H, ES⁺)。¹H NMR (DMSO-d₆) δ : 12.39 (br. s., 1H), 9.74 (br. s., 1H), 7.84 (d, J = 6.5Hz, 2H), 7.67 (d, J = 8.0Hz, 2H), 7.58 (d, J = 8.0Hz, 2H), 7.47 (d, J = 8.0Hz, 2H), 6.69-7.42 (m, 4H), 5.89 (br. s., 1H), 2.17 (br. s., 3H), 1.26-1.74 (m, 5H), 1.14-1.24 (m, 2H)。

[0227] 实施例 6

[0228] 1-(4'-{4-甲基-5-[(R)-1-(2-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸

[0229]



[0230] 步骤 1: [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-1-(2-三氟甲基-苯基)-乙酯

[0231] 在 20mL 反应小瓶中, 将 3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸 100mg, 0.354mmol)、(R)-1-(2-三氟甲基-苯基)乙醇 (67.4mg, 0.354mmol) 和三乙胺 (35.8mg, 49.3 μ L, 0.354mmol) 与甲苯 (2.5mL) 合并以给出黄色悬浮液, 并且向其加入二苯基磷酰基叠氮化物 (97.4mg, 76.3 μ L, 0.354mmol)。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 80℃ 加热 4h, 并且冷却至室温过夜。加入另外的试剂, (R)-1-(2-三氟甲基-苯基)

乙醇 (33.7mg, 0.177mmol)、三乙胺 (72.6mg, 100 μ L, 0.177mmol) 和二苯基磷酰基叠氮化物 (97.4mg, 76.3 μ L, 0.354mmol)。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 80℃ 加热 2h, 并且冷却至室温。将反应物负载在硅藻土上并通过快速色谱提纯 (硅胶, 12g Redisep, 20mL/分钟, 己烷中 0% 至 40% EtOAc)。将合适的级分合并, 浓缩, 由 DCM/己烷干燥, 以给出 [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-1-(2-三氟甲基-苯基)-乙酯 (99.7mg, 59.9% 产率), 为灰白色固体。LC/MS: $C_{19}H_{16}BrF_3N_4O_2$ (m/e) 计算值 468/470, 实测值 469/471 (M+H, ES⁺)。

[0232] 步骤 2: 1-(4'-{5-[(R)-1-(2-三氟甲基-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸甲酯

[0233] 在 20mL 小瓶中, 将 1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯 (69.4mg, 0.230mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-1-(2-三氟甲基-苯基)-乙酯 (90mg, 0.192mmol)、磷酸三钾 (122mg, 0.575mmol)、2-二环己膦基-2',6'-二甲氧基联苯 (SPhos) (23.6mg, 0.0575mmol) 和 Pd(OAc)₂ (6.5mg, 0.0288mmol) 与甲苯 (2mL) 和水 (0.5mL) (之前用氮吹扫 20 分钟) 合并以给出浅黄色悬浮液。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 100℃ 加热 4h, 并且冷却至室温过夜。将反应物用 EtOAc (8mL) 稀释, 通过硅藻土过滤, 用 EtOAc (2x6mL) 冲洗, 干燥, 溶解在最少 DCM 中并通过快速色谱提纯 (硅胶, 己烷中 0% 至 50% EtOAc)。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 1-(4'-{5-[(R)-1-(2-三氟甲基-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸甲酯 (50.3mg, 46.5% 产率), 为白色固体。LC/MS: $C_{30}H_{27}F_3N_4O_4$ (m/e) 计算值 564, 实测值 565 (M+H, ES⁺)。

[0234] 步骤 3: 1-(4'-{5-[(R)-1-(2-三氟甲基-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸

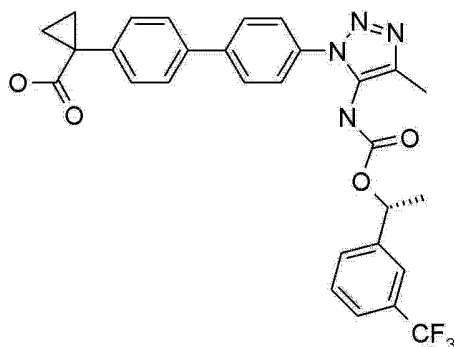
[0235] 在 20mL 圆底烧瓶中, 将 1-(4'-{5-[(R)-1-(2-三氟甲基-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸甲酯 (45mg, 0.0797mmol) 与 THF (2mL) 合并以给出黄色溶液。向其滴入水 (0.5mL) 中的 LiOH (33.5mg, 0.797mmol), 加热以部分地溶解。将小瓶密封并在油浴中在 60℃ 加热 11h, 并且冷却至室温过夜。将反应物用水稀释 (35mL) 并用 1N HCl 酸化。将所得到的沉淀物用 EtOAc (2x30mL) 萃取至有机层中, 用盐水 (30mL) 洗涤, 在 MgSO₄ 上干燥, 过滤, 浓缩, 并且由 DCM/己烷干燥, 产生 38.8mg 的不纯产物。将产物通过 RP-HPLC (Gilson, Pursuit 10 μ m, 20x100mm C18, 30mL/分钟, 30 至 100% ACN/H₂O, 8 分钟) 提纯。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥。将产物溶解在 DCM 中并且加入己烷沉淀。将固体过滤出并用己烷洗涤, 在室内真空中干燥, 产生 1-(4'-{5-[(R)-1-(2-三氟甲基-苯基)-乙氧基羰基氨基]-4-甲基-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸 (17.2mg, 39.2% 产率), 为灰白色固体。LC/MS: $C_{29}H_{25}F_3N_4O_4$ (m/e) 计算值 550, 实测值 551 (M+H, ES⁺)。 ¹H NMR (DMSO-d₆) δ : 12.40 (br. s., 1H), 9.77 (br. s., 1H), 7.83 (d, J = 7.3Hz, 2H), 7.63-7.78 (m, 5H), 7.39-7.62 (m, 5H), 5.96 (br. s., 1H), 2.15 (br. s., 3H), 1.50 (d, J = 2.3Hz, 5H), 1.20 (d, J = 2.0Hz, 2H)。

[0236] 实施例 7

[0237] 1-(4'-{4-甲基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]

三唑-1-基}-联苯-4-基)-环丙烷甲酸

[0238]



[0239] 步骤1:[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-(3-三氟甲基-苯基)-乙酯

[0240] 在20mL反应小瓶中,将3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸(195mg,0.691mmol)、(R)-1-(3-(三氟甲基)苯基)乙醇(197mg,1.04mmol)和三乙胺(145mg,0.2mL,1.43mmol)与甲苯(10mL)合并以给出黄色溶液,并且向其加入二苯基磷酰基叠氮化物(383mg,0.3mL,1.39mmol)。将小瓶的气氛用氮吹扫,密封,在油浴中在65℃加热2.5h,并且冷却至室温过夜。将反应物用EtOAc稀释并用水,饱和氯化铵,以及盐水洗涤。将水性层用EtOAc萃取一次。将有机层合并,在MgSO₄上干燥,过滤,浓缩,用DCM稀释,并且通过快速色谱(硅胶,己烷中0%至30%EtOAc)提纯。将合适的级分合并,浓缩,并且由DCM/己烷干燥,以获得[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-(3-三氟甲基-苯基)-乙酯(118.1mg,36.4%产率),为无色蜡状固体。LC/MS:C₁₉H₁₆BrF₃N₄O₂(m/e)计算值468/470,实测值469/471(M+H,ES⁺)。

[0241] 步骤2:1-(4'-{4-甲基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸甲酯

[0242] 在20mL小瓶中,将1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯(89.6mg,0.297mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-(3-三氟甲基-苯基)-乙酯(116mg,0.247mmol)、2-二环己磷基-2',6'-二甲氧基联苯(SPhos)(30.4mg,0.0742mmol)、磷酸三钾(157mg,0.742mmol)和Pd(OAc)₂(8.3mg,0.0371mmol)与甲苯(4mL)和水(1mL)合并(之前用氮吹扫20分钟)以给出浅黄色悬浮液。将小瓶的气氛用氮吹扫,密封,在油浴中在80℃加热3.5h,并且冷却至室温过夜。加入另外的试剂1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯(45mg,0.149mmol),2-二环己磷基-2',6'-二甲氧基联苯(SPhos)(32mg,0.0779mmol),磷酸三钾(57mg,0.269mmol)和Pd(OAc)₂(10mg,0.0445mmol)。将小瓶的气氛用氮吹扫,密封,在干燥区中在80℃加热4h,并且冷却至室温过夜。将反应物用EtOAc稀释并用水和盐水洗涤。将水性层用EtOAc萃取。将有机层合并,在MgSO₄上干燥,过滤,浓缩,溶解在最少DCM中并通过快速色谱提纯(硅胶,己烷中0%至50%EtOAc)。将合适的级分合并,浓缩,并且由DCM/己烷干燥,产生1-(4'-{4-甲基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸甲酯(63.5mg,45.5%产率),为白色固体。LC/MS:

$C_{30}H_{27}F_3N_4O_4$ (m/e) 计算值 564, 实测值 565 (M+H, ES⁺)。

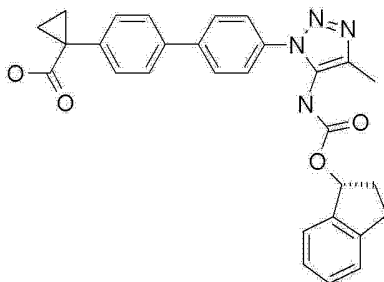
[0243] 步骤 3: 1-(4'-{4-甲基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸

[0244] 在 250mL 圆底烧瓶中, 将 1-(4'-{4-甲基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸甲酯 (214.5mg, 0.452mmol) 与 THF (8mL) 和乙醇 (8mL) 合并以给出黄色溶液。向其滴入 NaOH (1N, 4.5mL, 4.5mmol)。将反应物在室温搅拌过夜。将反应物用水稀释, 浓缩, 用更多水稀释并用 1N HCl 酸化。将所得到的沉淀物过滤, 用水和己烷洗涤并在室内真空下并在干燥器中干燥, 产生 1-(4'-{4-甲基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸 (174mg, 83.6% 产率), 为白色固体。LC/MS: $C_{26}H_{28}N_4O_4$ (m/e) 计算值 460, 实测值 461 (M+H, ES⁺)。¹H NMR (DMSO-d₆) δ : 12.39 (br. s., 1H), 9.47 (br. s., 1H), 7.88 (d, J = 7.8Hz, 2H), 7.64 (dd, J = 18.7, 8.2Hz, 4H), 7.46 (d, J = 8.3Hz, 2H), 4.67 (br. s., 1H), 2.36 (br. s., 1H), 2.20 (s, 3H), 1.54-2.02 (m, 6H), 1.43-1.53 (m, 2H), 1.17-1.31 (m, 2H), 1.05 (br. s., 3H)。

[0245] 实施例 8

[0246] 1-{4'-[5-((R)-茚满-1-基氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0247]



[0248] 步骤 1: [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-茚满-1-基酯

[0249] 在 20mL 反应小瓶中, 将 3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸 (100mg, 0.354mmol)、(R)-2,3-二氢-1H-茚-1-醇 (47.6mg, 0.354mmol) 和三乙胺 (35.8mg, 49.3 μ L, 0.354mmol) 与甲苯 (2.5mL) 合并以给出黄色悬浮液, 并且向其加入二苯基磷酰基叠氮化物 (97.4mg, 76.3 μ L, 0.354mmol)。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 80°C 加热 4h, 并且冷却至室温过夜。加入另外的试剂, (R)-2,3-二氢-1H-茚-1-醇 (23.8mg, 0.177mmol)、三乙胺 (72.6mg, 100 μ L, 0.717mmol) 和二苯基磷酰基叠氮化物 (97.4mg, 76.3 μ L, 0.354mmol)。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 80°C 加热 2h, 并且冷却至室温。将反应负载在硅藻土上并通过快速色谱提纯 (硅胶, 12g Redisep, 20mL/分钟, 己烷中 0% 至 40% EtOAc)。将合适的级分合并, 浓缩, 由 DCM/己烷干燥, 产生 [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-茚满-1-基酯 (81.6mg, 55.7% 产率), 为灰白色固体。LC/MS: $C_{19}H_{17}BrN_4O_2$ (m/e) 计算值 412/414, 实测值 413/415 (M+H, ES⁺)。

[0250] 步骤 2: 1-{4'-[5-((R)-茚满-1-基氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯

[0251] 在 20mL 小瓶中, 将 1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯 (64.1mg, 0.212mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-茚满-1-基酯 (73mg, 0.177mmol)、磷酸三钾 (112mg, 0.530mmol)、2-二环己膦基-2',6'-二甲氧基联苯 (SPhos) (21.8mg, 0.0530mmol) 和 Pd(OAc)₂ (6.0mg, 0.0265mmol) 与甲苯 (2mL) 和水 (0.5mL) (之前用氮吹扫 20 分钟) 合并以给出浅黄色悬浮液。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 100℃ 加热 4h, 并且冷却至室温过夜。将反应物用 EtOAc (8mL) 稀释, 通过硅藻土过滤, 用 EtOAc (2x6mL) 冲洗, 干燥, 溶解在最少 DCM 中并通过快速色谱提纯 (硅胶, 己烷中 0% 至 50% EtOAc)。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 1-{4'-[5-((R)-茚满-1-基氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (59.5mg, 66.2% 产率), 为白色固体。LC/MS: C₃₀H₂₆N₄O₄ (m/e) 计算值 508, 实测值 509 (M+H, ES⁺)。

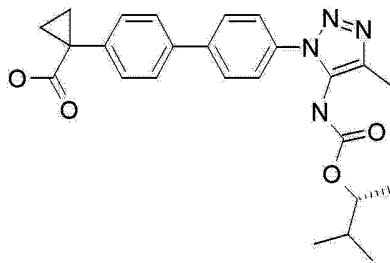
[0252] 步骤 3: 1-{4'-[5-((R)-茚满-1-基氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0253] 在 20mL 圆底烧瓶中, 将 1-{4'-[5-((R)-茚满-1-基氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (53mg, 0.104mmol) 与 THF (2mL) 合并以给出黄色溶液。向其滴入水 (0.5mL) 中的 LiOH (43.8mg, 1.04mmol), 加热以部分地溶解。将小瓶密封, 在油浴中在 60℃ 加热 11h, 并且冷却至室温过夜。将反应物用水稀释 (35mL) 并用 1N HCl 酸化。将所得到的沉淀物过滤出并用水和己烷洗涤, 并且在室内真空中干燥, 产生 1-{4'-[5-((R)-茚满-1-基氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸 (28mg, 54.3% 产率), 为白色固体。LC/MS: C₂₉H₂₆N₄O₄ (m/e) 计算值 494, 实测值 495 (M+H, ES⁺)。¹H NMR (DMSO-d₆) δ: 12.38 (br. s., 1H), 9.56 (br. s., 1H), 7.87 (d, J = 8.3Hz, 2H), 7.68 (d, J = 8.3Hz, 2H), 7.60 (br. s., 2H), 7.48 (d, J = 8.0Hz, 2H), 7.29 (br. s., 3H), 7.11-7.21 (m, 1H), 6.04 (br. s., 1H), 3.00 (br. s., 1H), 2.85 (br. s., 1H), 2.30-2.45 (m, 1H), 2.09-2.28 (m, 3H), 2.00 (br. s., 1H), 1.42-1.61 (m, 2H), 1.21 (d, J = 3.0Hz, 2H)。

[0254] 实施例 9

[0255] 1-{4'-[5-((R)-1,2-二甲基-丙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0256]



[0257] 步骤 1: [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-1,2-二甲基-丙酯

[0258] 在 20mL 反应小瓶中, 将 3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸 (100mg, 0.354mmol)、(R)-3-甲基丁-2-醇 (31.2mg, 38.6 μL, 0.354mmol) 和三乙胺

(35.8mg, 49.3 μ L, 0.354mmol) 与甲苯 (2.5mL) 合并以给出黄色悬浮液, 并且向其加入二苯基磷酰基叠氮化物 (97.4mg, 76.3 μ L, 0.354mmol)。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 80℃ 加热 4h, 并且冷却至室温过夜。加入另外的试剂, (R)-3-甲基丁-2-醇 (15.6mg, 19.3 μ L, 0.177mmol)、三乙胺 (72.6mg, 100 μ L, 0.717mmol) 和二苯基磷酰基叠氮化物 (97.4mg, 76.3 μ L, 0.354mmol)。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 80℃ 加热 2h, 并且冷却至室温。将反应物负载在硅藻土上并通过快速色谱提纯 (硅胶, 己烷中 0% 至 40% EtOAc)。将合适的级分合并, 浓缩, 由 DCM/己烷干燥, 产生 [3-(4-溴-苯基)-5-甲基-3H-[1,2,3] 三唑-4-基]-氨基甲酸 (R)-1,2-二甲基-丙酯 (93.6mg, 71.9% 产率), 为灰白色固体。LC/MS: $C_{15}H_{19}BrN_4O_2$ (m/e) 计算值 366/368, 实测值 367/369 (M+H, ES⁺)。

[0259] 步骤 2: 1-{4'-[5-((R)-1,2-二甲基-丙氧基羰基氨基)-4-甲基-[1,2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯

[0260] 在 20mL 小瓶中, 将 1-[4-(4,4,5,5-四甲基-[1,3,2] 二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯 (82.9mg, 0.274mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3] 三唑-4-基]-氨基甲酸 (R)-1,2-二甲基-丙酯 (84mg, 0.229mmol)、磷酸三钾 (146mg, 0.686mmol)、2-二环己膦基-2',6'-二甲氧基联苯 (SPhos) (28.2mg, 0.0686mmol) 和 Pd(OAc)₂ (7.7mg, 0.0343mmol) 与甲苯 (2mL) 和水 (0.5mL) (之前用氮吹扫 20 分钟) 合并以给出浅黄色悬浮液。将小瓶的气氛用氮替代, 密封, 在油浴中在 100℃ 加热 4h, 并且冷却至室温过夜。将反应物用 EtOAc (8mL) 稀释, 通过硅藻土过滤, 用 EtOAc (2x6mL) 冲洗, 干燥, 溶解在最少 DCM 中并通过快速色谱提纯 (硅胶, 己烷中 0% 至 50% EtOAc)。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 1-{4'-[5-((R)-1,2-二甲基-丙氧基羰基氨基)-4-甲基-[1,2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (80mg, 75.6% 产率), 为白色固体。LC/MS: $C_{26}H_{30}N_4O_4$ (m/e) 计算值 462, 实测值 463 (M+H, ES⁺)。

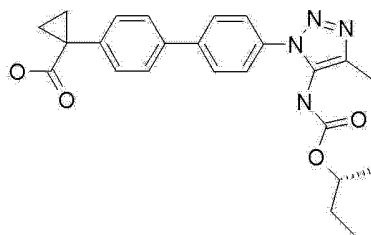
[0261] 步骤 3: 1-{4'-[5-((R)-1,2-二甲基-丙氧基羰基氨基)-4-甲基-[1,2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0262] 在 20mL 圆底烧瓶中, 将 1-{4'-[5-((R)-1,2-二甲基-丙氧基羰基氨基)-4-甲基-[1,2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (45mg, 0.0797mmol) 与 THF (2mL) 合并以给出黄色溶液。向其滴入水 (0.5mL) 中的 LiOH (33.5mg, 0.797mmol), 加热以部分地溶解。将小瓶密封并在油浴中在 60℃ 加热 6h, 并且冷却至室温过夜。将反应物用水稀释 (35mL) 并用 1N HCl 酸化。将所得到的沉淀物用 EtOAc (2x30mL) 萃取至有机层中, 用盐水 (30mL) 洗涤, 在 MgSO₄ 上干燥, 过滤, 浓缩, 并且由 DCM/己烷干燥, 产生 1-{4'-[5-((R)-1,2-二甲基-丙氧基羰基氨基)-4-甲基-[1,2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸 (42.4mg, 58.3% 产率), 为白色固体。LC/MS: $C_{25}H_{28}N_4O_4$ (m/e) 计算值 448, 实测值 (M+H, ES⁺)。 ¹H NMR (DMSO-d₆) δ : 12.37 (br. s., 1H), 9.43 (br. s., 1H), 7.88 (d, J = 8.0Hz, 2H), 7.57-7.73 (m, 4H), 7.46 (d, J = 8.3Hz, 2H), 4.50 (br. s., 1H), 2.21 (s, 3H), 1.71 (br. s., 1H), 1.40-1.57 (m, 2H), 1.00-1.32 (m, 5H), 0.84 (br. s., 6H)。

[0263] 实施例 10

[0264] 1-{4'-[5-((R)-仲丁氧基羰基氨基)-4-甲基-[1,2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0265]



[0266] 步骤1: [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-仲丁酯

[0267] 在20mL反应小瓶中,将3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸100mg,0.354mmol)、(R)-丁-2-醇(26.3mg,32.6 μ L,0.354mmol)和三乙胺(35.8mg,49.3 μ L,0.354mmol)与甲苯(2.5mL)合并以给出黄色悬浮液,并且向其加入二苯基磷酰基叠氮化物(97.4mg,76.3 μ L,0.354mmol)。将小瓶的气氛用氮吹扫,密封,在油浴中在80℃加热4h,并且冷却至室温过夜。加入另外的试剂,(R)-丁-2-醇(13.2mg,16.3 μ L,0.177mmol)、三乙胺(72.6mg,100 μ L,0.717mmol)和二苯基磷酰基叠氮化物(97.4mg,76.3 μ L,0.354mmol)。将小瓶的气氛用氮吹扫,密封,在油浴中在80℃加热2h,并且冷却至室温。将反应物负载在硅藻土上并通过快速色谱提纯(硅胶,己烷中0%至40% EtOAc)。将合适的级分合并、浓缩,并且由DCM/己烷干燥,产生[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-仲丁酯(99.5mg,79.5%产率),为灰白色固体。LC/MS: $C_{14}H_{17}BrN_4O_2$ (m/e) 计算值 352/354,实测值 353/355 (M+H, ES^+)。

[0268] 步骤2: 1-{4'-[5-((R)-仲丁氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯

[0269] 在20mL小瓶中,将1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯(92.4mg,0.306mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-仲丁酯(90mg,0.255mmol)、磷酸三钾(162mg,0.764mmol)、2-二环己膦基-2',6'-二甲氧基联苯(SPhos)(31.4mg,0.0764mmol)和Pd(OAc)₂(8.6mg,0.0382mmol)与甲苯(2mL)和水(0.5mL)(之前用氮吹扫20分钟)合并以给出浅黄色悬浮液。将小瓶的气氛用氮替代,密封,在油浴中在100℃加热4h,并且冷却至室温过夜。将反应物用EtOAc(8mL)稀释,通过硅藻土过滤,用EtOAc(2x6mL)冲洗,干燥,并且溶解在最少DCM中并通过快速色谱提纯(硅胶,己烷中0%至50% EtOAc)。将合适的级分合并、浓缩,并且由DCM/己烷干燥,产生1-{4'-[5-((R)-仲丁氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯(53.6mg,46.9%产率),为白色固体。LC/MS: $C_{25}H_{28}N_4O_4$ (m/e) 计算值 448,实测值 449 (M+H, ES^+)。

[0270] 步骤3: 1-{4'-[5-((R)-仲丁氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

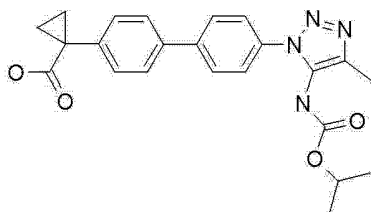
[0271] 在20mL圆底烧瓶中,将1-{4'-[5-((R)-仲丁氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯(37mg,0.0825mmol)与THF(2mL)合并以给出黄色溶液。向其滴入水(0.5mL)中的LiOH(34.6mg,0.825mmol),加热以部分地溶解。将小瓶密封并且在油浴中在60℃加热6h,并且冷却至室温过夜。将反应物用水稀释(35mL)并用1N HCl酸化。将所得到的沉淀物用EtOAc(2x30mL)萃取至有机层中,用盐水(30mL)洗涤,在MgSO₄上干燥,过滤,浓缩,并且由DCM/己烷干燥,产生1-{4'-[5-((R)-仲丁氧基羰基

氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基]-环丙烷甲酸(40mg,112%产率),为白色固体。LC/MS: $C_{24}H_{26}N_4O_4$ (m/e) 计算值 434,实测值 435(M+H, ES⁺)。¹H NMR(DMSO-d₆) δ: 12.37(br. s., 1H), 9.44(br. s., 1H), 7.88(d, J = 8.5Hz, 2H), 7.56-7.72(m, 4H), 7.46(d, J = 8.3Hz, 2H), 4.61(br. s., 1H), 2.21(s, 3H), 1.38-1.66(m, 4H), 1.03-1.34(m, 5H), 0.85(dd, J = 10.7, 6.9Hz, 3H)。

[0272] 实施例 11

[0273] 1-[4'-(5-异丙氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸

[0274]



[0275] 步骤 1:[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸异丙酯

[0276] 在 20mL 反应小瓶中,将 3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸(100mg,0.354mmol)、丙-2-醇(21.3mg,27.1 μL,0.354mmol)和三乙胺(35.8mg,49.3 μL,0.354mmol)与甲苯(2.5mL)合并以给出黄色悬浮液,并且向其加入二苯基磷酰基叠氮化物(97.4mg,76.3 μL,0.354mmol)。将小瓶的气氛用氮吹扫,密封,在油浴中在 80℃加热 4h,并且冷却至室温过夜。加入另外的试剂,丙-2-醇(10.7mg,13.6 μL,0.177mmol)、三乙胺(72.6mg,100 μL,0.717mmol)和二苯基磷酰基叠氮化物(97.4mg,76.3 μL,0.354mmol)。将小瓶的气氛用氮吹扫,密封,在油浴中在 80℃加热 2h,并且冷却至室温。将反应物负载在硅藻土上并通过快速色谱提纯(硅胶,己烷中 0%至 40% EtOAc)。将合适的级分合并,浓缩,由 DCM/己烷干燥,产生 [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸异丙酯(141mg,60%纯,70.4%产率),为灰白色固体。LC/MS: $C_{13}H_{15}BrN_4O_2$ (m/e) 计算值 338/340,实测值 339/341(M+H, ES⁺)。

[0277] 步骤 2:1-[4'-(5-异丙氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸甲酯

[0278] 在 20mL 小瓶中,将 1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯(83.4mg,0.276mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸异丙酯(130mg,0.230mmol)、磷酸三钾(146mg,0.690mmol),2-二环己膦基-2',6'-二甲氧基联苯(SPhos)(28.3mg,0.069mmol)和 Pd(OAc)₂(7.7mg,0.0345mmol)与甲苯(2mL)和水(0.5mL)合并(之前用氮吹扫 20 分钟)以给出浅黄色悬浮液。将小瓶的气氛用氮替代,密封,在油浴中在 100℃加热 4h,并且冷却至室温过夜。将反应物用 EtOAc(8mL)稀释,通过硅藻土过滤,用 EtOAc(2x6mL)冲洗,干燥,并且溶解在最少 DCM 中并通过快速色谱提纯(硅胶,己烷中 0%至 50% EtOAc)。将合适的级分合并,浓缩,并且由 DCM/己烷干燥,产生 1-[4'-(5-异丙氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸甲酯(44.3mg,44.3%产率),为固体。LC/MS: $C_{24}H_{26}N_4O_4$ (m/e) 计算值 434,实测值 435(M+H, ES⁺)。

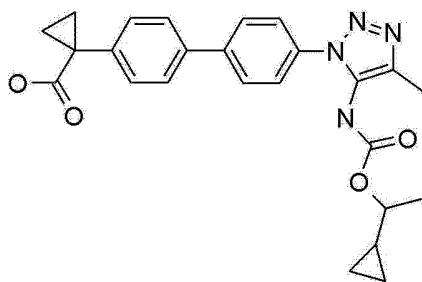
[0279] 步骤3: 1-[4'-(5-异丙氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸

[0280] 在20mL圆底烧瓶中,将1-[4'-(5-异丙氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸甲酯(39mg,0.0898mmol)与THF(2mL)合并以给出黄色溶液。向其滴入水(0.5mL)中的LiOH(37.7mg,0.898mmol),加热以部分地溶解。将小瓶密封并在油浴中在60℃加热6h,并且冷却至室温过夜。将反应物用水稀释(35mL)并用1N HCl酸化。将所得到的沉淀物用EtOAc(2x30mL)萃取至有机层中,用盐水(30mL)洗涤,在MgSO₄上干燥,过滤,浓缩,由DCM/己烷干燥,产生1-[4'-(5-异丙氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸(32.5mg,86.1%产率),为白色固体。LC/MS:C₂₃H₂₄N₄O₄(m/e)计算值420,实测值421(M+H⁺)。¹H NMR(DMSO-d₆) δ:12.38(br. s., 1H),9.43(br. s., 1H),7.89(d, J = 8.3Hz, 2H),7.57-7.74(m, 4H),7.46(d, J = 8.0Hz, 2H),4.76(br. s., 1H),2.20(s, 3H),1.43-1.57(m, 2H),1.02-1.34(m, 8H)。

[0281] 实施例12

[0282] 1-{4'-[5-(1-环丙基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0283]



[0284] 步骤1:[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸1-环丙基-乙酯

[0285] 在20mL反应小瓶中,将3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸(300mg,1.06mmol)、1-环丙基乙醇(139mg,1.61mmol)和三乙胺(218mg,0.3mL,2.15mmol)与甲苯(10mL)合并以给出黄色溶液,并且向其加入二苯基磷酰基叠氮化物(585mg,0.458mL,2.13mmol)。将小瓶的气氛用氮吹扫,密封,在油浴中在65℃加热2.5h,并且冷却至室温过夜。将反应物用EtOAc稀释并用水,饱和氯化铵,以及盐水洗涤。将水性层用EtOAc萃取一次。将有机层合并,在MgSO₄上干燥,过滤,浓缩,用DCM稀释,并且通过快速色谱(硅胶,己烷中0%至50% EtOAc)提纯。将合适的级分合并,浓缩,并且由DCM/己烷干燥,产生[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸1-环丙基-乙酯(267mg,68.9%产率),为无色蜡状固体。LC/MS:C₁₅H₁₇BrN₄O₂(m/e)计算值364/366,实测值365/367(M+H, ES⁺)。

[0286] 步骤2:1-{4'-[5-(1-环丙基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯

[0287] 在20mL小瓶中,将1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯(238mg,0.789mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸1-环丙基-乙酯(240mg,0.657mmol)、2-二环己磷

基-2',6'-二甲氧基联苯 (SPhos) (80.9mg, 0.197mmol)、磷酸三钾 (418mg, 1.97mmol) 和 $\text{Pd}(\text{OAc})_2$ (22.1mg, 0.0986mmol) 与甲苯 (8mL) 和水 (2mL) (之前用氮吹扫 20 分钟) 合并以给出浅黄色悬浮液。将小瓶的气氛用氮替代, 密封, 在干燥区中在 80℃ 加热 2.5h, 并且冷却至室温过夜。将反应物用 EtOAc 稀释并用水和盐水洗涤。将水性层用 EtOAc 萃取。将有机层合并, 在 MgSO_4 上干燥, 过滤, 浓缩, 溶解在最少 DCM 中并通过快速色谱提纯 (硅胶, 己烷中 0% 至 50% EtOAc)。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 1-{4'-[5-(1-环丙基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (214.2mg, 70.8% 产率), 为白色固体。LC/MS: $\text{C}_{26}\text{H}_{28}\text{N}_4\text{O}_4$ (m/e) 计算值 460, 实测值 461 (M+H, ES⁺)。

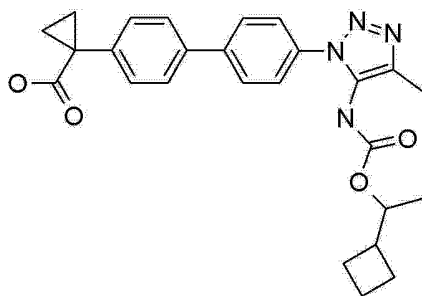
[0288] 步骤 3: 1-{4'-[5-(1-环丙基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0289] 在 250mL 圆底烧瓶中, 将 1-{4'-[5-(1-环丙基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (205mg, 0.447mmol) 与 THF (8mL) 和乙醇 (8mL) 合并以给出黄色溶液。向其滴入 NaOH (1N, 4.5mL, 4.5mmol)。将反应物在室温搅拌过夜。将反应物用水稀释, 浓缩, 用更多水稀释并用 1N HCl 酸化。将所得到的沉淀物过滤, 用水和己烷洗涤并在室内真空下并在干燥器中干燥, 产生 1-{4'-[5-(1-环丙基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸 (165.4mg, 82.9% 产率), 为白色固体。LC/MS: $\text{C}_{25}\text{H}_{26}\text{N}_4\text{O}_4$ (m/e) 计算值 446, 实测值 447 (M+H, ES⁺)。¹H NMR (DMSO-d₆) δ : 12.37 (br. s., 1H), 9.47 (br. s., 1H), 7.88 (d, J = 8.3Hz, 2H), 7.55-7.74 (m, 4H), 7.45 (d, J = 8.0Hz, 2H), 4.12 (br. s., 1H), 2.20 (s, 3H), 1.41-1.55 (m, 2H), 0.84-1.32 (m, 6H), -0.03-0.59 (m, 4H)。

[0290] 实施例 13

[0291] 1-{4'-[5-(1-环丁基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0292]



[0293] 步骤 1: [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 1-环丁基-乙酯

[0294] 在 20mL 反应小瓶中, 将 3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸 (300mg, 1.06mmol)、1-环丁基乙醇 (170mg, 1.70mmol) 和三乙胺 (218mg, 0.3mL, 2.15mmol) 与甲苯 (10mL) 合并以给出黄色溶液, 并且向其加入二苯基磷酰基叠氮化物 (585mg, 0.458mL, 2.13mmol)。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 65℃ 加热 2.5h, 并且冷却至室温过夜。将反应物用 EtOAc 稀释并用水, 饱和氯化铵, 以及盐水洗涤。将水性层用

EtOAc 萃取一次。将有机层合并,在 MgSO_4 上干燥,过滤,浓缩,用 DCM 稀释,并且通过快速色谱(硅胶,己烷中 0% 至 50% EtOAc)提纯。将合适的级分合并,浓缩,并且由 DCM/己烷干燥,产生 [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 1-环丙基-乙酯 (295.2mg, 73.2% 产率),为无色蜡状固体。LC/MS: $\text{C}_{16}\text{H}_{19}\text{BrN}_4\text{O}_2$ (m/e) 计算值 378/380,实测值 379/381 (M+H, ES^+)。

[0295] 步骤 2: 1-{4'-[5-(1-环丁基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯

[0296] 在 20mL 小瓶中,将 1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯 (258mg, 0.854mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 1-环丁基-乙酯 (270mg, 0.712mmol)、2-二环己磷基-2',6'-二甲氧基联苯 (SPhos) (87.7mg, 0.214mmol)、磷酸三钾 (453mg, 2.14mmol) 和 $\text{Pd}(\text{OAc})_2$ (24.0mg, 0.107mmol) 与甲苯 (8mL) 和水 (2mL) 合并(之前用氮吹扫 20 分钟)以给出浅黄色悬浮液。将小瓶的气氛用氮吹扫,密封,在干燥区中在 80°C 加热 2.5h,并且冷却至室温过夜。将反应物用 EtOAc 稀释并用水和盐水洗涤。将水性层用 EtOAc 萃取。将有机层合并,在 MgSO_4 上干燥,过滤,浓缩,溶解在最少 DCM 中并通过快速色谱提纯(硅胶,己烷中 0% 至 50% EtOAc)。将合适的级分合并,浓缩,并且从 DCM/己烷干燥,产生 1-{4'-[5-(1-环丁基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (223.6mg, 66.2% 产率),为白色固体。LC/MS: $\text{C}_{27}\text{H}_{30}\text{N}_4\text{O}_4$ (m/e) 计算值 474,实测值 475 (M+H, ES^+)。

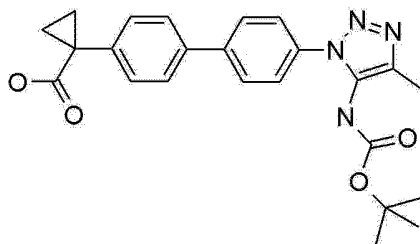
[0297] 步骤 3: 1-{4'-[5-(1-环丁基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0298] 在 250mL 圆底烧瓶中,将 1-{4'-[5-(1-环丁基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (214.5mg, 0.452mmol) 与 THF (8mL) 和乙醇 (8mL) 合并以给出黄色溶液。向其滴入 NaOH (1N, 4.5mL, 4.5mmol)。将反应物在室温搅拌过夜。将反应物用水稀释,浓缩,用更多水稀释并用 1N HCl 酸化。将所得到的沉淀物过滤,用水和己烷洗涤,并在室内真空下并在干燥器中干燥,产生 1-{4'-[5-(1-环丁基-乙氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸 (174mg, 83.6% 产率),为白色固体。LC/MS: $\text{C}_{26}\text{H}_{28}\text{N}_4\text{O}_4$ (m/e) 计算值 460,实测值 461 (M+H, ES^+)。 ^1H NMR (DMSO- d_6) δ : 12.39 (br. s., 1H), 9.47 (br. s., 1H), 7.88 (d, $J = 7.8\text{Hz}$, 2H), 7.64 (dd, $J = 18.7, 8.2\text{Hz}$, 4H), 7.46 (d, $J = 8.3\text{Hz}$, 2H), 4.67 (br. s., 1H), 2.36 (br. s., 1H), 2.20 (s, 3H), 1.54-2.02 (m, 6H), 1.43-1.53 (m, 2H), 1.17-1.31 (m, 2H), 1.05 (br. s., 3H)。

[0299] 实施例 14

[0300] 1-[4'-[5-(5-叔丁氧基羰基氨基)-4-甲基-[1,2,3]三唑-1-基]-联苯-4-基]-环丙烷甲酸

[0301]



[0302] 步骤 1: [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸叔丁酯

[0303] 在 20mL 反应小瓶中, 将 3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸 (500mg, 1.77mmol)、2-甲基丙-2-醇 (197mg, 2.66mmol) 和三乙胺 (359mg, 0.494mL, 3.54mmol) 与甲苯 (10mL) 合并以给出黄色溶液, 并且向其加入二苯基磷酰基叠氮化物 (946mg, 0.764mL, 3.54mmol)。将小瓶的气氛用氮吹扫, 密封, 在油浴中在 65°C 加热 2h, 并且冷却至室温过夜。将反应浓缩, 用 DCM 稀释, 并且通过快速色谱 (硅胶, 己烷中 0% 至 40% EtOAc) 提纯。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 [3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸叔丁酯 (420mg, 67.1% 产率), 为白色固体。LC/MS: $C_{14}H_{17}BrN_4O_2$ (m/e) 计算值 352/354, 实测值 353/355 (M+H, ES^+)。

[0304] 步骤 2: 1-[4'-(5-叔丁氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸甲酯

[0305] 在 20mL 小瓶中, 将 1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯 (395mg, 1.31mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸叔丁酯 (420mg, 1.19mmol)、2-二环己磷基-2',6'-二甲氧基联苯 (SPhos) (146mg, 0.357mmol)、磷酸三钾 (757mg, 3.57mmol) 和 $Pd(OAc)_2$ (40mg, 0.178mmol) 与甲苯 (10mL) 和水 (2mL) (之前用氮吹扫 20 分钟) 合并以给出浅黄色悬浮液。将小瓶的气氛用氮吹扫, 密封, 在干燥区中在 100°C 加热 4h, 并且冷却至室温过夜。将反应物过滤, 用水 (5mL) 和 EtOAc (60mL) 冲洗。将滤液用水稀释 (50mL) 并用 EtOAc 萃取。将水性层再次用 EtOAc (40mL) 萃取。将有机层用盐水洗涤, 合并, 在 $MgSO_4$ 上干燥, 过滤, 浓缩, 溶解在最少 DCM 中并通过快速色谱提纯 (硅胶, 己烷中 0% 至 50% EtOAc)。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 1-[4'-(5-叔丁氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸甲酯 (420mg, 78.8% 产率), 为白色固体。LC/MS: $C_{25}H_{28}N_4O_4$ (m/e) 计算值 448, 实测值 449 (M+H, ES^+)。

[0306] 步骤 3: 1-[4'-(5-叔丁氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸

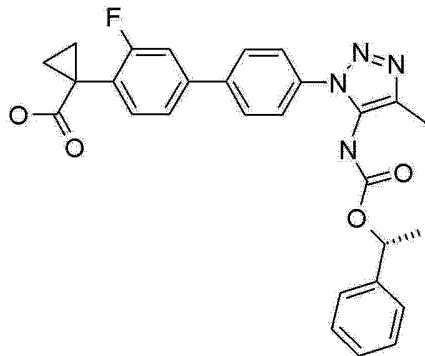
[0307] 在 8mL 小瓶中, 将 1-[4'-(5-叔丁氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸甲酯 (22.1mg, 0.047mmol) 与 THF (4mL) 合并并且向其滴入 NaOH (1N, 0.5mL, 0.5mmol)。将反应物在室温搅拌 30 分钟, 加入水 (2mL), 并且之后搅拌过夜。将反应物用水稀释, 浓缩, 用更多水稀释, 并且用 1N HCl 酸化。将所得到的沉淀物过滤, 用水和己烷洗涤, 并且在室内真空下并在干燥器中干燥, 产生 1-[4'-(5-叔丁氧基羰基氨基-4-甲基-[1,2,3]三唑-1-基)-联苯-4-基]-环丙烷甲酸 (17.1mg, 83.7% 产率), 为白色固体。LC/MS: $C_{24}H_{26}N_4O_4$ (m/e) 计算值 434, 实测值 435 (M+H, ES^+)。 1H NMR ($DMSO-d_6$) δ : 12.40 (br. s., 1H), 9.24 (br. s., 1H), 7.90 (d, $J = 8.0$ Hz, 2H), 7.58-7.71 (m, 4H), 7.46 (d, J

= 8.3Hz, 2H), 2.20 (s, 3H), 1.16-1.55 (m, 13H)。

[0308] 实施例 15

[0309] 1-{3- 氟 -4'-[4- 甲基 -5-((R)-1- 苯基 - 乙氧基 羰基 氨基)-[1,2,3] 三唑 -1- 基]- 联苯 -4- 基 }- 环丙烷 甲酸

[0310]



[0311] 步骤 1:1-(4- 溴 -2- 氟 - 苯基)- 环丙烷 甲腈

[0312] 在 0.5L 圆底烧瓶中,将溶解在 THF (50mL) 中的 2-(4- 溴 -2- 氟 - 苯基) 乙腈 (10g, 46.7mmol) 在氮下滴加至 NaH (矿物油中 60% 分散液, 4.11g, 103mmol) 在 DMF (100mL) 中的浆液。将反应物在冰浴中搅拌 30 分钟。向该冷却的混合物加入 1,2- 二溴乙烷 (8.78g, 5.71mL, 46.7mmol)。将反应物在氮下在冰浴中搅拌并且允许在 3h 内升温至室温。将反应物用 EtOAc (500mL) 稀释,过滤,并且用水和盐水洗涤。将水性层用 EtOAc (250mL) 萃取。将有机层合并,在 MgSO_4 上干燥,过滤,并且浓缩,产生 1-(4- 溴 -2- 氟 - 苯基) 环丙烷 甲腈 (13.7g, 122% 产率),为红色蜡 / 固体 / 油。LC/MS: $\text{C}_{10}\text{H}_7\text{BrFN}$ (m/e) 计算值 239/241,实测值 240/242 (M+H, ES^+)。

[0313] 步骤 2:1-(4- 溴 -2- 氟 - 苯基)- 环丙烷 甲酸

[0314] 在 1L 圆底烧瓶中,将 1-(4- 溴 -2- 氟 苯基) 环丙烷 甲腈 (11.2g, 46.7mmol) 和 LiOH (58g, 1.38mol) 与水 (230mL) 合并以给出黄色悬浮液。将混合物在油浴中在 100℃ 加热过夜。将混合物用水和冰稀释至 1L,并且用乙醚 (3x300mL) 萃取。在相之间存在一些不包含在水性层中的白色不溶材料。将水性层用浓 HCl (约 110mL) 在加入冰的情况下缓慢地酸化。形成非常细的沉淀物,该乳状溶液不过滤,但用 DCM (4x250mL) 萃取。将有机层合并,在 MgSO_4 上干燥,过滤,并且浓缩,产生 1-(4- 溴 -2- 氟 苯基) 环丙烷 甲酸 (10.87g, 89.9% 产率),为黄色固体。LC/MS: $\text{C}_{10}\text{H}_8\text{BrFO}_2$ (m/e) 计算值 258/260,实测值 259/261 (M+H, ES^+)。

[0315] 步骤 3:1-(4- 溴 -2- 氟 - 苯基)- 环丙烷 甲酸 甲酯

[0316] 在 1L 圆底烧瓶中,将 1-(4- 溴 -2- 氟 苯基) 环丙烷 甲酸 (10.8g, 41.7mmol) 与 DMF (180mL) 合并以给出黄色溶液并且向该磁力搅拌溶液加入 K_2CO_3 (17.3g, 125mmol)。在 1h 内向其滴入溶解在 DMF (20mL) 中的甲基碘 (47.3g, 20.9mL, 333mmol)。将黄色悬浮液在 RT 搅拌过夜。将反应物浓缩,用水稀释 (500mL),并且用 EtOAc (2x500mL) 萃取。将 EtOAc 层用水盐水 (250mL) 洗涤,合并,在 MgSO_4 上干燥,过滤,并且浓缩,产生 1-(4- 溴 -2- 氟 - 苯基)- 环丙烷 甲酸 甲酯 (10.3g, 90.5% 产率),为浅棕色油。LC/MS: $\text{C}_{11}\text{H}_{10}\text{BrFO}_2$ (m/e) 计算值 272/274,实测值 273/275 (M+H, ES^+)。

[0317] 步骤 4:1-[2- 氟 -4-(4,4,5,5- 四甲基 -[1,3,2] 二氧杂硼杂环戊烷 -2- 基)- 苯

基]-环丙烷甲酸甲酯

[0318] 在 350mL 反应小瓶中, 将 1-(4-溴-2-氟-苯基)-环丙烷甲酸甲酯 (10.3g, 37.7mmol)、BISPIN (11.5g, 45.3mmol) 和乙酸钾 (7.4g, 75.4mmol) 与 1,4-二噁烷 (77.2mL) 合并以给出浅棕色悬浮液。将混合物用氮吹扫 (5 分钟), 加入 PdCl₂(DPPF)-DCM (1.54g, 1.89mmol)。将小瓶密封并在油浴中在 80℃ 加热 4h。将反应物通过硅藻土过滤, 用 DCM 冲洗, 浓缩, 用乙醚 (500mL) 稀释, 并且用水洗涤 (2x500mL)。将第一水性层过滤以移除黑色固体并且用乙醚冲洗。将该滤液与第二水性层合并并用乙醚 (500mL) 萃取。将有机层用盐水 (250mL) 洗涤, 合并, 在 MgSO₄ 上干燥, 过滤, 并且浓缩为红色油。将粗材料通过快速色谱 (硅胶, 己烷中 0% 至 20% EtOAc) 提纯。将合适的级分合并并浓缩, 产生粗产物 (12.32g), 为黄色油。

[0319] 粗产物为原材料和产物的混合物, 因而使其再次经受相同的反应条件。在含有粗产物和 1,4-二噁烷 (200mL) 的 350mL 反应小瓶中, 加入 BISPIN (13.6g, 53.6mmol) 和乙酸钾 (8.77g, 89.3mmol), 给出浅棕色悬浮液。将混合物用氮吹扫 (5 分钟), 并且加入 PdCl₂(DPPF) (3.65g, 4.47mmol)。将小瓶密封, 并且将反应物在油浴中在 80℃ 加热 3.5h。将反应冷却至室温 5 天。将反应物用 EtOAc 和水稀释, 浓缩, 并且用更多的 EtOAc (200mL) 和水 (200mL) 稀释。所得到的黑色混合物是不可分的。将部分量 (200mL) 的水性层 (第一水性层) 从分液漏斗移除, 并且将余下的混合物用盐水 (2x200mL, 第二和第三水性 / 盐水层) 洗涤。将留在分液漏斗中的黑色混合物过滤, 得到滤液中的两相。将其分离, 并且将有机层 (第一有机层) 在 MgSO₄ 上干燥。向第一水性和第二水性 / 盐水层加入 EtOAc (各 200mL), 混合, 通过相同的漏斗过滤, 分离, 并且将每个有机层用第三水性 / 盐水层洗涤。将第二和第三有机层与含有 MgSO₄ 的第一层合并, 干燥, 过滤, 并且浓缩产生粗产物 (24g)。将该材料溶解在最少 DCM 中并通过快速色谱提纯 (硅胶, 己烷中 0% 至 20% EtOAc)。将合适的级分浓缩, 并且由 DCM/Hex 干燥, 产生 1-[2-氟-4-(4,4,5,5-四甲基-[1,3,2] 二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯 (6.9g, 48.2% 产率), 为油状物, 其当冷却至室温时固化 (结晶) 为白色固体。LC/MS : C₁₇H₂₂BF₄O₄ (m/e) 计算值 320, 实测值 321 (M+H, ES⁺)。

[0320] 步骤 5 : 1-{3-氟-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯

[0321] 在 20mL 小瓶中, 将 1-[2-氟-4-(4,4,5,5-四甲基-[1,3,2] 二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯 (383mg, 0.320mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3] 三唑-4-基]-氨基甲酸叔丁酯 (400mg, 0.997mmol)、2-二环己膦基-2',6'-二甲氧基联苯 (SPhos) (123mg, 0.299mmol)、磷酸三钾 (635mg, 2.99mmol) 和 Pd(OAc)₂ (33.6mg, 0.150mmol) 与甲苯 (10mL) 和水 (2mL) (之前用氮吹扫 20 分钟) 合并以给出浅黄色悬浮液。将小瓶的气氛用氮吹扫, 密封, 在干燥区中在 80℃ 加热 4.5h, 并且冷却至室温过夜。将反应物用 EtOAc 稀释, 用水和盐水洗涤, 在 MgSO₄ 上干燥, 过滤, 浓缩, 溶解在最少 DCM 中, 并通过快速色谱提纯 (硅胶, 己烷中 0% 至 50% EtOAc)。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 1-{3-氟-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (380mg, 74.1% 产率), 为白色固体。LC/MS : C₂₉H₂₇FN₄O₄ (m/e) 计算值 514, 实测值 515 (M+H, ES⁺)。

[0322] 步骤 6 : 1-{3-氟-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3] 三

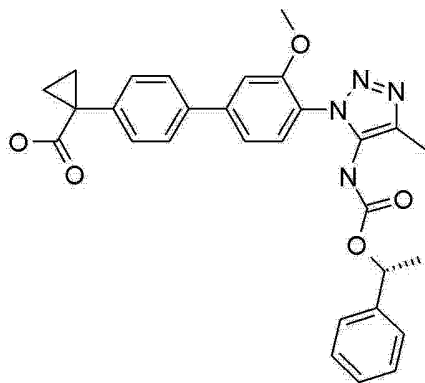
唑-1-基]-联苯-4-基}-环丙烷甲酸

[0323] 在 200mL 圆底烧瓶中,将 1-{3-氟-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)]-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (380mg, 0.739mmol) 与 THF (10mL) 和 MeOH (10mL) 合并以给出黄色溶液。向其滴入 1M NaOH (7.39mL, 7.39mmol)。将反应物在室温搅拌 1.5 天,储存在冰箱中 2.5 天。将反应物用水稀释,浓缩,用更多水稀释并用 1N HCl 酸化。将所得到的沉淀物过滤,用水和己烷洗涤,并且在室内真空下并在干燥器中干燥,产生 1-{3-氟-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)]-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸 (303mg, 82% 产率),为白色固体。LC/MS: $C_{28}H_{25}FN_4O_4$ (m/e) 计算值 500, 实测值 501 (M+H, ES⁺)。¹H NMR (DMSO-d₆) δ : 12.50 (br. s., 1H), 9.70 (br. s., 1H), 7.89 (d, J = 6.5Hz, 2H), 7.43-7.71 (m, 5H), 6.86-7.42 (m, 5H), 5.70 (br. s., 1H), 2.17 (s, 3H), 1.26-1.64 (m, 5H), 1.16-1.25 (m, 2H)。

[0324] 实施例 16

[0325] 1-{3'-甲氧基-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)]-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0326]



[0327] 步骤 1: 1-叠氮基-4-溴-2-甲氧基-苯

[0328] 向 4-溴-2-甲氧基苯基硼酸 (5g, 21.7mmol)、叠氮化钠 (2.11g, 32.5mmol) 和乙酸铜 (II) (393mg, 2.17mmol) 在 100mL 2 颈圆底烧瓶中的混合物在室温在氮气氛下加入甲醇 (40mL)。将所得到的棕色溶液在室温搅拌 15h, 并且通过移除一个塞子将烧瓶开放至空气。将数分钟内, 它开始改变颜色至棕色悬浮液并且之后将塞子再次关闭。在室温 15h 之后, 它基本上保持为相同的棕色。之后, 再次将塞子打开, 它缓慢地变暗。TLC 分析显示新斑点的存在。之后, 将反应混合物用热枪加热以完成反应。在该过程中, 它变为浅黑色悬浮液并且在环境温度 1h 之后, 将反应混合物倒入至饱和氯化铵和氢氧化铵的混合物中。将有机化合物萃取至二乙醚 (2x100mL) 中并将合并的萃取物用盐水溶液洗涤并在无水 MgSO₄ 上干燥。过滤和浓缩给出粗油, 将其使用 ISCO (120g) 柱色谱用己烷洗脱提纯。将级分合并并将溶剂在真空下移除以获得 1-叠氮基-4-溴-2-甲氧基-苯浅黄色油 (4.14g, 84% 产率)。

[0329] 步骤 2: 3-(4-溴-2-甲氧基-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸甲酯

[0330] 将 1-叠氮基-4-溴-2-甲氧基-苯 (3.95g, 17.3mmol) 和丁-2-炔酸甲酯 (1.7g, 17.3mmol) 在甲苯 (36mL) 中的溶液加热至 150°C 并且在该温度搅拌 15h, 此时 TLC 分析显示两个新斑点的存在。在 15h 搅拌过程中, 它缓慢地从浅黄色溶液变为暗棕色溶液。之后, 停止加热并且将甲苯在真空下移除以获得暗棕色油 (~ 8.0g), 将其使用 ISCO (120g) 柱色谱

用己烷中的 0-50% EA 洗脱提纯,以获得所有斑点。将所需的区域异构体 3-(4-溴-2-甲氧基-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸甲酯分离,为暗棕色粘性油(250mg,4.5%产率)。LC/MS: $C_{12}H_{12}BrN_3O_3$ (m/e) 计算值 326,实测值 328[M+H, ES⁺]。

[0331] 步骤 3:3-(4-溴-2-甲氧基-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸

[0332] 向 1-(4-溴-2-甲氧基-苯基)-4-甲基-1H-1,2,3-三唑-5-甲酸甲酯(220mg, 0.68mmol) 在 THF(4mL) 中的溶液在室温加入水(1.0mL) 中的过量的氢氧化锂单水合物(283mg, 6.75mmol)。将所得到的棕色溶液在油浴中加热至 50℃持续 3h,此时 LCMS 分析显示不存在原材料。之后,将其冷却至室温并且将溶剂在真空下移除。在用 NaOH(~5mL) 和水(50mL) 稀释之后,将中性杂质萃取至二乙醚(2x50mL) 中。将碱性水性层用 1N HCl 中和并将所得到的固体通过过滤收集并用水和己烷洗涤。在空气干燥之后,将 155mg(74%产率) 的 3-(4-溴-2-甲氧基-苯基)-5-甲基-3H-[1,2,3]三唑-4-甲酸分离,为灰白色固体。LC/MS: $C_{11}H_{10}BrN_3O_3$ (m/e) 计算值 312,实测值 314.0[M+H, ES⁺]。

[0333] 步骤 4:[3-(4-溴-2-甲氧基-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-苯基-乙酯

[0334] 向小瓶中的 1-(4-溴-2-甲氧基-苯基)-4-甲基-1H-1,2,3-三唑-5-甲酸(152mg, 0.49mmol) 在甲苯(4mL) 中的悬浮液在室温在氮气氛下加入三乙胺(49.3mg, 67.9 μL, 0.489mmol)。向所得到的棕色溶液加入二苯基磷酰基叠氮化物(134mg, 105 μL, 0.49mmol),之后在室温在氮气氛下加入(R)-1-苯基乙醇(59.5mg, 58.8 μL, 0.49mmol)。之后,将橡胶隔膜用帽替代并将棕色溶液加热至 80℃,并将其在该温度搅拌 3h。之后,将反应混合物冷却至室温并将溶剂在真空下移除。将棕色油使用 ISCO(80g) 柱色谱用己烷中的 0-100% EA 洗脱提纯。将所需的级分合并并将溶剂在真空下移除,以获得 [3-(4-溴-2-甲氧基-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-苯基-乙酯(173mg, 82%产率),为白色固体。LC/MS: $C_{19}H_{19}BrN_4O_3$ (m/e) 计算值 431,实测值 432.9[M+H, ES⁺]。

[0335] 步骤 5:1-{3'-甲氧基-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯

[0336] 向 [3-(4-溴-2-甲氧基-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-苯基-乙酯(100mg, 0.23mmol)、1-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)环丙烷甲酸甲酯(105mg, 0.35mmol)、乙酸钡(II)(7.81mg, 0.035mmol)、2-二环己基膦基-2',6'-二甲氧基联苯(28.6mg, 0.69mmol) 和磷酸三钾(148mg, 0.69mmol) 的混合物在室温在氮气氛下加入之前脱气的甲苯(4.5mL) 和水(1.0mL)。将所得到的浅黄色悬浮液加热至 105℃并搅拌 2h,此时 TLC 分析显示不存在原材料。在 1h 内,将反应混合物转化为黑色反应混合物。在 2h 之后,将反应混合物冷却至室温并倒入至水和盐水溶液的混合物中。将有机化合物萃取至 EA(2x50mL) 中并将合并的萃取物用盐水溶液洗涤并在无水 MgSO₄ 上干燥。过滤和浓缩给出粗残留物,将其通过使用 ISCO(40g) 柱色谱用己烷中的 0-100% EA 洗脱提纯。将所需的级分合并并将溶剂在真空下移除以分离 1-{3'-甲氧基-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯(95mg, 75%产率),为灰白色固体。LC/MS: $C_{30}H_{30}N_4O_5$ (m/e) 计算值 526,实测值 527.1[M+H, ES⁺]。

[0337] 步骤 6:1-{3'-甲氧基-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,

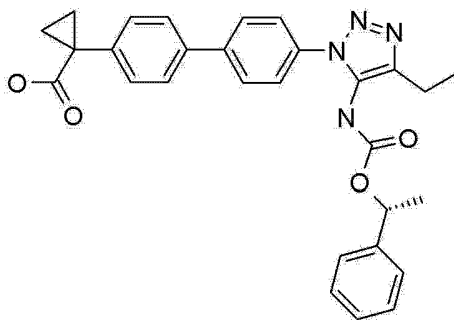
2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0338] 向 1-{2'-甲氧基-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (87mg, 0.17mmol) 在 THF (4.5mL) 和乙醇 (4.5mL) 中的溶液在室温加入过量的 1M 氢氧化钠 (1.65mL, 1.65mmol)。将所得到的无色溶液搅拌 15h, 此时 LCMS 分析显示不存在原材料。之后, 将溶剂在真空下移除并且将碱性水层用水稀释并且用 1N HCl 中和。将所得到的固体通过过滤收集, 并用水和己烷洗涤。在空气干燥之后, 将 50mg (59% 产率) 的 1-{3'-甲氧基-4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸分离, 为白色固体。LC/MS: $C_{29}H_{28}N_4O_5$ (m/e) 计算值 512, 实测值 513.1 [M+H, ES⁺]⁺。¹H NMR (DMSO-d₆) δ : 12.40 (br. s., 1H), 9.43 (br. s., 1H), 7.70 (d, J = 8.3Hz, 2H), 7.41-7.51 (m, 3H), 7.18-7.39 (m, 7H), 5.70 (d, J = 6.3Hz, 1H), 3.74 (s, 3H), 2.16 (s, 3H), 1.34-1.56 (m, 5H), 1.16-1.24 (m, 2H)。

[0339] 实施例 17

[0340] 1-{4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0341]



[0342] 步骤 1: 3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-甲酸乙酯

[0343] 向 1-叠氮基-4-溴苯 (5g, 25.2mmol) 在甲苯 (50mL) 中的溶液加入 250mL 密封管中的净 2-戊炔酸乙酯 (3.19g, 25.2mmol), 并且之后将其在氮气氛下保持 2 分钟。之后, 将烧瓶用紧密盖密封并且将所得到的浅黄色溶液加热至 150°C 并且搅拌 2h, 此时 TLC 分析显示两个新斑点的存在, 并且 LCMS 分析显示所需的质量的存在。之后, 将暗棕色反应混合物冷却至室温并且将溶剂在真空下移除。将所得到的暗棕色残留物 (8.3g) 使用 ISCO (330g) 柱色谱用己烷中 0-50% EA 洗脱提纯。将 TLC 中的顶部斑点分离为所需的 3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-甲酸乙酯, 为灰白色固体 (2.83g, 34.6% 产率) 并且底部斑点证实为错误的区域异构体, 3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-甲酸乙酯, 将其分离, 为浅棕色油 (3.44g, 42% 产率)。LC/MS: $C_{13}H_{14}BrN_3O_2$ (m/e) 计算值 324, 实测值 326 [M+H, ES⁺]⁺。

[0344] 步骤 2: 3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-甲酸

[0345] 向 3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-甲酸乙酯 (2.8g, 8.64mmol) 在 THF (40mL) 中的棕色溶液在室温加入氢氧化锂单水合物 (1.81g, 43.2mmol) 在水 (10mL) 中的溶液。将所得到的棕色溶液在室温搅拌 15h, 此时 LCMS 分析显示不存在原材料。之后, 将溶剂在真空下移除。在用 NaOH (~5mL) 和水 (50mL) 稀释之后, 将中性杂质萃取至二乙醚 (100mL) 中并且其也移除棕色。将碱性水性层用 1N HCl 中和并将所得到的白色固体通

过过滤收集,并且用水和己烷洗涤。在空气干燥之后,将 2.13g(83%产率)的 3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-甲酸分离,为灰白色固体。LC/MS: $C_{11}H_{10}BrN_3O_2$ (m/e) 计算值 296,实测值 297.7[M+H, ES⁺]。

[0346] 步骤 3:[3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-苯基-乙酯

[0347] 向小瓶中的 3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-甲酸(592mg, 2.0mmol)在甲苯(10mL)中的悬浮液在室温在氮气氛下加入三乙胺(202mg, 279 μ L, 2.0mmol)。向所得到的棕色溶液加入二苯基磷酰基叠氮化物(550mg, 431 μ L, 2.0mmol),之后在室温在氮气氛下加入(R)-1-苯基乙醇(244mg, 241 μ L, 2.0mmol)。之后,将所得到的浅棕色溶液加热至 80℃并且在该温度搅拌 2h。之后,将浅棕色反应混合物冷却至室温,并且将溶剂在真空下移除。将棕色油使用 ISCO(80g)柱色谱用己烷中的 0-100% EA 洗脱提纯,以获得所需的 [3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-苯基-乙酯(696mg, 89%产率),为白色固体。LC/MS: $C_{19}H_{19}BrN_4O_2$ (m/e) 计算值 415,实测值 417[M+H, ES⁺]。

[0348] 步骤 4:1-{4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯

[0349] 向 [3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-苯基-乙酯(300mg, 0.72mmol)、1-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)环丙烷甲酸甲酯(327mg, 1.08mmol)、乙酸钡(II)(24.3mg, 0.11mmol)、2-二环己基膦基-2',6'-二甲氧基联苯(89.0mg, 0.22mmol)和磷酸三钾(460mg, 2.17mmol)的混合物在室温在氮气氛下加入之前脱气的甲苯(9.0mL)和水(2.0mL)。将所得到的浅黄色悬浮液加热至 105℃并且搅拌 2h,此时 TLC 分析显示不存在原材料。之后,将反应混合物冷却至室温并倒入至水和盐水溶液的混合物中。将有机化合物萃取至 EA(2x50mL)中并将合并的萃取物用盐水溶液洗涤并在无水 MgSO₄上干燥。过滤和浓缩给出粗残留物,将其通过使用 ISCO(80g)柱色谱用己烷中的 0-100% EA 洗脱提纯。将所需的级分合并并将溶剂在真空下移除,以分离所需的 1-{4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯(240mg, 65%产率)。LC/MS: $C_{30}H_{30}N_4O_4$ (m/e) 计算值 510,实测值 511.1[M+H, ES⁺]。

[0350] 步骤 5:1-{4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

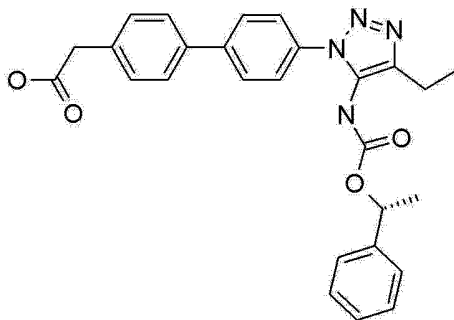
[0351] 向 1-{4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯(234mg, 0.46mmol)在 THF(10mL)和乙醇(10mL)中的溶液在室温加入过量的 1.0M 氢氧化钠(4.58mL, 4.58mmol)溶液。将所得到的无色溶液搅拌 15h,此时 LCMS 分析显示不存在原材料。之后,将溶剂在真空下移除,并且将碱性水层用水稀释,并且用 1N HCl 中和。将所得到的固体通过过滤收集并用水和己烷洗涤。在空气干燥之后,将 193mg(85%产率)的 1-{4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸分离,为白色固体。LC/MS: $C_{29}H_{28}N_4O_4$ (m/e) 计算值 496,实测值 497.1[M+H, ES⁺]。¹H NMR(DMSO-d₆) δ : 12.40(br. s., 1H), 9.66(br. s., 1H), 7.83(d, J = 6.5Hz, 2H), 7.67(d, J = 8.0Hz, 2H), 7.58(d, J = 7.3Hz, 2H), 7.47(d, J =

8.0Hz, 2H), 7.34 (br. s., 5H), 5.71 (br. s., 1H), 2.56 (d, $J = 7.5$ Hz, 2H), 1.36-1.60 (m, 5H), 1.16-1.23 (m, 5H)。

[0352] 实施例 18

[0353] {4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸

[0354]



[0355] 步骤 1:{4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯

[0356] 向 (R)-1-(4-溴苯基)-4-乙基-1H-1,2,3-三唑-5-基氨基甲酸-1-苯基乙酯 (200mg, 0.48mmol)、2-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)乙酸乙酯 (210mg, 0.72mmol)、乙酸钼 (II) (16.2mg, 0.072mmol)、2-二环己基膦基-2',6'-二甲氧基联苯 (59.3mg, 0.144mmol) 和磷酸三钾 (307mg, 1.44mmol) 的混合物在室温在氮气氛围下加入之前脱气的甲苯 (4.5mL) 和水 (1.0mL)。将所得到的浅黄色悬浮液加热至 105℃ 并搅拌 1h, 此时 TLC 分析显示不存在原材料。之后, 将反应混合物冷却至室温并倒入至水和盐水溶液的混合物中。将有机化合物萃取至 EA (2x50mL) 中并将合并的萃取物用盐水溶液洗涤并在无水 $MgSO_4$ 上干燥。过滤和浓缩给出粗残留物, 将其通过使用 ISCO (80g) 柱色谱用己烷中的 0-100% EA 洗脱提纯。将所需的级分合并并将溶剂在真空下移除, 以分离 {4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯 (133mg, 55% 产率)。LC/MS: $C_{28}H_{28}N_4O_4$ (m/e) 计算值 498, 实测值 499.1 [M+H, ES^+]。

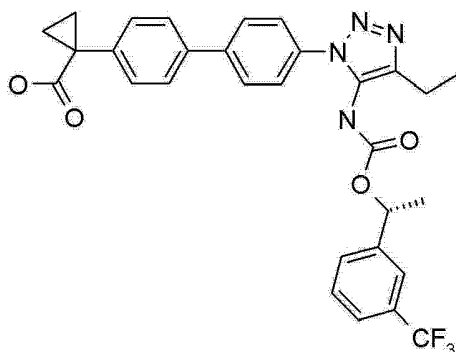
[0357] 步骤 2:{4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸

[0358] 向 {4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯 (105mg, 0.21mmol) 在 THF (5mL) 和乙醇 (5.0mL) 中的溶液在室温加入水中的过量的 1M 氢氧化钠 (2.11mL, 2.11mmol) 溶液。将所得到的无色溶液在室温搅拌 15h, 此时 LCMS 分析显示不存在原材料。之后, 将溶剂在真空下移除并将碱性水溶液用 1N HCl 中和。将所得到的固体通过过滤收集并用水和己烷洗涤。在空气干燥之后, 将 74mg (75% 产率) 的 {4'-[4-乙基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸分离, 为白色固体。LC/MS: $C_{27}H_{26}N_4O_4$ (m/e) 计算值 470, 实测值 470.1 [M+H, ES^+]。 1H NMR (DMSO- d_6) δ : 12.43 (br. s., 1H), 9.16-9.88 (m, 1H), 7.84 (d, $J = 6.0$ Hz, 2H), 7.70 (d, $J = 8.0$ Hz, 2H), 7.52-7.64 (m, 2H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.07-7.38 (m, 5H), 5.70 (br. s., 1H), 3.66 (s, 2H), 2.57 (d, $J = 7.0$ Hz, 2H), 1.48 (br. s., 3H), 1.20 (t, $J = 7.5$ Hz, 3H)。

[0359] 实施例 19

[0360] 1-(4'-{4-乙基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸

[0361]



[0362] 步骤 1:[3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-(3-三氟甲基-苯基)-乙酯

[0363] 向小瓶中 1-(4-溴苯基)-4-乙基-1H-1,2,3-三唑-5-甲酸 (623mg, 2.1mmol) 在甲苯 (10mL) 中的悬浮液在室温在氮气氛下加入三乙胺 (213mg, 293 μ L, 2.1mmol)。向所得到的棕色溶液在室温在氮气氛下加入二苯基磷酰基叠氮化物 (579mg, 453 μ L, 2.1mmol) 和 (R)-1-(3-(三氟甲基)苯基)乙醇 (400mg, 2.1mmol)。之后,将所得到的浅棕色溶液加热至 80°C 并且在该温度搅拌 2.5h。之后,将澄清的浅棕色反应混合物冷却至室温并且将溶剂在真空下移除。将所得到的棕色油使用 ISCO (80g) 柱色谱用己烷中的 0-100% EA 洗脱提纯。将所需的级分合并,并且将溶剂在真空下移除,以获得 [3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-(3-三氟甲基-苯基)-乙酯 (735mg, 72% 产率), 为白色固体。LC/MS: $C_{20}H_{18}BrF_3N_4O_2$ (m/e) 计算值 483, 实测值 484.9 [M+H, ES⁺]。

[0364] 步骤 2:1-(4'-{4-乙基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸甲酯

[0365] 向小瓶中 [3-(4-溴-苯基)-5-乙基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-(3-三氟甲基-苯基)-乙酯 (300mg, 0.62mmol)、1-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)环丙烷甲酸甲酯 (281mg, 0.93mmol)、乙酸钡 (II) (20.9mg, 0.09mmol)、2-二环己基磷基-2',6'-二甲氧基联苯 (76.5mg, 0.19mmol) 和磷酸三钾 (395mg, 1.86mmol) 的混合物在室温在氮气氛下加入新脱气的甲苯 (4.5mL) 和水 (1.0mL)。之后,将帽关闭并将所得到的浅黄色悬浮液加热至 105°C 并且搅拌 1h, 此时 TLC 分析显示不存在原材料。之后,将反应混合物冷却至室温并倒入至水和盐水溶液的混合物中。将有机化合物萃取至 EA (2x50mL) 中并且将合并的萃取物用盐水溶液洗涤,并在无水 $MgSO_4$ 上干燥。过滤和浓缩给出粗残留物,将其通过使用 ISCO (80g) 柱色谱用己烷中的 0-100% EA 洗脱提纯。将所需的级分合并并将溶剂在真空下移除,以分离 1-(4'-{4-乙基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸甲酯 (245mg, 68% 产率)。LC/MS: $C_{31}H_{29}F_3N_4O_4$ (m/e) 计算值 578, 实测值 579.4 [M+H, ES⁺]。

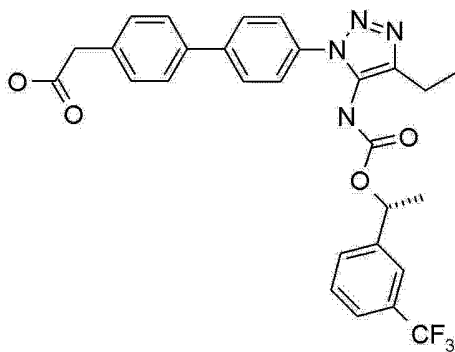
[0366] 步骤 3:1-(4'-{4-乙基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基}-联苯-4-基)-环丙烷甲酸

[0367] 向 1-(4'-[4-乙基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基]-联苯-4-基)-环丙烷甲酸甲酯 (240mg, 0.42mmol) 在 THF (5mL) 和乙醇 (5mL) 中的溶液在室温加入水中的过量的 1.0N 氢氧化钠 (4.15mL, 4.15mmol) 溶液。将所得到的溶液在室温搅拌 15h, 此时 TLC 分析显示不存在原材料。之后, 将其用水稀释, 并将溶剂在真空下移除。将中性杂质萃取至二乙醚 (100mL) 中, 并将碱性水性层用 1.0N HCl 中和。将所得到的沉淀物萃取至 EA (2x45mL) 中并将合并的萃取物用盐水溶液洗涤。在干燥和过滤之后, 将溶剂在真空下移除以获得 1-(4'-[4-乙基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基]-联苯-4-基)-环丙烷甲酸 (219mg, 93.5% 产率)。LC/MS: $C_{30}H_{27}F_3N_4O_4$ (m/e) 计算值 564, 实测值 565.3 [M+H, ES⁺]⁺。¹H NMR (DMSO-d₆) δ : 12.24 (br. s., 1H), 9.28-9.93 (m, 1H), 7.82 (d, J = 6.8Hz, 2H), 7.53-7.76 (m, 7H), 7.47 (d, J = 8.3Hz, 3H), 5.80 (br. s., 1H), 2.54-2.64 (m, 2H), 1.37-1.61 (m, 5H), 1.13-1.23 (m, 5H)。

[0368] 实施例 20

[0369] {4'-[4-乙基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸

[0370]



[0371] 步骤 1: {4'-[4-乙基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯

[0372] 向小瓶中 (R)-1-(4-溴苯基)-4-乙基-1H-1,2,3-三唑-5-基氨基甲酸-1-(3-(三氟甲基)苯基)乙酯 (200mg, 0.41mmol)、2-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)乙酸乙酯 (120mg, 0.41mmol)、乙酸钡 (II) (13.9mg, 0.06mmol)、2-二环己基磷基-2',6'-二甲氧基联苯 (51.0mg, 0.12mmol) 和磷酸三钾 (264mg, 1.24mmol) 的混合物在室温在氮气氛下加入新脱气的甲苯 (4.5mL) 和水 (1.0mL)。之后, 将帽封闭并将所得到的浅黄色悬浮液加热至 105°C 并搅拌 1h, 此时 TLC 分析显示不存在原材料。之后, 将反应混合物冷却至室温并倒入至水和盐水溶液的混合物中。将有机化合物萃取至 EA (2x50mL) 中并将合并的萃取物用盐水溶液洗涤并在无水 MgSO₄ 上干燥。过滤和浓缩给出粗残留物, 将其通过使用 ISCO (80g) 柱色谱用己烷中的 0-100% EA 洗脱提纯。将所需的级分合并并将溶剂在真空下移除, 以分离 {4'-[4-乙基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯 (194mg, 83% 产率)。LC/MS: $C_{30}H_{29}F_3N_4O_4$ (m/e) 计算值 566, 实测值 567.4 [M+H, ES⁺]⁺。

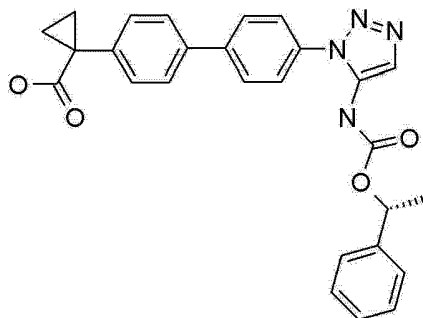
[0373] 步骤 2: {4'-[4-乙基-5-[(R)-1-(3-三氟甲基-苯基)-乙氧基羰基氨基]-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸

[0374] 向 {4'-[4-乙基-5-((R)-1-(3-三氟甲基-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯 (185mg, 0.33mmol) 在 THF (5mL) 和乙醇 (5mL) 中的溶液在水中在室温加入过量的 1.0N 氢氧化钠 (3.27mL, 3.27mmol) 溶液。将所得到的无色溶液在室温搅拌 15h, 此时 TLC 分析显示不存在原材料。之后, 将其用水稀释 (~15mL) 并将溶剂在真空下移除。将碱性水性层用 1.0N HCl 中和。将所得到的沉淀物萃取至 EA (2x45mL) 中并且将合并的萃取物用盐水溶液洗涤。在无水 MgSO₄ 上干燥和过滤之后, 将溶剂在真空下移除以获得所需的酸, 将其溶解在二氯甲烷 (~5mL) 中, 并且之后用己烷稀释。作为结果, 形成固体, 并且将它们通过过滤收集并用己烷洗涤。在空气干燥之后, 将 135mg (77% 产率) 的 {4'-[4-乙基-5-((R)-1-(3-三氟甲基-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸分离, 为白色固体。LC/MS: C₂₈H₂₅F₃N₄O₄ (m/e) 计算值 538, 实测值 539.3 [M+H, ES⁺]¹H NMR (DMSO-d₆) δ: 12.40 (s, 1H), 9.30-9.92 (m, 1H), 7.83 (d, J = 6.8Hz, 2H), 7.53-7.76 (m, 7H), 7.41 (d, J = 8.0Hz, 3H), 5.79 (d, J = 15.6Hz, 1H), 3.66 (s, 2H), 2.55 (d, J = 7.3Hz, 2H), 1.51 (br. s., 3H), 1.18 (t, J = 7.4Hz, 3H)。

[0375] 实施例 21

[0376] 1-{4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0377]



[0378] 步骤 1: 3-(4-溴-苯基)-3H-[1,2,3]三唑-4-甲酸甲酯

[0379] 在 350mL 反应小瓶中, 将 1-叠氮基-4-溴-苯 (5g, 25.2mmol) 和丙酸甲酯 (2.12g, 2.11mL, 25.2mmol) 与甲苯 (50mL) 合并以给出黄色悬浮液。将小瓶密封并在油浴中在 150°C 加热 5.5h。将反应物过滤, 将固体用甲苯和 EtOAc 洗涤。将滤液浓缩, 溶解在最少的 DCM 中, 并且通过快速色谱 (硅胶, 己烷中 0% 至 50% EtOAc) 提纯。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 3-(4-溴-苯基)-3H-[1,2,3]三唑-4-甲酸甲酯 (1.5g, 21.1% 产率), 为浅棕色固体。LC/MS: C₁₀H₈BrN₃O₂ (m/e) 计算值 281/283, 实测值 282/284 (M+H, ES⁺)。

[0380] 步骤 2: 3-(4-溴-苯基)-3H-[1,2,3]三唑-4-甲酸

[0381] 向含有溶解在 THF (30mL) (棕色溶液) 中的 3-(4-溴-苯基)-3H-[1,2,3]三唑-4-甲酸甲酯 (1.0g, 3.54mmol) 的 200mL 圆底烧瓶加入水 (10mL) 中的 LiOH (0.81g, 34mmol), 加热以部分地溶解。将溶液在室温搅拌 20h。将反应物浓缩, 稀释在水 (总体积, 200mL) 中, 用乙醚 (2x100mL) 萃取。将水性层用 1N HCl 酸化并将所得到的沉淀物过滤, 用水和己烷洗涤, 并且在室内真空干燥, 产生 3-(4-溴-苯基)-3H-[1,2,3]三唑-4-甲酸 (0.78g, 81.7% 产率), 为浅棕色固体。LC/MS: C₉H₆N₃O₂ (m/e) 计算值 267/269, 实测值 268/270 (M+H, ES⁺)。

[0382] 步骤3:[3-(4-溴-苯基)-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-苯基-乙酯

[0383] 在40mL反应小瓶中,将3-(4-溴-苯基)-3H-[1,2,3]三唑-4-甲酸(399mg, 1.45mmol)、(R)-1-苯基乙醇(265mg,0.83mL,2.17mmol)和三乙胺(293mg,0.4mL,2.9mmol)与甲苯(17mL)合并以给出黄色溶液,并且向其加入二苯基磷酰基叠氮化物(797mg, 0.624mL,2.89mmol)。将小瓶的气氛用氮吹扫,密封,在油浴中在65℃加热3.5h,并且冷却至室温过夜。将反应物浓缩,用EtOAc稀释,用水和盐水洗涤,并且在MgSO₄上干燥,过滤,浓缩,溶解在最少DCM中,并且通过快速色谱(硅胶,己烷中0%至50% EtOAc)提纯。将合适的级分合并,浓缩,并且由DCM/己烷干燥,产生[3-(4-溴-苯基)-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-苯基-乙酯(408mg,72.8%产率),为白色固体。LC/MS:C₁₇H₁₅BrN₄O₂(m/e) 计算值386/388,实测值387/389(M+H, ES⁺)。

[0384] 步骤4:1-{4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯

[0385] 在20mL小瓶中,将1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯(93.6mg,0.310mmol),[3-(4-溴-苯基)-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-苯基-乙酯(100mg,0.258mmol),2-二环己磷基-2',6'-二甲氧基联苯(SPhos)(31.8mg,0.0775mmol),Pd(OAc)₂(8.7mg,0.039mmol),和磷酸三钾(164mg,0.0775mmol)与甲苯(8mL)和水(2mL)(之前用氮吹扫20分钟)合并,以给出浅黄色溶液。将小瓶的气氛用氮替代,密封,在干燥区中在80℃加热4h,并且冷却至室温过夜。将反应物用EtOAc(70mL)稀释并用水(100mL)和盐水(50mL)洗涤。将水性层用EtOAc(60mL)萃取。将有机层合并,在MgSO₄上干燥,过滤,浓缩,溶解在最少DCM中,并且通过快速色谱(硅胶,己烷中0%至50% EtOAc)提纯。将合适的级分合并,浓缩,并且从DCM/己烷干燥,产生1-{4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯(45.1mg,36.2%产率),为淡黄色固体。LC/MS:C₂₈H₂₆N₄O₄(m/e) 计算值482,实测值483(M+H, ES⁺)。

[0386] 步骤5:1-{4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸

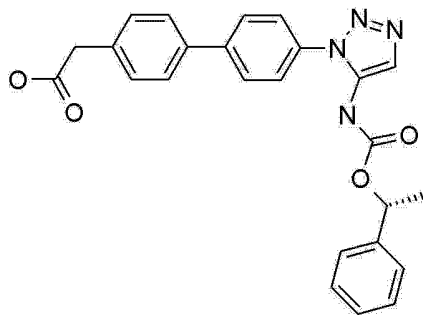
[0387] 在200mL圆底烧瓶中,将1-{4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯(40mg,0.0829mmol)与THF(2mL)和MeOH(2mL)合并,以给出黄色溶液。向其滴入NaOH(1M,1mL,1mmol)。将反应物在室温搅拌过夜。将反应物用水稀释,浓缩,用更多水稀释并用1N HCl酸化。将所得到的沉淀物过滤,用水和己烷洗涤,并且在室内真空下并在干燥器中干燥,产生1-{4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸(28.7mg,73.9%产率),为浅棕色固体。LC/MS:C₂₇H₂₄N₄O₄(m/e) 计算值468,实测值469(M+H, ES⁺)。 ¹H NMR(DMSO-d₆) δ:12.38(br. s., 1H),10.04(br. s., 1H),7.87(d, J = 8.3Hz, 2H),7.82(s, 1H),7.68(d, J = 8.3Hz, 2H),7.62(d, J = 8.3Hz, 2H),7.48(d, J = 8.0Hz, 2H),7.17-7.41(m, 5H),5.74(d, J = 5.8Hz, 1H),1.34-1.62(m, 5H),1.21(d, J = 2.5Hz, 2H)。

[0388] 实施例22

[0389] {4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联

苯-4-基}-乙酸

[0390]



[0391] 步骤 1: {4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯

[0392] 在 20mL 小瓶中, 将 1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-乙酸乙酯 (89.9mg, 0.310mmol)、[3-(4-溴-苯基)-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-1-苯基-乙酯 (100mg, 0.258mmol)、2-二环己膦基-2',6'-二甲氧基联苯 (SPHOS) (31.8mg, 0.0775mmol)、Pd(OAc)₂ (8.7mg, 0.039mmol) 和磷酸三钾 (164mg, 0.0775mmol) 与甲苯 (7mL) 和水 (2mL) (之前用氮吹扫 20 分钟) 合并, 以给出浅黄色溶液。将小瓶的气氛用氮吹扫, 密封, 在干燥区中在 80℃ 加热 4h, 并且冷却至室温过夜。加入另外的 1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-乙酸乙酯 (89.9mg, 0.310mmol)、2-二环己膦基-2',6'-二甲氧基联苯 (SPHOS) (31.8mg, 0.0775mmol) 和 Pd(OAc)₂ (8.7mg, 0.039mmol)。将小瓶的气氛用氮吹扫, 密封, 在干燥区中在 80℃ 加热 4h, 并且冷却至室温过夜。将反应物用 EtOAc (70mL) 稀释并用水 (100mL) 和盐水 (50mL) 洗涤。将水性层用 EtOAc (60mL) 萃取并将有机层合并, 在 MgSO₄ 上干燥, 过滤, 浓缩, 溶解在最少 DCM 中并通过快速色谱提纯 (硅胶, 己烷中 0% 至 50% EtOAc)。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 {4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯 (46mg, 37.9% 产率), 为淡黄色固体。LC/MS (ES): C₂₇H₂₆N₄O₄ (m/e) 计算值 470, 实测值 471 (M+H, ES⁺)。

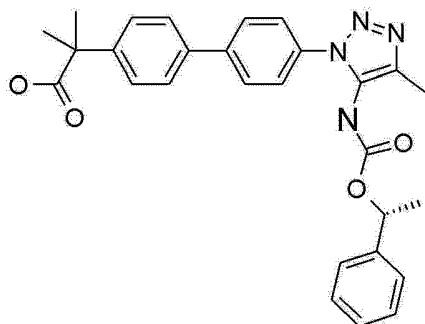
[0393] 步骤 2: {4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸

[0394] 在 200mL 圆底烧瓶中, 将 1-{4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (41mg, 0.087mmol) 与 THF (2mL) 和 MeOH (2mL) 合并以给出黄色溶液。向其滴入 NaOH (1M, 1mL, 1mmol)。将反应物在室温搅拌过夜。将反应物用水稀释, 浓缩, 用更多水稀释, 并且用 1N HCl 酸化。将所得到的沉淀物过滤, 用水和己烷洗涤, 并且在室内真空下并在干燥器中干燥, 产生 {4'-[5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸 (28.6mg, 74.2% 产率), 为黄色固体。LC/MS: C₂₅H₂₂N₄O₄ (m/e) 计算值 442, 实测值 443 (M+H, ES⁺)。¹H NMR (DMSO-d₆) δ: 12.39 (br. s., 1H), 10.03 (br. s., 1H), 7.88 (d, J = 8.3Hz, 2H), 7.82 (s, 1H), 7.72 (d, J = 8.0Hz, 2H), 7.62 (d, J = 8.3Hz, 2H), 7.42 (d, J = 8.0Hz, 2H), 7.13-7.39 (m, 5H), 5.74 (d, J = 5.3Hz, 1H), 3.66 (s, 2H), 1.46 (br. s., 3H)。

[0395] 实施例 23

[0396] 2-甲基-2-{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-丙酸

[0397]



[0398] 步骤1: {5-甲基-3-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-3H-[1,2,3]三唑-4-基}-氨基甲酸(R)-1-苯基-乙酯

[0399] 在20mL小瓶中,将1-(4-溴苯基)-4-甲基-1H-1,2,3-三唑-5-基氨基甲酸(R)-1-苯基乙酯(2.39g,5.96mmol)、BISPIN(1.82g,7.15mmol)和乙酸钾(1.17g,11.9mmol)与1,4-二噁烷(59.8mL)合并以给出白色悬浮物,将其用氮吹扫5分钟。向混合物加入PdCl₂(DPPF)(0.486g,0.596mmol)。将小瓶密封,在干燥区中在80℃搅拌3.5h,并且冷却至室温过夜。将反应物过滤,用EtOAc冲洗,浓缩,用EtOAc(200mL)稀释,并且再次过滤。将滤液用水(200mL)和盐水(100mL)洗涤。将水性层用EtOAc(200mL)萃取。将有机层合并,在MgSO₄上干燥,过滤,浓缩,并且将粗材料通过快速色谱(硅胶,己烷中0%至50%EtOAc)提纯。将合适的级分合并,产生{5-甲基-3-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-3H-[1,2,3]三唑-4-基}-氨基甲酸(R)-1-苯基-乙酯(2.24g,83%产率),为澄清油,其当冷却至室温时固化为白色结晶。LC/MS:C₂₄H₂₉BN₄O₄(m/e)计算值448,实测值449(M+H,ES⁺)。

[0400] 步骤2: 2-甲基-2-{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-丙酸甲酯

[0401] 在20mL小瓶中,将2-(4-溴-苯基)-2-甲基-丙酸甲酯(130mg,0.506mmol)、{5-甲基-3-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-3H-[1,2,3]三唑-4-基}-氨基甲酸(R)-1-苯基-乙酯(212mg,0.473mmol)、2-二环己膦基-2',6'-二甲氧基联苯(SPhos)(59mg,0.144mmol)、磷酸三钾(292mg,1.38mmol)和Pd(OAc)₂(17mg,0.075mmol)与甲苯(8mL)和水(2mL)(之前用氮吹扫20分钟)合并以给出浅黄色悬浮液。将小瓶的气氛用氮吹扫,密封,在干燥区中在80℃加热4h,并且冷却至室温过夜。将反应物用EtOAc稀释,用水和盐水洗涤,在MgSO₄上干燥,过滤,浓缩,溶解在最少DCM中并通过快速色谱提纯(硅胶,己烷中0%至50%EtOAc)。将合适的级分合并,浓缩,并且由DCM/己烷干燥,产生2-甲基-2-{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-丙酸甲酯(106mg,45%产率),为白色固体。LC/MS:C₂₉H₃₀N₄O₄(m/e)计算值498,实测值499(M+H,ES⁺)。

[0402] 步骤3: 2-甲基-2-{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-丙酸

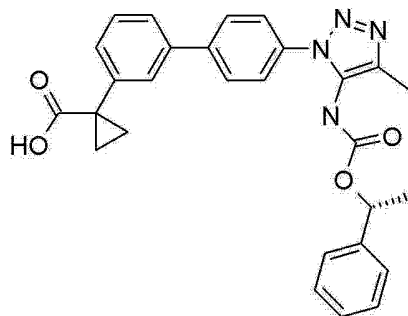
[0403] 在200mL圆底烧瓶中,将2-甲基-2-{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-丙酸甲酯(106mg,45%产率),为白色固体。

基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-丙酸甲酯(100mg,0.201mmol)与THF(4mL)和MeOH(4mL)合并以给出黄色溶液。向其滴入1M NaOH(2mL,2.0mmol)。将反应物在室温搅拌2天并且储存在冰箱中1.5天。将反应物再次在室温搅拌1天并且之后加入更多的1M NaOH(1mL,1mmol)。将反应物在干燥区中在40℃加热6h,并且之后冷却至室温过夜。将反应物用水稀释,浓缩,用更多水稀释并用1N HCl酸化。将所得到的沉淀物过滤,用水和己烷洗涤,并且在室内真空下并在干燥器中干燥,产生2-甲基-2-{4'-[4-甲基-5-((R)-1-苯基-乙氧基)羰基氨基]-[1,2,3]三唑-1-基]-联苯-4-基}-丙酸(79.6mg,81.9%产率),为白色固体。LC/MS: $C_{28}H_{28}N_4O_4$ (m/e)计算值484,实测值485(M+H, ES⁺)。¹H NMR(DMSO-d₆) δ :12.43(br. s., 1H), 9.68(br. s., 1H), 7.84(d, J = 7.0Hz, 2H), 7.71(d, J = 8.3Hz, 2H), 7.58(d, J = 7.5Hz, 2H), 7.50(d, J = 8.3Hz, 2H), 7.06-7.43(m, 5H), 5.70(br. s., 1H), 2.18(s, 3H), 1.33-1.73(m, 9H)。

[0404] 实施例 24

[0405] (R)-1-(4'-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)联苯-3-基)环丙烷甲酸

[0406]



[0407] 步骤1:1-(3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)环丙烷甲酸乙酯

[0408] 350mL 密封帽容器装有1-(3-溴苯基)环丙烷甲酸乙酯(3.56g,13.2mmol)、4,4,4',4',5,5,5',5'-八甲基-2,2'-双(1,3,2-二氧杂硼杂环戊烷)(4.03g,15.9mmol)和乙酸钾(2.6g,26.5mmol),并且之后加入1,4-二噁烷(40mL)以给出白色悬浮物。之后将混合物用氮气鼓泡通过反应混合物10分钟,之后在室温在氮气氛下加入[1,1'-双(二苯基膦基)二茂铁]二氯化钡(II)(484mg,0.66mmol)。之后,将烧瓶用帽密封并且将棕色反应混合物在油浴中在80℃加热5h。之后,将其冷却至室温并且倒入至水(100mL)和盐水(100mL)的溶液中,并且将有机化合物萃取至EA(2x150mL)中(因为黑色混合物,难以看到两个层)。将合并的萃取物用盐水溶液洗涤并且在无水MgSO₄上干燥。过滤和浓缩给出粗黑色油(~11.11g),将其使用ISCO(120g)柱色谱用己烷中0-60%EA洗脱提纯。将所需的级分(20-40)合并并将溶剂在真空下移除,以获得1-(3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)环丙烷甲酸乙酯,为粘性油(2.55g,61%产率)。LC/MS: $C_{18}H_{25}BO_4$ (m/e)计算值316,实测值317.2[M+H, ES⁺]。

[0409] 步骤2:(R)-1-(4'-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)联苯-3-基)环丙烷甲酸乙酯

[0410] 向50mL密封管中的1-(3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)

苯基) 环丙烷甲酸乙酯 (236mg, 0.75mmol)、1-(4-溴苯基)-4-甲基-1H-1,2,3-三唑-5-基氨基甲酸 (R)-1-苯基乙酯 (200mg, 0.5mmol)、乙酸钡 (II) (16.8mg, 0.075mmol)、2-二环己基膦基-2',6'-二甲氧基联苯 (61.4mg, 0.15mmol) 和磷酸三钾 (317mg, 1.5mmol) 的混合物在室温在氮气氛下加入新脱气的甲苯 (4.5mL) 和水 (1.0mL)。之后, 将橡胶隔膜用帽替代并且将所得到的浅黄色悬浮液用油浴加热至 110℃。在该期间的过程中, 它变为黑色悬浮液。之后, 将反应混合物冷却至室温并倒入至水和盐水溶液中。将有机化合物萃取至 EA (2x50mL) 中并将合并的萃取物用盐水溶液洗涤, 并在无水 MgSO₄ 上干燥。过滤和浓缩给出粗产物, 将其使用 ISCO (80g) 柱色谱用己烷中 0-100% EA 洗脱提纯。将所需的级分合并并将溶剂在真空下移除, 以获得 (R)-1-(4'-(4-甲基-5-((1-苯基乙氧基) 羰基氨基)-1H-1,2,3-三唑-1-基) 联苯-3-基) 环丙烷甲酸乙酯, 为无定形固体 (144mg, 56.6% 产率)。LC/MS: C₃₀H₃₀N₄O₄ (m/e) 计算值 510, 实测值 511.2 [M+H, ES⁺]。

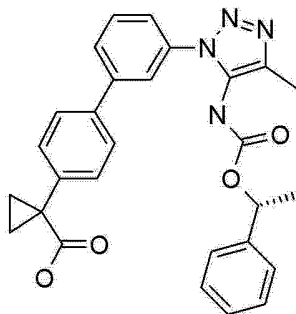
[0411] 步骤 3: (R)-1-(4'-(4-甲基-5-((1-苯基乙氧基) 羰基氨基)-1H-1,2,3-三唑-1-基) 联苯-3-基) 环丙烷甲酸

[0412] 向 (R)-1-(4'-(4-甲基-5-((1-苯基乙氧基) 羰基氨基)-1H-1,2,3-三唑-1-基) 联苯-3-基) 环丙烷甲酸乙酯 (162mg, 0.32mmol) 在乙醇 (6mL) 中的溶液在室温加入过量的水中的 1N 氢氧化钠 (1.59mL, 1.59mmol) 溶液。之后, 将所得到的浑浊溶液搅拌 20h, 此时 LCMS 分析显示仍有一些原材料存在。之后, 将浑浊反应混合物在油浴中加热至 55℃ 并且搅拌 3h, 此时 LCMS 分析显示不存在原材料。之后, 将其冷却至室温并将溶剂在真空下移除, 并且将残留物用水稀释。将碱性水性层用 1N HCl 中和。将所得到的固体通过过滤收集并用水洗涤。在空气干燥之后, 将 130mg (81.6% 产率) 的 (R)-1-(4'-(4-甲基-5-((1-苯基乙氧基) 羰基氨基)-1H-1,2,3-三唑-1-基) 联苯基-3-基) 环丙烷甲酸分离, 为白色固体。LC/MS: C₂₈H₂₆N₄O₄ (m/e) 计算值 482, 实测值 483.1 [M+H, ES⁺]。¹H NMR (DMSO-d₆) δ: 12.39 (br. s., 1H), 9.32-10.31 (m, 1H), 7.80 (d, J = 6.8Hz, 2H), 7.70 (br. s., 2H), 7.53-7.64 (m, 2H), 7.39-7.52 (m, 4H), 7.35 (d, J = 7.5Hz, 3H), 5.80 (br. s., 1H), 3.05-3.57 (m, 3H), 1.35-1.74 (m, 5H), 1.25 (br. s., 2H)。

[0413] 实施例 25

[0414] 1-{3'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3] 三唑-1-基]-联苯-4-基}-环丙烷甲酸

[0415]



[0416] 步骤 1: 3-(3-溴-苯基)-5-甲基-3H-[1,2,3] 三唑-4-甲酸甲酯

[0417] 在 350mL 反应小瓶中, 将 1-叠氨基-3-溴-苯 (2.47g, 12.5mmol) 和丁-2-炔酸甲酯 (1.35g, 1.37mL, 13.7mmol) 与甲苯 (106mL) 合并以给出黄色悬浮液。将小瓶密封并在

油浴中在 150℃ 意外加热 2.5 天（预期 4h）。将反应物过滤，将固体用甲苯洗涤。将滤液浓缩，溶解在最少 DCM 中，并且通过快速色谱（硅胶，己烷中 0% 至 30% EtOAc）提纯。将合适的级分合并，浓缩，并且由 DCM/ 己烷干燥，产生 3-(3- 溴 - 苯基)-5- 甲基-3H-[1,2,3] 三唑-4- 甲酸甲酯 (1.04g, 28.2% 产率)，为浅棕色固体。LC/MS : $C_{11}H_{10}BrN_3O_2$ 计算值 295/297，实测值 296/298 (M+H, ES^+)。

[0418] 步骤 2 : 3-(3- 溴 - 苯基)-5- 甲基-3H-[1,2,3] 三唑-4- 甲酸

[0419] 向含有溶解在 THF (40mL) (棕色溶液) 中的 3-(3- 溴 - 苯基)-5- 甲基-3H-[1,2,3] 三唑-4- 甲酸甲酯 (1.0g, 3.38mmol) 的 250mL 圆底烧瓶加入水 (10mL) 中的 LiOH (0.81g, 34mmol)，加热以部分地溶解。将溶液在室温搅拌过夜。将反应物浓缩，在水中稀释（总体积，200mL），用乙醚 (2x100mL) 萃取。将水性层用 1N HCl 酸化。将所得到的沉淀物过滤，用水和己烷洗涤，并且在室内真空下并在干燥器中干燥，产生 3-(3- 溴 - 苯基)-5- 甲基-3H-[1,2,3] 三唑-4- 甲酸 (0.913g, 95.8% 产率)，为浅棕色固体。LC/MS : $C_{10}H_8N_3O_2$ (m/e) 计算值 281/283，实测值 281/284 (M+H, ES^+)。

[0420] 步骤 3 : [3-(3- 溴 - 苯基)-5- 甲基-3H-[1,2,3] 三唑-4- 基]-氨基甲酸 (R)-1- 苯基 - 乙酯

[0421] 在 40mL 反应小瓶中，将 3-(3- 溴 - 苯基)-5- 甲基-3H-[1,2,3] 三唑-4- 甲酸 (0.91g, 3.2mmol)、(R)-1- 苯基乙醇 (0.84g, 0.83mL, 6.9mmol) 和三乙胺 (0.91g, 1.3mL, 9.0mmol) 与甲苯 (28mL) 合并以给出黄色溶液，并且向其加入二苯基磷酰基叠氮化物 (2.5g, 1.9mL, 9.0mmol)。将小瓶的气氛用氮吹扫，密封，在油浴中在 65℃ 加热 2.5h，并且冷却至室温过夜。将反应物浓缩，为黄色粘性油，用 DCM 稀释，并且通过快速色谱（硅胶，己烷中 0% 至 50% EtOAc）提纯。将合适的级分合并，浓缩，从 DCM/ 己烷干燥，产生 [3-(3- 溴 - 苯基)-5- 甲基-3H-[1,2,3] 三唑-4- 基]-氨基甲酸 (R)-1- 苯基 - 乙酯 (0.86g, 66% 产率)，为淡黄色固体 / 胶。LC/MS : $C_{18}H_{17}BrN_4O_2$ (m/e) 计算值 400/402，实测值 401/403 (M+H, ES^+)。

[0422] 步骤 4 : 1-{3' -[4- 甲基-5-((R)-1- 苯基 - 乙氧基羰基氨基)-[1,2,3] 三唑-1- 基]-联苯-4- 基}-环丙烷甲酸甲酯

[0423] 在 40mL 小瓶中，将 1-[4-(4,4,5,5- 四甲基-[1,3,2] 二氧杂硼杂环戊烷-2-基)-苯基]-环丙烷甲酸甲酯 (356mg, 1.18mmol)、[3-(3- 溴 - 苯基)-5- 甲基-3H-[1,2,3] 三唑-4- 基]-氨基甲酸 (R)-1- 苯基 - 乙酯 (430mg, 1.07mmol)、2- 二环己磷基-2', 6' - 二甲氧基联苯 (SPhos) (132mg, 0.321mmol) 和 $Pd(OAc)_2$ (36.1mg, 0.161mmol) 与甲苯 (34mL) (之前用氮吹扫 20 分钟) 合并以给出浅黄色溶液。向其加入溶解在水 (9mL) (之前用氮吹扫 20 分钟) 中的磷酸三钾 (682mg, 3.21mmol)。将小瓶的气氛用氮吹扫，密封，在油浴中在 100℃ 意外加热 2.5 天（预期 4h）并且冷却至室温 1h。将反应物过滤，用 EtOAc (50mL) 稀释并用水 / 盐水 (100/50mL) 和盐水 (150mL) 洗涤。将水性层用 EtOAc (2x150mL) 萃取。将有机层合并，在 $MgSO_4$ 上干燥，过滤，浓缩，溶解在最少 DCM 中，并且通过快速色谱（硅胶，己烷中 0% 至 100% EtOAc）提纯。将合适的级分合并，浓缩，并且由 DCM/ 己烷干燥，产生 1-{3' -[4- 甲基-5-((R)-1- 苯基 - 乙氧基羰基氨基)-[1,2,3] 三唑-1- 基]-联苯-4- 基}-环丙烷甲酸甲酯 (142g, 26.7% 产率)，为白色固体。LC/MS : $C_{29}H_{28}N_4O_4$ (m/e) 计算值 496，实测值 497 (M+H, ES^+)。

[0424] 步骤 5 : 1-{3' -[4- 甲基-5-((R)-1- 苯基 - 乙氧基羰基氨基)-[1,2,3] 三

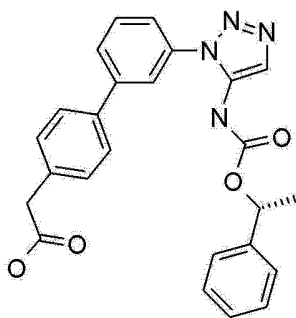
唑-1-基]-联苯-4-基}-环丙烷甲酸

[0425] 在 100mL 圆底烧瓶中, 将 1-{3'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸甲酯 (141mg, 0.284mmol) 与 THF (10mL) 合并以给出无色溶液。向其滴入 NaOH (1M, 2.8mL, 2.8mmol)。将反应物在室温搅拌并且加入额外的水和 THF。在 18h 之后, 将反应物用水稀释, 浓缩, 用更多水稀释并用 1N HCl 酸化。将所得到的沉淀物过滤, 用水和己烷洗涤, 并且在室内真空中干燥, 产生 1-{3'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸 (49mg, 35.8% 产率), 为白色固体。LC/MS: $C_{28}H_{26}N_4O_4$ (m/e) 计算值 482, 实测值 483 (M+H, ES^+)。 1H NMR (DMSO- d_6) δ : 12.39 (br. s., 1H), 9.72 (br. s., 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 7.77 (s, 1H), 7.56-7.73 (m, 3H), 7.51 (d, $J = 7.3$ Hz, 1H), 7.43 (d, $J = 8.0$ Hz, 2H), 7.28 (br. s., 5H), 5.70 (br. s., 1H), 2.12-2.27 (m, 3H), 1.27-1.65 (m, 5H), 1.19 (d, $J = 2.8$ Hz, 2H)。

[0426] 实施例 26

[0427] {3'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸

[0428]



[0429] 步骤 1: {3'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯

[0430] 在 40mL 小瓶中, 将 1-[4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-苯基]-乙酸乙酯 (311mg, 1.07mmol)、[3-(3-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-1-苯基-乙酯 (430mg, 1.07mmol)、2-二环己膦基-2',6'-二甲氧基联苯 (SPHOS) (132mg, 0.321mmol) 和 $Pd(OAc)_2$ (36.1mg, 0.161mmol) 与甲苯 (12mL) (之前用氮吹扫 20 分钟) 合并以给出浅黄色溶液。向其加入溶解在水 (4mL) (之前用氮吹扫 20 分钟) 中的磷酸三钾 (682mg, 3.21mmol)。将小瓶的气氛用氮替代, 密封, 在油浴中在 100°C 意外加热 2.5 天 (预期 4h) 并且冷却至室温 1h。将反应物过滤, 用 EtOAc (50mL) 稀释并用水/盐水 (100/50mL) 和盐水 (150mL) 洗涤。将水性层用 EtOAc (2x150mL) 萃取。将有机层合并, 在 $MgSO_4$ 上干燥, 过滤, 浓缩, 溶解在最少的 DCM 中, 并且通过快速色谱 (硅胶, 己烷中 0% 至 100% EtOAc) 提纯。将合适的级分合并, 浓缩, 并且从 DCM/己烷干燥, 产生 {3'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯 (96.7mg, 18.6% 产率), 为白色固体。LC/MS: $C_{28}H_{28}N_4O_4$ (m/e) 计算值 484, 实测值 485 (M+H, ES^+)。

[0431] 步骤 2: {3'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三

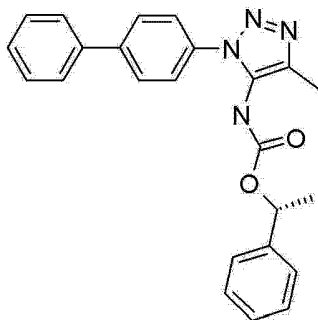
唑-1-基]-联苯-4-基}-乙酸

[0432] 在100mL圆底烧瓶中,将{3'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-乙酸乙酯(90mg,0.186mmol)与THF(5mL)合并以给出无色溶液。向其滴入水(1mL)中的LiOH(78mg,1.86mmol),加热以部分地溶解。将反应物在室温搅拌17h。将反应物用水稀释,浓缩,用更多水稀释并用1N HCl酸化。将所得到的沉淀物过滤,用水和己烷洗涤,并且在室内真空干燥,产生1-{3'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸(64.7mg,76.3%产率),为白色固体。LC/MS: $C_{26}H_{24}N_4O_4$ (m/e)计算值456,实测值457(M+H,ES⁺)。¹H NMR(DMSO-d₆) δ: 12.41(br. s., 1H), 9.72(br. s., 1H), 7.85(d, J = 7.8Hz, 1H), 7.78(s, 1H), 7.59-7.73(m, 3H), 7.51(d, J = 7.5Hz, 1H), 7.39(d, J = 8.0Hz, 2H), 7.06-7.34(m, 5H), 5.69(br. s., 1H), 3.65(s, 2H), 2.19(s, 3H), 1.44(br. s., 3H)。

[0433] 实施例 27

[0434] (3-联苯-4-基-5-甲基-3H-[1,2,3]三唑-4-基)-氨基甲酸(R)-1-苯基-乙酯

[0435]

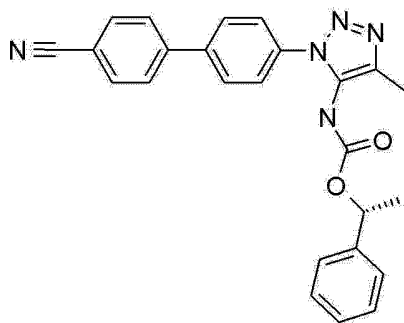


[0436] 在20mL小瓶中,将苯基硼酸(6.9mg,0.057mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸叔丁酯(18.9mg,0.0471mmol)、2-二环己磷基-2',6'-二甲氧基联苯(SPhos)(7.7mg,0.019mmol)、磷酸三钾(30mg,0.14mmol)和Pd(OAc)₂(2.0mg,0.0089mmol)与甲苯(4mL)和水(1mL)(之前用氮吹扫20分钟)合并,以给出浅黄色悬浮液。将小瓶的气氛用氮替代,密封,在干燥区中在100℃加热3.5h,并且冷却至室温过夜。将反应物通过硅藻土过滤,用EtOAc冲洗,浓缩,溶解在最少DCM中,并且通过快速色谱(硅胶,己烷中0%至100% EtOAc)提纯。将合适的级分合并,浓缩,并且从DCM/己烷干燥,产生(3-联苯-4-基-5-甲基-3H-[1,2,3]三唑-4-基)-氨基甲酸(R)-1-苯基-乙酯(12.4mg,66.1%产率),为白色固体。LC/MS: $C_{24}H_{22}N_4O_2$ (m/e)计算值398,实测值399(M+H,ES⁺)。¹H NMR(DMSO-d₆) δ: 9.67(br. s., 1H), 7.86(d, J = 7.5Hz, 2H), 7.76(d, J = 7.3Hz, 2H), 7.49-7.68(m, 4H), 7.41-7.49(m, 1H), 6.92-7.40(m, 5H), 5.70(br. s., 1H), 2.18(s, 3H), 1.49(br. s., 3H)。

[0437] 实施例 28

[0438] [3-(4'-氰基-联苯-4-基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸(R)-1-苯基-乙酯

[0439]

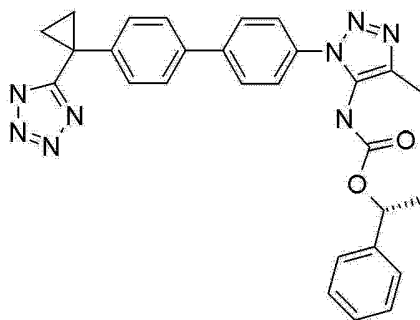


[0440] 在 20mL 小瓶中, 将 4-氰基苯基硼酸 (20.1mg, 0.137mmol)、[3-(4-溴-苯基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸叔丁酯 (50mg, 0.125mmol)、2-二环己磷基-2',6'-二甲氧基联苯 (SPhos) (15.3mg, 0.0374mmol)、磷酸三钾 (79.4mg, 0.374mmol) 和 $\text{Pd}(\text{OAc})_2$ (4.2mg, 0.0187mmol) 与甲苯 (2mL) 和水 (0.5mL) (之前用氮吹扫 20 分钟) 合并, 以给出浅黄色悬浮液。将小瓶的气氛用氮替代, 密封, 在干燥区中在 100°C 加热 4h, 并且冷却至室温过夜。将反应物过滤并用水 (5mL) 和 EtOAc (60mL) 冲洗。将滤液用水 (50mL) 和盐水 (50mL) 洗涤。将水性层用 EtOAc (60mL) 萃取。将有机层用相同的盐水洗涤。将有机层合并, 浓缩, 溶解在最少 DCM 中, 并且通过快速色谱 (硅胶, 己烷中 0% 至 50% EtOAc) 提纯。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 [3-(4'-氰基-联苯-4-基)-5-甲基-3H-[1,2,3]三唑-4-基]-氨基甲酸 (R)-1-苯基-乙酯 (20mg, 0.047mmol, 38% 产率), 为白色固体。LC/MS: $\text{C}_{25}\text{H}_{21}\text{N}_4\text{O}_2$ (m/e) 计算值 423, 实测值 424 (M+H, ES^+)。 ^1H NMR (DMSO- d_6) δ : 9.72 (br. s., 1H), 7.86-8.07 (m, 6H), 7.65 (d, J = 8.3Hz, 2H), 6.80-7.48 (m, 5H), 5.69 (br. s., 1H), 2.18 (s, 3H), 1.48 (br. s., 3H)。

[0441] 实施例 29

[0442] 1-(4'-(1-(1H-四唑-5-基)环丙基)联苯-4-基)-4-甲基-1H-1,2,3-三唑-5-基氨基甲酸 (R)-1-苯基-乙酯

[0443]



[0444] 步骤 1: 1-(4'-(1-氰基环丙基)联苯-4-基)-4-甲基-1H-1,2,3-三唑-5-基氨基甲酸 (R)-1-苯基-乙酯

[0445] 向小瓶中 4-甲基-1-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)-1H-1,2,3-三唑-5-基氨基甲酸 (R)-1-苯基乙酯 (485mg, 1.08mmol)、1-(4-溴苯基)环丙烷甲腈 (360mg, 1.62mmol)、乙酸钪 (II) (36.4mg, 0.16mmol)、2-二环己基磷基-2',6'-二甲氧基联苯 (133mg, 0.33mmol) 和磷酸三钾 (689mg, 3.25mmol) 的混合物在室温在氮气氛围下加入甲苯 (9mL) 和水 (2.0mL)。之后, 将帽关闭并将所得到的浅棕色悬浮液加热至 105°C, 并搅拌 3h, 此时 TLC 分析显示新斑点的存在。之后, 将反应混合物冷却并将其用

水稀释。将有机化合物萃取至 EA (2x50mL) 中并将合并的萃取物用盐水溶液洗涤,并且在无水 MgSO_4 上干燥。过滤和浓缩给出粗残留物,将其通过使用 ISCO (80g) 柱色谱用己烷中 0-100% EA 洗脱提纯。将所需的级分合并并且将溶剂在真空下移除,以分离 1-(4'-(1-氰基环丙基)联苯-4-基)-4-甲基-1H-1,2,3-三唑-5-基氨基甲酸 (R)-1-苯基-乙酯 (190mg, 38% 产率), 为白色固体。LC/MS: $\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}_2$ (m/e) 计算值 463, 实测值 464.8 [M+H, ES^+]。

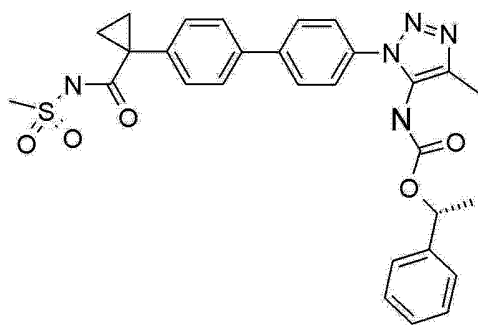
[0446] 步骤 2: 1-(4'-(1-(1H-四唑-5-基)环丙基)联苯-4-基)-4-甲基-1H-1,2,3-三唑-5-基氨基甲酸 (R)-1-苯基-乙酯

[0447] 向 1-(4'-(1-氰基环丙基)联苯-4-基)-4-甲基-1H-1,2,3-三唑-5-基氨基甲酸 (R)-1-苯基乙酯 (50mg, 0.11mmol) 在甲苯 (5mL) 中的溶液在室温在氮气氛下加入二-正丁基氧化锡 (5.37mg, 0.22mmol) 和叠氮基三甲基硅烷 (12.4mg, 14.3 μL , 0.11mmol)。将所得到的浑浊溶液加热至 100°C 并且搅拌 15h, 此时 LCMS 和 TLC 分析显示不存在原材料。之后, 将其冷却至室温并倒入至盐水溶液和 EA 中。将两层分离并将水性层用 EA 萃取另外一次。将合并的萃取物用盐水溶液洗涤并且在无水 MgSO_4 上干燥。过滤和浓缩给出粗产物, 将其使用 ISCO (40g) 柱色谱用己烷中的 0-100% EA 和二氯甲烷中的 10% 甲醇洗脱提纯。所需的产物与二氯甲烷中的 10% 甲醇一起出来, 并且将级分合并, 并且将溶剂在真空下移除, 以获得 1-(4'-(1-(1H-四唑-5-基)环丙基)联苯-4-基)-4-甲基-1H-1,2,3-三唑-5-基氨基甲酸 (R)-1-苯基-乙酯, 为白色固体 (25mg, 46% 产率)。LC/MS: $\text{C}_{28}\text{H}_{26}\text{N}_8\text{O}_2$ (m/e) 计算值 506, 实测值 507.1 [M+H, ES^+]。 ^1H NMR ($\text{DMSO}-d_6$) δ : 16.08 (br. s., 1H), 9.20-9.84 (m, 1H), 7.85 (d, $J = 7.0\text{Hz}$, 2H), 7.73 (d, $J = 8.3\text{Hz}$, 2H), 7.52-7.65 (m, 2H), 7.46 (d, $J = 8.3\text{Hz}$, 2H), 7.34 (br. s., 5H), 5.52-5.84 (m, 1H), 2.17 (s, 3H), 1.51-1.63 (m, 4H), 1.15-1.35 (m, 3H)。

[0448] 实施例 30

[0449] {3-[4'-(1-甲磺酰氨基羰基-环丙基)-联苯-4-基]-5-甲基-3H-[1,2,3]三唑-4-基}-氨基甲酸 (R)-1-苯基-乙酯

[0450]



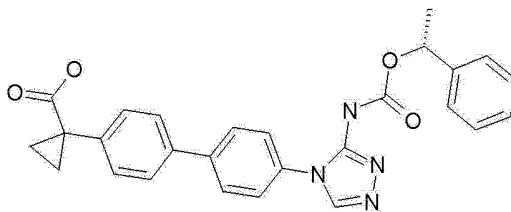
[0451] 在 50mL 圆底烧瓶中, 将 1-{4'-[4-甲基-5-((R)-1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-环丙烷甲酸 (50mg, 0.201mmol) 与 DCM (1ml) 和 DMF (滴) 在氮下合并以给出白色悬浮物。以两份 (在加入之间间隔 10 分钟) 向其逐滴加入草酰氯 (26.3mg, 18.1 μL , 0.207mmol)。将反应物在室温搅拌 1.5h。将反应物浓缩, 由 DCM/甲苯和 DCM/己烷干燥, 并且溶解在 THF (1.00ml) 中。在 5mL 小瓶中, 将甲磺酰胺 (29.6mg, 311 μmol) 与 DCM (1ml) 在氮下合并以给出无色溶液。向其加入 NaH (矿物油中 60% 分散液, 7.46mg, 0.311mmol), 并且将白色悬浮物在室温搅拌 1.5h。将该酰氯 THF 溶液 (用 THF 冲洗, 1x1mL) 滴加至磺酰胺混合物。将反应物在室温搅拌 1 天。将反应物储存在冰箱中 3 天。加入

另外的 NaH (矿物油中的 60% 分散液, 7.46mg, 0.311mmol) 并将反应物在室温搅拌 1 天。加入另外的 NaH (矿物油中 60% 分散液, 7.46mg, 0.311mmol) 并将反应物在室温搅拌 1 天。将反应物用 EtOAc 稀释并用水和盐水洗涤, 在 MgSO_4 上干燥, 过滤, 浓缩, 溶解在最少 DCM 中, 并且通过快速色谱 (硅胶, DCM 中 0% 至 5% MeOH) 提纯。将合适的级分合并, 浓缩, 并且由 DCM/己烷干燥, 产生 {3-[4'-(1-甲磺酰氨基羰基-环丙基)-联苯-4-基]-5-甲基-3H-[1,2,3]三唑-4-基}-氨基甲酸 (R)-1-苯基-乙酯 (5.6mg, 9.7% 产率), 为白色固体。LC/MS: $\text{C}_{29}\text{H}_{29}\text{N}_5\text{O}_5$ (m/e) 计算值 559, 实测值 560 (M+H, ES^+)。 ^1H NMR ($\text{DMSO}-d_6$) δ : 11.24 (br. s., 1H), 9.68 (br. s., 1H), 7.85 (d, $J = 7.0\text{Hz}$, 2H), 7.72 (d, $J = 8.3\text{Hz}$, 2H), 7.59 (d, $J = 7.8\text{Hz}$, 2H), 7.45 (d, $J = 8.3\text{Hz}$, 2H), 7.34 (br. s., 5H), 5.70 (br. s., 1H), 3.23 (s, 3H), 2.17 (s, 3H), 1.29-1.73 (m, 5H), 1.23 (br. s., 2H)。

[0452] 实施例 31

[0453] 1-{4'-[3-((R)-1-苯基-乙氧基羰基氨基)-[1,2,4]三唑-4-基]-联苯-4-基}-环丙烷甲酸

[0454]



[0455] 步骤 1: 1-溴-4-异硫氰酸根合苯

[0456] 在 250mL 圆底烧瓶中, 将碳酸钙 (6.11g, 61.0mmol, 当量: 2.1) 和 4-溴苯胺 (5g, 29.1mmol) 与二氯甲烷 (25mL) 和水 (25.0mL) 合并以给出浅棕色悬浮液。将反应混合物冷却至 0°C , 并且在 4 分钟内逐滴加入二氯硫化碳 (3.68g, 2.45mL, 32.0mmol, 当量: 1.1)。将反应物在 0°C 搅拌 30 分钟, 之后在 25°C 搅拌 19h。将反应混合物通过硅藻土过滤并将滤饼用二氯甲烷洗涤。将水性层用二氯甲烷 (1x25mL) 反萃取。将有机层合并, 用 H_2O (1x25mL)、饱和 NaCl (1x20mL) 洗涤, 在 Na_2SO_4 上干燥并在真空中浓缩。将浅棕色固体在真空中干燥以给出 5.43g (87%) 的所需的产物。 ^1H NMR ($\text{DMSO}-d_6$) δ ppm 7.55-7.74 (m, 2H), 7.28-7.50 (m, 2H)。

[0457] 步骤 2: (4-溴苯基)-硫脲

[0458] 在 500mL 圆底烧瓶中, 将 1-溴-4-异硫氰酸根合苯 (1.5g, 7.01mmol) 与 THF 中的 0.4M 氨 (52.5mL, 21.0mmol, 当量: 3) 合并, 以给出黄色溶液。将反应物在 25°C 搅拌过夜。将粗反应混合物在真空中浓缩以给出所需的产物, 为浅棕色固体。 $(\text{M}+\text{H})^+ = 230.9/233.0$ (m/e)。

[0459] 步骤 3: N-(4-溴苯基)-胍甲脒硝酸盐

[0460] 在 250mL 圆底烧瓶中, 将 1-(4-溴苯基)硫脲 (1.62g, 7.01mmol) 与甲醇 (50mL) 合并以给出浅棕色悬浮液。加入 MeI (1.09g, 482 μL , 7.71mmol, 当量: 1.1) 并将反应混合物在 25°C 搅拌 17h。将粗反应混合物在真空中浓缩以产生浅棕色粉末。将该物质在不进一步提纯的情况下使用。

[0461] 在 250mL 圆底烧瓶中, 将 1-(4-溴苯基)-2-甲基-异硫脲氢碘酸盐 (2.61g,

7.00mmol) 与水 (10mL) 和乙醇 (10.0mL) 合并以给出浅棕色溶液。加入胍单水合物 (525mg, 509 μ L, 10.5mmol, 当量 :1.5) 并且将反应物在 25°C 搅拌 20h。将粗反应混合物在真空中浓缩至约一半体积并在激烈搅拌下加入硝酸银 (1.19g, 7.00mmol)。将灰色 / 棕色固体通过硅藻土过滤并且将滤饼用沸水洗涤两次。将滤液在真空中浓缩以给出稠的黄色油。将该油在真空下在略微加热下干燥以给出 2.27g (111%) 的所需的材料。将该产物在不进一步提纯的情况下使用。 $(M+H)^+ = 229.1/231.0$ (m/e)

[0462] 步骤 4 : 4-(4-溴苯基)-4H-[1,2,4] 三唑-3-基胺

[0463] 在 500mL 圆底烧瓶中, 将 N'-(4-溴苯基)-胍甲脒硝酸盐 (2.27g, 7.77mmol) 和甲酸 (715mg, 596 μ L, 15.5mmol, 当量 :2) 合并以给出黄色溶液。将反应混合物加热至 120°C 持续 3.5h。将反应物冷却并用 3M NaOH 碱化。将混合物用 150mL 二氯甲烷稀释并激烈搅拌。将不溶固体过滤并使相分离。将有机相在 Na₂SO₄ 上干燥并过滤。将水性相丢弃。将过滤的固体与干燥的有机相合并并在真空中浓缩。将残留物置于回流乙醇中, 并热过滤以移除少量的白色不溶固体。将浅棕色滤液气提为棕褐色粉末, 并且在真空下干燥以给出 1.665g (90%) 的所需的材料。 $(M+H)^+ = 239.0/240.9$ (m/e)。 ¹H NMR (DMSO-d₆) δ ppm 8.20 (s, 1H), 7.66-7.81 (m, 2H), 7.34-7.54 (m, 2H), 5.86 (s, 2H)。

[0464] 步骤 5 : 1-[4'-(3-氨基-[1,2,4] 三唑-4-基)-联苯-4-基]-环丙烷甲酸甲酯

[0465] 在 20mL 密封管中, 将 4-(4-溴苯基)-4H-1,2,4-三唑-3-胺 (349mg, 1.46mmol)、4-(1-(甲氧基羰基)环丙基)苯基硼酸 (450mg, 2.04mmol, 当量 :1.4) 和 2M Na₂CO₃ (2.19mL, 4.38mmol, 当量 :3) 与二噁烷 (6mL) 合并以给出浅黄色悬浮液。加入 PdCl₂(dppf) (95.4mg, 117 μ mol, 当量 :0.08) 并将反应物用氩吹扫。将反应混合物密封并在氩下加热至 100°C 持续 24h。将反应物冷却并用 EtOAc 和水稀释。将混合物过滤并将滤液用水和盐水洗涤。将有机层在 Na₂SO₄ 上干燥, 与过滤的固体合并并在真空中浓缩。将硅藻土加入至残留物并将混合物用回流甲醇研磨。将混合物过滤并将滤饼用回流甲醇洗涤两次。将滤液在真空中汽提并将粗材料通过快速色谱 (硅胶, 80g, 二氯甲烷中 0% 至 10% 甲醇) 提纯, 以给出 257mg (53%) 的所需的产物, 为浅棕色粉末。 $(M+H)^+ = 335.1$ (m/e)。 ¹H NMR (DMSO-d₆) δ ppm 8.24 (s, 1H), 7.79-7.86 (m, 2H), 7.62-7.70 (m, 2H), 7.53-7.60 (m, 2H), 7.41-7.49 (m, 2H), 5.86 (s, 2H), 3.58 (s, 3H), 1.42-1.61 (m, 2H), 1.16-1.35 (m, 2H)。

[0466] 步骤 6 : 1H-咪唑-1-甲酸 (R)-1-苯基乙酯

[0467] 在 250mL 圆底烧瓶中, 将 (R)-1-苯基乙醇 (2.01g, 16.5mmol) 和羰基二咪唑 (2.67g, 16.5mmol, 当量 :1.00) 与乙酸乙酯 (40mL) 合并以给出无色溶液。将反应混合物在氩下回流 20h, 冷却并用 EtOAc 稀释。将混合物用 H₂O (2x40mL), 饱和 NaCl (1x20mL) 洗涤, 在 Na₂SO₄ 上干燥并在真空中浓缩。将所结晶的物质静置以给出 3.42g (96%) 的所需的产物, 为灰白色针。 ¹H NMR (DMSO-d₆) δ ppm 8.42 (s, 1H), 7.65 (dd, J = 1.8, 1.3Hz, 1H), 7.45-7.54 (m, 2H), 7.22-7.45 (m, 3H), 7.09 (dd, J = 1.6, 0.9Hz, 1H), 6.05 (q, J = 6.6Hz, 1H), 1.66 (d, J = 6.6Hz, 3H)。

[0468] 步骤 7 : 1-[4'-(3-((R)-1-苯基-乙氧基羰基氨基)-[1,2,4] 三唑-4-基)-联苯-4-基]-环丙烷甲酸甲酯

[0469] 在 250mL 圆底烧瓶中, 将 1-(4'-(3-氨基-4H-1,2,4-三唑-4-基)联苯-4-基)环丙烷甲酸甲酯 (115mg, 344 μ mol) 与 THF (6mL) 合并以给出浅棕色悬浮液。加入 THF 中

的 1M LiHMDS(447 μ l, 447 μ mol, 当量 :1.3), 并将棕色溶液在 25℃ 在氩下搅拌 15 分钟。加入 1ml THF 中的 1H-咪唑-1-甲酸(R)-1-苯基乙酯(112mg, 516 μ mol, 当量 :1.5), 并且将反应混合物在 25℃ 搅拌 15 分钟。将反应用水猝灭, 并用二氯甲烷中的 10% 甲醇稀释。加入 Na₂SO₄ 并将混合物通过硅藻土过滤并将棕色滤液在真空中浓缩。将粗材料通过快速色谱(硅胶, 24g, 二氯甲烷中 0% 至 10% 甲醇) 提纯, 以给出 85mg(51%) 的所需的产物, 为灰白色固体。(M+H)⁺ = 483.1(m/e)。¹H NMR(DMSO-d₆) δ ppm 10.01(s, 1H), 8.87(s, 1H), 7.76-7.93(m, 2H), 7.58-7.75(m, 2H), 7.38-7.57(m, 4H), 7.12-7.38(m, 5H), 5.62(d, J = 6.8Hz, 1H), 3.58(s, 3H), 1.47-1.60(m, 2H), 1.34(d, J = 5.6Hz, 2H), 1.15-1.31(m, 3H)。

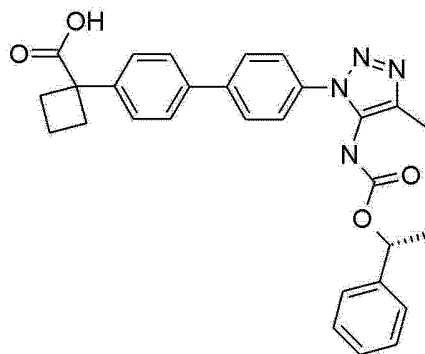
[0470] 步骤 8 : 1-{4'-[3-((R)-1-苯基-乙氧基羰基氨基)-[1,2,4]三唑-4-基]-联苯-4-基}-环丙烷甲酸

[0471] 在 250mL 圆底烧瓶中, 将 1-{4'-[3-((R)-1-苯基-乙氧基羰基氨基)-[1,2,4]三唑-4-基]-联苯-4-基}-环丙烷甲酸甲酯(110mg, 228 μ mol) 与四氢呋喃(5mL) 和甲醇(1mL) 合并以给出黄色溶液。加入 1M LiOH(2mL, 2.00mmol, 当量 :8.77) 并将反应物在 25℃ 搅拌 17 小时。将粗反应混合物在真空中浓缩, 用 1M HCl 酸化并用 EtOAc 稀释。使相分离并将有机层用 H₂O(1x15mL)、饱和 NaCl(1x15mL) 洗涤, 在 Na₂SO₄ 上干燥并在真空中浓缩。将粗材料通过快速色谱(硅胶, 12g, 二氯甲烷中 0% 至 10% 甲醇) 提纯, 以给出 86mg(80%) 的所需的产物, 为白色固体。(M+H)⁺ = 469.2(m/e)。¹H NMR(DMSO-d₆) δ ppm 12.39(br. s., 1H), 10.01(br. s., 1H), 8.87(br. s., 1H), 7.81(d, J = 8.3Hz, 2H), 7.65(d, J = 8.3Hz, 2H), 7.39-7.59(m, 4H), 7.10-7.39(m, 5H), 5.62(d, J = 6.3Hz, 1H), 1.45-1.54(m, 2H), 1.40(br. s., 1H), 1.09-1.37(m, 4H)。

[0472] 实施例 32 和 33

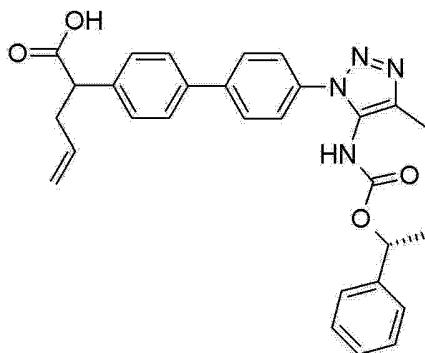
[0473] (R)-1-(4'-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)-联苯-4-基)环丁烷甲酸(实施例 32)

[0474]



[0475] (R)-2-{4'-[4-甲基-5-((1-苯基乙氧基)羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-戊-4-烯酸(实施例 33)

[0476]



[0477] 步骤1: 1-(4-溴苯基)环丁烷甲酸乙酯和 2-(4-溴苯基)-戊-4-烯酸乙酯

[0478] 将 2-(4-溴苯基)乙酸乙酯 (5.98g, 24.6mmol) 在 DMF (60mL) 中的溶液冷却至 0℃ 并且之后以五份在 10 分钟的期间内加入固体氢化钠 (2.17g, 54.4mmol)。在加入的过程中, 其剧烈反应产生泡沫并且反应混合物变为黄色悬浮液。另外的 10mL 的 DMF 用于洗涤氢化钠。将所得到的黄色悬浮液搅拌 20 分钟, 并且在该温度加入净 1,3-二溴丙烷 (5.46g, 2.75mL, 27.1mmol)。在 5 分钟之后, 将冷却浴移除并允许反应混合物升温至室温。在该过程中, 反应混合物变为无色浑浊溶液, 并且将其搅拌 1h。之后, 将反应混合物倒入至 0.1N HCl 中, 并将有机化合物萃取至 EA (2x100mL) 中。将合并萃取物用水和盐水溶液洗涤, 并且在无水 MgSO₄ 上干燥。干燥剂的过滤和滤液的浓缩给出粗白色悬浮物, 将其使用 ISCO (120g) 柱色谱用己烷中的 EA (0-15%) 洗脱提纯。两种化合物, 1-(4-溴苯基)环丁烷甲酸乙酯和 2-(4-溴苯基)-戊-4-烯酸乙酯, 作为混合物分离。

[0479] 步骤2: (R)-1-(4'-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)联苯-4-基)环丁烷甲酸乙酯和 (R)-2-{4'-[4-甲基-5-(1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-戊-4-烯酸乙酯

[0480] 向 100mL 圆底烧瓶中 4-甲基-1-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)-1H-1,2,3-三唑-5-基氨基甲酸 (R)-1-苯基乙酯 (1.34g, 3mmol)、1-(4-溴苯基)环丁烷甲酸乙酯和 2-(4-溴苯基)-戊-4-烯酸乙酯 (1.02g, 3.6mmol)、乙酸钡 (II) (135mg, 0.6mmol)、2-二环己基膦基-2',6'-二甲氧基联苯 (493mg, 1.2mmol) 和磷酸三钾 (1.91g, 9.0mmol) 的悬浮液在室温在氮气氛下加入甲苯 (18mL) 和水 (4.0mL)。之后, 将所得到的浅棕色悬浮液加热至 105℃ 并且搅拌 3h, 此时 TLC 分析显示不存在原材料。之后, 将黑色反应混合物冷却至室温并用水稀释。将有机化合物萃取至 EA (2x100mL) 中, 并且将合并的萃取物用盐水溶液洗涤并在无水 MgSO₄ 上干燥。干燥剂的过滤和滤液的浓缩给出粗残留物, 将其通过使用 ISCO (120g) 柱色谱用己烷中的 EA (0-100%) 洗脱提纯, 以获得 (R)-1-(4'-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)联苯-4-基)环丁烷甲酸乙酯和 (R)-2-{4'-[4-甲基-5-(1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-戊-4-烯酸乙酯, 为混合物。LC/MS: C₃₁H₃₂N₄O₄ (m/e) 计算值 524, 实测值 525.3 [M+H, ES⁺]。

[0481] 步骤3: ((R)-1-(4'-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)联苯-4-基)环丁烷甲酸和 (R)-2-{4'-[4-甲基-5-(1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-戊-4-烯酸

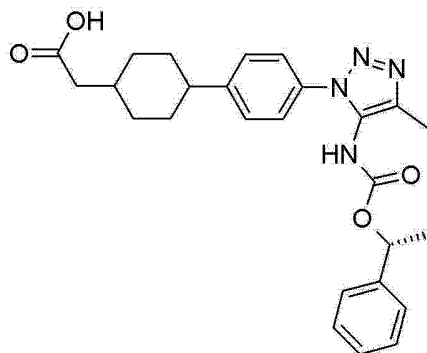
[0482] 向所获得的 (R)-1-(4'-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三

唑-1-基)联苯-4-基)环丁烷甲酸乙酯和(R)-2-{4'-[4-甲基-5-(1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-戊-4-烯酸乙酯(120mg,0.229mmol)的混合物在THF(6.0mL)和EtOH(6.0mL)中的溶液在室温加入水中的过量的1N氢氧化钠(2.29mL,2.29mmol)溶液。将所得到的浅黄色溶液在室温搅拌2天,此时TLC分析显示不存在原材料。之后,将溶剂在真空下移除并且将碱性水性层用1N HCl中和。将所得到的白色浑浊溶液用EA(2x50mL)萃取并将合并的萃取物用盐水溶液洗涤。干燥和移除溶剂以给出粗混合物,将其使用DAICEL 01柱提纯(3x25cm,40%甲醇和CO₂,70mL/分钟并且在220nm收集峰。收集峰1并且将溶剂移除以获得(R)-2-{4'-[4-甲基-5-(1-苯基-乙氧基羰基氨基)-[1,2,3]三唑-1-基]-联苯-4-基}-戊-4-烯酸(12mg,10.5%产率,实施例33)。¹H NMR(氯仿-d) δ :7.29-7.61(m,8H),7.19(s,6H),5.44-5.83(m,2H),4.92-5.14(m,2H),3.67(t,J=6.4Hz,1H),2.81(dt,J=14.2,7.2Hz,1H),2.41-2.60(m,1H),2.24(s,3H),1.12-1.30(m,3H)。并且,收集峰2并且将溶剂移除以获得((R)-1-(4'-(4-甲基-5-(1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)联苯-4-基)环丁烷甲酸(26mg,23%产率,实施例32)。¹H NMR(氯仿-d) δ :7.29-7.55(m,8H),7.19(s,6H),5.69(br.s.,1H),2.78-2.91(m,2H),2.45-2.59(m,2H),2.24(s,3H),1.99-2.11(m,1H),1.87(td,J=10.0,4.5Hz,1H),1.10-1.35(m,3H)。LC/MS计算:C₂₉H₂₈N₄O₄(m/e)496,实测值497.3[M+H,ES⁺]。

[0483] 实施例 34

[0484] (R)-2-(4-(4-(4-甲基-5-(1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)苯基)环己基)乙酸

[0485]



[0486] 步骤 1:2-(4-碘环己基)-乙酸乙酯

[0487] 向2-(4-羟基环己基)乙酸乙酯(3g,16.1mmol)、碘(6.13g,24.2mmol)、咪唑(1.64g,24.2mmol)和三苯基膦(6.34g,24.2mmol)的混合物在室温在氮气氛下加入二氯甲烷(100mL)。将所得到的棕悬浮液搅拌15h,此时TLC分析显示不存在原材料。之后,将溶剂在真空下移除并且将大部分残留物溶解在EA(~500mL)中,并且一些残留物不溶解,通过¹H NMR发现其为Ph₃P=O。将EA溶液用水和甲醇的溶液(3:1)洗涤两次以移除余下的三苯基膦氧化物,并且之后用盐水溶液洗涤。将有机层在无水MgSO₄上干燥,过滤,并且浓缩给出粗残留物,将其使用ISCO(120g)柱色谱用己烷中的EA(0-50%)洗脱提纯。将所需的级分合并并将溶剂在真空下移除以获得2-(4-碘环己基)乙酸乙酯(3.39g,71.1%产率),为粘性浅黄色油。该产物的¹H NMR显示它含有~30-40%的消除副产物(烯烃),并且在TLC上不可分。

[0488] 步骤 2: 1-[4-(4-(2-乙氧基-2-氧代乙基)环己基)苯基]-5-甲基-1H-1,2,3-三唑-甲酸叔丁酯

[0489] 在配备有加液漏斗和温度计的 3 颈 50mL 圆底烧瓶中在室温在氮气氛下装入锌尘, 99.9% (490mg, 7.5mmol)。之后, 将烧瓶在真空下用氮吹扫并且加入 THF (2mL) 以覆盖锌尘。加入 1,2-二溴乙烷 (60.6mg, 27.8 μ L, 0.322mmol) 并且将混合物用热枪加热直至乙烯气的释放终止。之后, 将悬浮液冷却至室温并且加入氯三甲基硅烷 (35.0mg, 40.8 μ L, 0.322mmol) 并将混合物在室温搅拌 15 分钟。之后, 将 2-(4-碘环己基)乙酸乙酯 (740mg, 2.5mmol) 在 THF (2mL 和 1mL 用于洗涤) 中的溶液逐滴加入, 历时 5 分钟。在加入之后, 将反应混合物用油浴加热至 $\sim 60^{\circ}\text{C}$ 并搅拌 3h, 此时水解的反应混合物的 TLC 分析显示不存在原材料。之后, 停止加热并且允许过量的锌尘沉淀 (15h), 以给出顶部层, 为无色溶液。

[0490] 在另一个 2 颈 25mL 圆底烧瓶中, 装入乙酸钬 (II) (24.9mg, 0.111mmol) 和 2-二环己基膦基-2',6'-二甲氧基联苯 (91.0mg, 0.222mmol), 并且将烧瓶用氮气吹扫。之后, 加入 THF (1mL) 并且将所得到的浅棕色悬浮液搅拌 5 分钟, 之后在室温在氮气氛下加入 1-(4-溴苯基)-4-甲基-1H-1,2,3-三唑-5-甲酸叔丁酯 (150mg, 0.444mmol) 在 THF (3mL) 中的溶液。之后, 将以上制备的无色锌溶液加入至该混合物。在加入之后, 它变为暗棕色溶液, 之后将其加热至 60°C , 并且搅拌 8h, 此时水解反应混合物的 TLC 分析显示不存在原材料。之后, 将其冷却至室温并用饱和氯化铵溶液和 EA 稀释。将两层分离并且将水性层用 EA 萃取。将合并有机萃取物用盐水溶液洗涤并在无水 MgSO_4 上干燥。干燥剂的过滤和滤液的浓缩给出粗浅黄色残留物, 将其使用 ISCO (80g) 柱用己烷中 EA (0-60%) 洗脱提纯。将所需的级分合并并将溶剂在真空下移除以获得 1-[4-(4-(2-乙氧基-2-氧代乙基)环己基)苯基]-5-甲基-1H-1,2,3-三唑-甲酸叔丁酯 (55mg, 29% 产率), 为浅棕色油。LC/MS: $\text{C}_{24}\text{H}_{33}\text{N}_3\text{O}_4$ (m/e) 计算值 427, 实测值 428.1 [M+H, ES^+]。

[0491] 步骤 3: 1-[4-(4-(2-乙氧基-2-氧代乙基)环己基)苯基]-5-甲基-1H-1,2,3-三唑-甲酸

[0492] 向 1-(4-(4-(2-乙氧基-2-氧代乙基)环己基)苯基)-4-甲基-1H-1,2,3-三唑-5-甲酸叔丁酯 (96mg, 0.225mmol) 在二氯甲烷 (5mL) 中的浅黄色溶液在室温在氮气氛下加入过量的 TFA (2.56g, 1.73mL, 22.5mmol)。将所得到的浅黄色溶液搅拌 20h, 此时 TLC 分析显示不存在原材料。之后, 将溶剂在真空下移除并将残留物与甲苯共沸。将残留物在高真空下干燥以获得 1-[4-(4-(2-乙氧基-2-氧代乙基)环己基)苯基]-5-甲基-1H-1,2,3-三唑-甲酸 (85mg, 97% 产率), 为浅棕色固体。LC/MS: $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_4$ (m/e) 计算值 371, 实测值 372.1 [M+H, ES^+]。

[0493] 步骤 4: (R)-2-(4-(4-(4-甲基-5-(1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)苯基)环己基)乙酸乙酯

[0494] 向 1-(4-(4-(2-乙氧基-2-氧代乙基)环己基)苯基)-4-甲基-1H-1,2,3-三唑-5-甲酸 (85mg, 0.229mmol) 在甲苯 (5mL) 中的具有少量固体的浅棕色溶液在室温加入三乙胺 (46.3mg, 63.8 μ L, 0.458mmol)。在室温向所得到的溶液加入二苯基磷酰基叠氮化物 (69.3mg, 54.2 μ L, 0.252mmol), 之后加入 (R)-1-苯基乙醇 (30.8mg, 30.4 μ L, 0.252mmol)。将所得到的溶液用油浴加热至 81°C 并且搅拌 1h, 此时 TLC 分析显示新斑点的存在。之后, 将反应混合物冷却至室温并将溶剂在真空下移除。将粗残留物 ($\sim 450\text{mg}$) 悬浮在二氯甲

烷中并过滤。将滤液置于 ISCO(40g) 柱色谱上用己烷中 EA(0-100%) 洗脱。将所需的级分合并并将溶剂在真空下移除以获得 (R)-2-(4-(4-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)苯基)环己基)乙酸乙酯 (50mg, 45% 产率), 为白色固体。LC/MS: $C_{28}H_{34}N_4O_4$ (m/e) 计算值 490, 实测值 491.3 [M+H, ES⁺]。

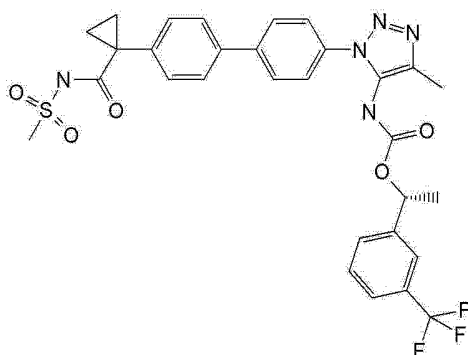
[0495] 步骤 5: (R)-2-(4-(4-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)苯基)环己基)乙酸

[0496] 向 (R)-2-(4-(4-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)苯基)环己基)乙酸乙酯 (46mg, 0.94mmol) 在 THF(5mL) 和 EtOH(5mL) 中的无色溶液加入过量的氢氧化钠在水中的 1M 溶液 (2.81mL, 2.81mmol)。将所得到的无色溶液在室温搅拌 15h, 此时 LC/MS 和 TLC 分析显示不存在原材料。之后, 将溶剂在真空下移除并且将碱性水性层用 1N HCl 中和。将所得到的白色固体通过过滤收集并用水和己烷洗涤。在空气干燥之后, 将 (R)-2-(4-(4-(4-甲基-5-((1-苯基乙氧基)羰基氨基)-1H-1,2,3-三唑-1-基)苯基)环己基)乙酸 (35mg, 80.7% 产率) 分离, 为白色固体。¹H NMR(DMSO-d₆) δ : 12.05(s, 1H), 9.15-9.74(m, 1H), 6.97-7.64(m, 9H), 5.70(br. s., 1H), 2.54-2.72(m, 1H), 2.07-2.26(m, 5H), 1.62-1.91(m, 5H), 1.36-1.59(m, 4H), 1.04-1.32(m, 3H)。LC/MS: $C_{26}H_{30}N_4O_4$ (m/e) 计算值 462, 实测值 463.3 [M+H, ES⁺]。

[0497] 实施例 35

[0498] {3-[4'-(1-甲磺酰氨基羰基-环丙基)-联苯-4-基]-5-甲基-3H-[1,2,3]三唑-4-基}-氨基甲酸 (R)-1-(3-三氟甲基-苯基)-乙酯

[0499]



[0500] 步骤 1: N-[1-(4-溴-苯基)-环丙烷羰基]-甲磺酰胺

[0501] 在 100mL 圆底烧瓶中, 将 1-(4-溴-苯基)-环丙烷甲酸 (4g, 16.6mmol) 与 DCM(15mL) 和 3 滴的 DMF 合并, 以给出白色悬浮物。向其滴加溶解在 DCM(6mL) 中的草酰氯 (6.96g, 4.8mL, 54.8mmol) 的澄清溶液。在 10 分钟之后, 混合物变为澄清并且将反应物在室温搅拌 2 小时。将反应物浓缩, 从甲苯和己烷干燥, 并且储存在冷冻器中过夜。在 200mL 圆底烧瓶中, 将 NaH(60% 矿物油分散液, 876mg, 36.5mmol) 用己烷洗涤并将所得到的固体用 DMF(6mL) 稀释, 以给出白色悬浮物。将悬浮液在冰浴中冷却, 并且在氮下滴加溶解在 DMF(6mL) 中的甲磺酰胺 (3.16g, 33.2mmol)。在加入之后 (5 分钟), 将冰浴移除并将反应升温至室温过夜。将反应物在冰浴中冷却, 逐滴加入预先制备并溶解在 DMF(6mL) 中的酰氯, 并且将反应升温至室温过夜。将反应物用 0.2N HCl(200mL) 稀释并用 EtOAc(2x100mL) 萃取。将有机层用盐水洗涤, 合并, 在 MgSO₄ 上干燥, 并且浓缩。将粗材料溶解在最少 DCM 中

并通过快速色谱提纯（硅胶，己烷中 0% 至 60% EtOAc, 0.5% AcOH）。将合适的级分合并，浓缩，并且由 DCM/ 己烷干燥，产生 N-[1-(4- 溴 - 苯基) - 环丙烷羰基] - 甲磺酰胺 (2.74g, 51.9% 产率)，为白色固体。LC/MS : $C_{11}H_{12}BrNO_3S$ (m/e) 计算值 317/319, 实测值 318/320 (M+H, ES⁺)。

[0502] 步骤 2 : N-{1-[4-(4,4,5,5- 四甲基 -[1,3,2] 二氧杂硼杂环戊烷 -2- 基) - 苯基] - 环丙烷羰基} - 甲磺酰胺

[0503] 在含有 N-[1-(4- 溴 - 苯基) - 环丙烷羰基] - 甲磺酰胺 (2.71g, 8.52mmol) 的 350mL 反应小瓶中加入双 - 频哪醇合二硼 (3.24g, 12.8mmol) 和乙酸钾 (2.51g, 25.6mmol, 当量 : 3) 和 1,4 二噁烷 (63.8mL) 以给出白色悬浮物。将混合物用氮吹扫 20 分钟并且之后加入 $PdCl_2(dppf)CH_2Cl_2$ (701mg, 859 μ mol)。将小瓶密封并在油浴中在 80℃ 加热 16 小时。将反应物用 EtOAc (150mL) 稀释，过滤，用 0.2M HCl (200mL) 和 EtOAc (50mL) 冲洗。将合并的滤液剧烈地搅拌，过滤，并且分离。将水性层用 EtOAc (150mL) 萃取一次。将有机层用盐水洗涤，合并，在 $MgSO_4$ 上干燥，过滤，浓缩，并且由 DCM/ 己烷干燥，为棕色固体 (4g)。将粗材料负载在硅藻土上并通过快速色谱提纯（硅胶，己烷中 0 至 60% EtOAc, 0.5% AcOH）。将合适的级分合并，浓缩，并且由 DCM/ 己烷干燥，产生 N-{1-[4-(4,4,5,5- 四甲基 -[1,3,2] 二氧杂硼杂环戊烷 -2- 基) - 苯基] - 环丙烷羰基} - 甲磺酰胺 (2.75g, 88.4% 产率)，为白色固体。LC/MS : $C_{17}H_{24}BNO_5S$ (m/e) 计算值 365, 实测值 366 (M+H, ES⁺)。

[0504] 步骤 3 : {3-[4' - (1- 甲磺酰氨基羰基 - 环丙基) - 联苯 -4- 基] -5- 甲基 -3H-[1,2,3] 三唑 -4- 基} - 氨基甲酸 (R) -1-(3- 三氟甲基 - 苯基) - 乙酯

[0505] 在 8mL 小瓶中，将 [3-(4- 溴 - 苯基) -5- 甲基 -3H-[1,2,3] 三唑 -4- 基] - 氨基甲酸 (R) -1-(3- 三氟甲基 - 苯基) - 乙酯 (47mg, 100 μ mol)、N-{1-[4-(4,4,5,5- 四甲基 -[1,3,2] 二氧杂硼杂环戊烷 -2- 基) - 苯基] - 环丙烷羰基} - 甲磺酰胺 (40.2mg, 110 μ mol)、DPPF (8.33mg, 15.0 μ mol) 和 $PdCl_2(dppf)CH_2Cl_2$ (12.3mg, 15.0 μ mol) 与 DMF (1mL) (预先用氮吹扫 20 分钟) 合并，以给出浅棕色 / 红色溶液。向其加入 2N Na_2CO_3 (200 μ L, 401 μ mol) (预先用氮吹扫 20 分钟) 并且形成沉淀物。将所得到的红色混合物用氮吹扫 1 分钟。将小瓶密封，放置在干燥区中，并且在 80℃ 加热 2 小时。将反应物用 EtOAc (50mL) 和 0.1N HCl (50mL) 稀释，混合，过滤，并且分离。将水性层用 EtOAc (50mL) 萃取。将有机层用盐水洗涤，合并，在 $MgSO_4$ 上干燥，过滤，浓缩，并且从 DCM/ 己烷干燥，为黄色膜 (120mg)。将粗材料负载在硅藻土上并通过快速色谱提纯（硅胶，己烷中 0% 至 60% EtOAc, 0.5% AcOH）。将合适的级分合并，浓缩，由 DCM/ 己烷和 DCM 干燥，产生 {3-[4' - (1- 甲磺酰氨基羰基 - 环丙基) - 联苯 -4- 基] -5- 甲基 -3H-[1,2,3] 三唑 -4- 基} - 氨基甲酸 (R) -1-(3- 三氟甲基 - 苯基) - 乙酯 (32mg, 50.9% 产率)，为淡黄色固体。LC/MS : $C_{30}H_{28}F_3N_5O_5S$ (m/e) 计算值 627, 实测值 628 (M+H, ES⁺)。 1H NMR (DMSO- d_6) δ : 11.23 (br. s., 1H), 9.80 (br. s., 1H), 7.85 (d, J = 6.5Hz, 2H), 7.49-7.77 (m, 8H), 7.45 (d, J = 8.3Hz, 2H), 5.68-5.95 (m, 1H), 3.23 (s, 3H), 2.17 (br. s., 3H), 1.44-1.64 (m, 4H), 1.23 (br. s., 3H)。

[0506] 实施例 36

[0507] 使用荧光成像读板仪 (FLIPR) 的钙流量试验

[0508] 细胞培养条件 : 含有人重组 LPA1 溶血磷脂受体的 ChemiScreen 钙优化的稳定细胞系购自 Chemicon International, Inc./Millipore。将细胞在补充有 10% 胎牛血清、2mM

谷氨酰胺、100U/mL 青霉素 /100 μ g/mL 链霉素、1X 非必要氨基酸、10mM HEPES 和 0.25mg/mL 遗传霉素 (Geneticin) 的 DMEM- 高葡萄糖中培养。将细胞用胰蛋白酶-EDTA 收获并使用 ViaCount 试剂计数。用完全培养基将细胞悬浮液体积调节至 2.0×10^5 细胞 /mL。将 50 μ L 等份分配至 384 孔黑色 / 透明组织培养处理过的板 (BD), 并且将微板放置在 37°C 培养箱中过夜。之后数天, 将该板在试验中使用。

[0509] 染料加载和测试: 通过将一瓶的内含物溶解至含有 20mM HEPES 和 2.5mM 丙磺舒 (probenecid) 的 100mL Hank's Balanced Salt Solution 中制备加载缓冲液 (Loading Buffer) (FLIPR 钙-4, Molecular Devices)。将板装载至 Biotek 洗板器上, 将培养基移除并用含有 20mM HEPES 和 2.5mM 丙磺舒 (probenecid) 的 20 μ L 的 Hank's Balanced Salt Solution 替代, 接着是 25 μ L 的加载缓冲液。之后将板在 37°C 温育 30 分钟。

[0510] 在温育过程中, 通过加入 90 μ L 的 HBSS/20mM HEPES/0.1% BSA 缓冲液至 2 μ L 的连续稀释的化合物制备测试化合物。为制备连续稀释物, 在 100% DMSO 中制备 10mM 的化合物原液。如下建立化合物稀释板: 孔 #1 接收 29 μ L 的化合物原液和 31 μ L DMSO; 孔 2-10 接收 40 μ L 的 DMSO; 将 20 μ L 的溶液从孔 #1 混合并转移至孔 #2 中; 继续用 1 : 3 连续稀释 10 步; 将 2 μ L 的稀释化合物转移至 384 孔“试验板”的孔中, 一式两份, 并且之后加入 90 μ L 的缓冲液。

[0511] 在温育之后, 将细胞板和“试验”板两者置于 FLIPR, 并且将 20 μ L 的稀释化合物通过 FLIPR 转移至细胞板。通过 FLIPR 监控化合物加入以检测化合物的任何激动活性。之后将板在室温避光温育 30 分钟。在温育之后, 将板返回至 FLIPR, 并且将 20 μ L 的 4.5X 浓缩激动剂加入至细胞板。在试验过程中, 每 1.5 秒由细胞板的所有 384 孔同时取得荧光读数。取五次读数, 以建立稳定基线, 之后将 20 μ L 的样品迅速地 (30 μ L/ 秒) 并同时地加入至细胞板的每个孔。在样品加入之前、过程中和之后在 100 秒的全部经过时间内连续地监控荧光。测定在激动剂加入之后每个孔中的响应 (峰值荧光的增加)。在配体刺激之前, 使用来自每个孔的初始荧光读数作为用于来自该孔的数据的零基线值。将响应表示为缓冲液对照的 % 抑制。通过将 10 浓度的百分比抑制数据使用 Genedata Condoseo 程序拟合至 S 形剂量响应 (4 参数逻辑) 模型 [模型 205, $F(x) = (A + (B - A) / (1 + ((C/x)^D)))$], 计算被定义为缓冲液对照的 50% 抑制所需的化合物浓度的 IC_{50} 值, 并且结果在下表 1 中给出:

[0512] 表 1

[0513] LPA1 和 LPA3 拮抗剂活性

[0514]

实施例#	LPA1 IC ₅₀ (μM)或 (抑制%@μM)	LPA3 IC ₅₀ (μM)或 (抑制%@μM)
1	0.025	>30
2	>30 (40% @ 30)	>30
3	>30	>30
4	>30	>30
5	0.035	>30
6	0.112	25.9 (55.2% @ 30)
7	0.174	6.86
8	>30	>30
9	0.217	>30
10	0.398	>30
11	>30	>30
12	0.134	>30
13	0.161	>30
14	0.985	>30
15	0.022	(46.3% @ 30)
16	0.245	>30
17	0.043	21.73 (63.7% @ 30)
18	1.228 (79.8% @ 30)	>30
19	0.412	4.82
20	21.23 (58.3% @ 30)	14.3 (72.5% @ 30)
21	0.036	>30 (22% @ 30)
22	>30	>30

[0515]

23	0.796 (80.9% @ 30)	>30
24	>30	>30
25	>30	>30
26	>30	>30
27	>30	>30
28	>30	>30
29	0.023	>30
30	0.033	>30
31	>30 (11% @ 30)	>30
32	0.174	>30
33	0.088	>30
34	9.478	>30
35	4.534	5.736

[0516] 应当明白的是,本发明不限于上面描述的本发明的特定实施方案,因为可以进行特定实施方案的变体并且仍落在后附权利要求书的范围之内。