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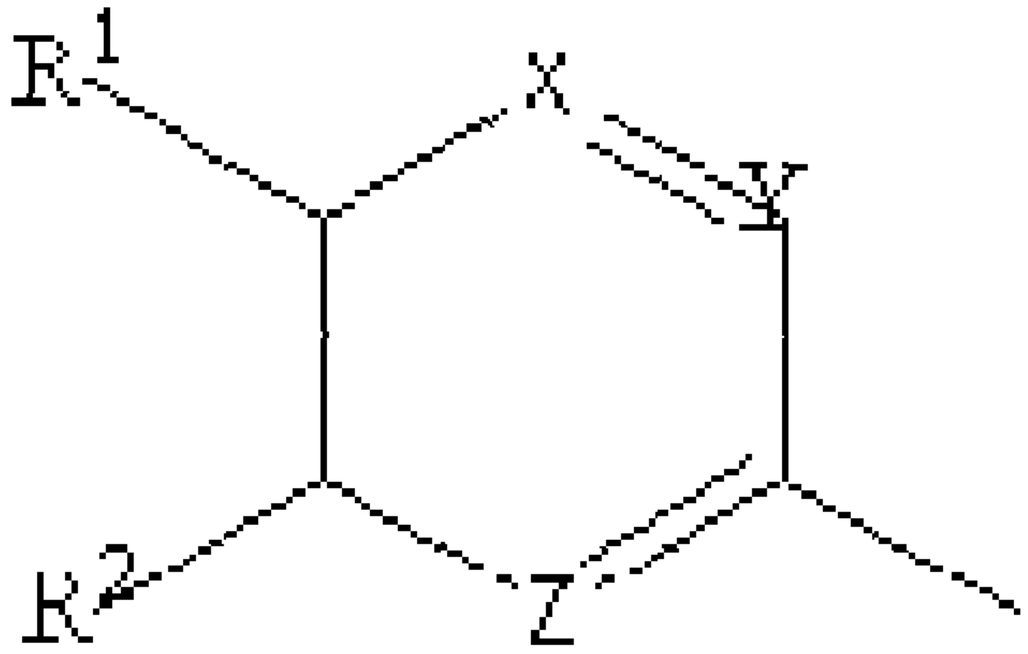
(54) Titre : COMPOSES HETEROAROMATIQUES PRESENTANT UNE ACTIVITE BIOLOGIQUE AGONISTE ET/OU ANTAGONISTE SUR LE RECEPTEUR SPHINGOSINE-1-PHOSPHATE (S1P)

(54) Title: HETEROAROMATIC COMPOUNDS HAVING SPHINGOSINE-1-PHOSPHATE (S1P) RECEPTOR AGONIST AND/OR ANTAGONIST BIOLOGICAL ACTIVITY



(57) Abrégé/Abstract:
A novel compound having antagonist activity at the S1P3 receptor represented by the formula (I); $[C(R^3)_2]_a(W)_b[C(R^3)_2]_c[P(O)(OR^3)_2]_d[C(V)_x(OR^4)_y(R^4)_z]_e$ wherein X is selected from the group consisting of CR^3 and N; Y is selected from the group consisting of CR^3 and N; Z is selected from the group consisting of CR^3 and N; and at least one of X, Y and Z is N; W is NR^3 or O; V is oxo or represents two H atoms; provided that when V is two H atoms, z is 0; R^1 is an aryl group; R^2 is an aryl group; R^3 is selected from the group consisting of H and alkyl and lower alkyl; R^4 is selected from the group consisting of H and alkyl; and 2 of said R^3 or R^4 may together form a cyclic alkyl ring having from 3 to 6 carbon atoms; a is 0 or an integer of from 1 to 6; b is 0 or 1; c is O or an integer of from 1 to 6; d is 0 or 1; e is 0 or 1; x is 1; y is 0 or an integer of from 1 to 3; z is 0 or an integer of from 1 to 3; provided however that when d is 0, e is 1, and when e is 0, d is 1, and when y is 0, z is 1 and when z is 0, y is 1.

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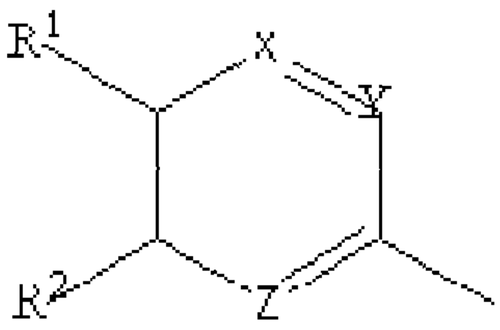

(57) Abstract: A novel compound having antagonist activity at the S1P3 receptor represented by the formula (I); $[C(R^3)_2]_a(W)_b[C(R^3)_2]_c[P(O)(OR^3)_2]_d[C(V)_x(OR4)y(R^4)_z]_e$ wherein X is selected from the group consisting of CR^3 and N; Y is selected from the group consisting of CR^3 and N; Z is selected from the group consisting of CR^3 and N; and at least one of X, Y and Z is N; W is NR^3 or O; V is oxo or represents two H atoms; provided that when V is two H atoms, z is 0; R^1 is an aryl group; R^2 is an aryl group; R^3 is selected from the group consisting of H and alkyl and lower alkyl; R^4 is selected from the group consisting of H and alkyl; and 2 of said R^3 or R^4 may together form a cyclic alkyl ring having from 3 to 6 carbon atoms; a is 0 or an integer of from 1 to 6; b is 0 or 1; c is O or an integer of from 1 to 6; d is 0 or 1; e is 0 or 1; x is 1; y is 0 or an integer of from 1 to 3; z is 0 or an integer of from 1 to 3; provided however that when d is 0, e is 1, and when e is 0, d is 1, and when y is 0, z is 1 and when z is 0, y is 1.

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HETEROAROMATIC COMPOUNDS HAVING SPHINGOSINE-1-PHOSPHATE (S1P) RECEPTOR AGONIST AND/OR ANTAGONIST BIOLOGICAL ACTIVITY

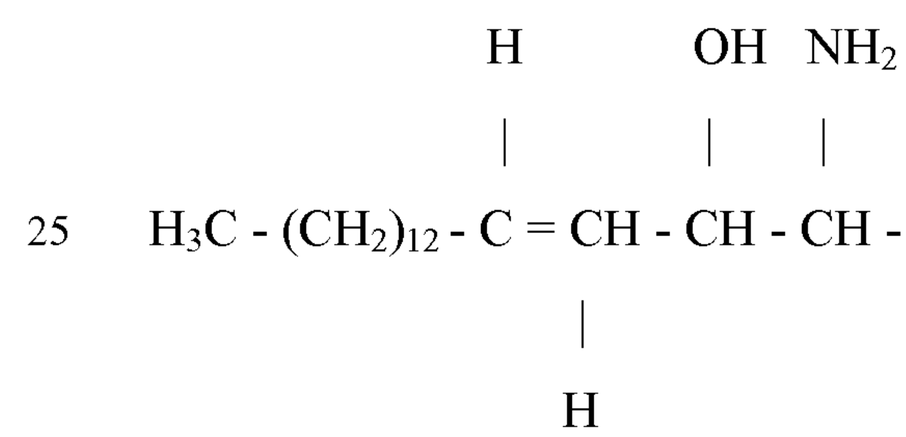
BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to derivatives and/or analogues of sphingosine and pharmaceutical compositions, including such derivatives and/or analogues, which are useful as drugs for the treatment of fungal infections, allergic diseases, immune disorders, etc.

2. Summary of the Art

Sphingosine is a compound having the chemical structure shown in the general formula described below, in which Y^1 is hydrogen. It is known that various sphingolipids, having sphingosine as a constituent, are widely distributed in the living body including on the surface of cell membranes of cells in the nervous system.



A sphingolipid is one of the lipids having important roles in the living body. A disease called lipidosis is caused by accumulation of a specified sphingolipid in the body. Sphingolipids present on cell membranes function to regulate cell growth; participate in the development and differentiation of cells; function in nerves; are involved in the infection and malignancy of cells; etc. Many of the physiological

roles of sphingolipids remain to be solved. Recently the possibility that ceramide, a derivative of sphingosine, has an important role in the mechanism of cell signal transduction has been indicated, and studies about its effect on apoptosis and cell cycle have been reported.

Sphingosine-1-phosphate is an important cellular metabolite, derived from ceramide that is synthesized de novo or as part of the sphingomeyeline cycle (in animals cells). It has also been found in insects, yeasts and plants.

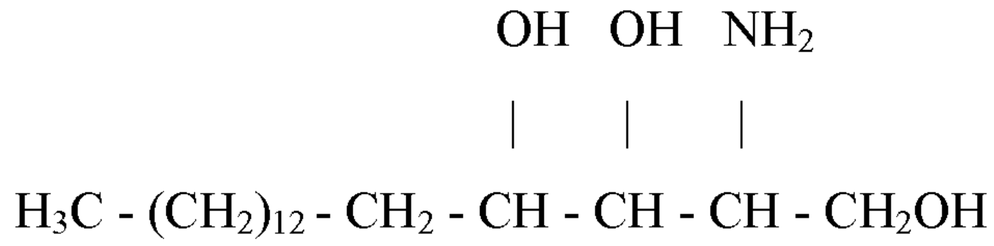
The enzyme, ceramidase, acts upon ceramides to release sphingosine, which is phosphorylated by spingosine kinase, a ubiquitous enzyme in the cytosol and endoplasmic reticulum, to form sphingosine-1-phosphate. The reverse reaction can occur also by the action of sphingosine phosphatases, and the enzymes act in concert to control the cellular concentrations of the metabolite, which concentrations are always low. In plasma, such concentration can reach 0.2 to 0.9 μM, and the metabolite is found in association with the lipoproteins, especially the HDL. It should also be noted that sphingosine-1-phosphate formation is an essential step in the catabolism of sphingoid bases.

Like its precursors, sphingosine-1-phosphate is a potent messenger molecule that perhaps uniquely operates both intra- and inter-cellularly, but with very different functions from ceramides and sphingosine. The balance between these various sphingolipid metabolites may be important for health. For example, within the cell, sphingosine-1-phosphate promotes cellular division (mitosis) as opposed to cell death (apoptosis), which it inhibits. Intracellularly, it also functions to regulate calcium mobilization and cell growth in response to a variety of extracellular stimuli. Current opinion appears to suggest that the balance between sphingosine-1-phosphate and ceramide and/or spingosine levels in cells is critical for their viability. In common with the lysophospholipids, especially lysophosphatidic acid,

with which it has some structural similarities, sphingosine-1-phosphate exerts many of its extra-cellular effects through interaction with five specific G protein-coupled receptors on cell surfaces. These are important for the growth of new blood vessels, vascular maturation, cardiac development and immunity, and for directed cell movement.

Sphingosine-1 phosphate is stored in relatively high concentrations in human platelets, which lack the enzymes responsible for its catabolism, and it is released into the blood stream upon activation of physiological stimuli, such as growth factors, cytokines, and receptor agonists and antigens. It may also have a critical role in platelet aggregation and thrombosis and could aggravate cardiovascular disease. On the other hand the relatively high concentration of the metabolite in high-density lipoproteins (HDL) may have beneficial implications for atherogenesis. For example, there are recent suggestions that sphingosine-1-phosphate, together with other lysolipids such as sphingosylphosphorylcholine and lysosulfatide, are responsible for the beneficial clinical effects of HDL by stimulating the production of the potent antiatherogenic signaling molecule nitric oxide by the vascular endothelium. In addition, like lysophosphatidic acid, it is a marker for certain types of cancer, and there is evidence that its role in cell division or proliferation may have an influence on the development of cancers. These are currently topics that are attracting great interest amongst medical researchers, and the potential for therapeutic intervention in sphingosine-1-phosphate metabolism is under active investigation.

Fungi and plants have sphingolipids and the major sphingosine contained in these organisms has the formula described below. It is known that these lipids have important roles in the cell growth of fungi and plants, but details of the roles remain to be solved.



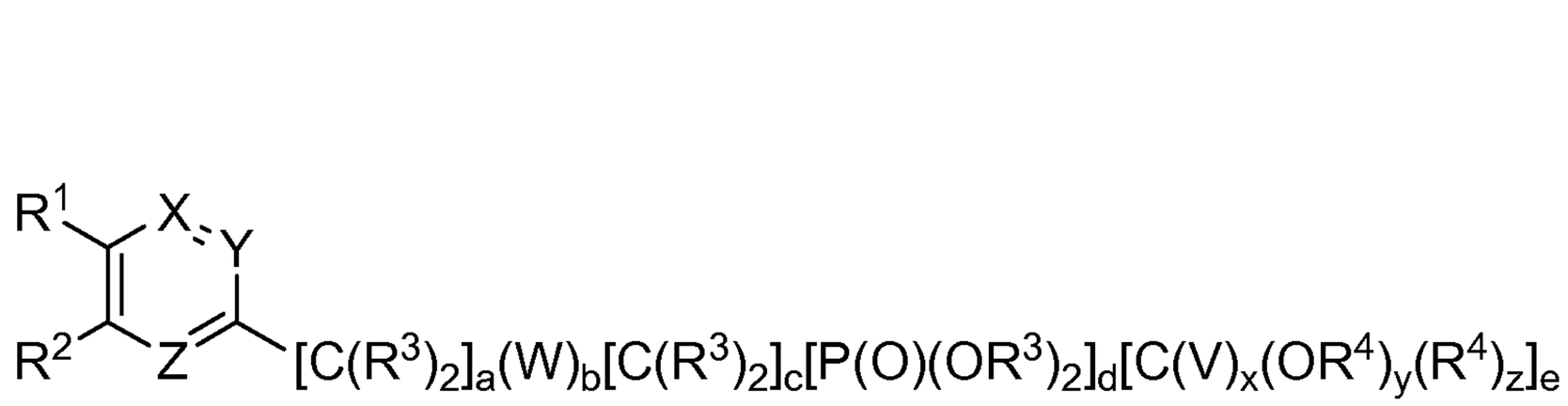
Recently it has been known that derivatives of sphingolipids and their related compounds exhibit a variety of biological activities through inhibition or stimulation of the metabolism pathways. These compounds include inhibitors of protein kinase C, inducers of apoptosis, immuno-suppressive compounds, antifungal compounds, and the like. Substances having these biological activities are expected to be useful compounds for various diseases.

Derivatives of sphingosine have been prepared in various patents. For example, see U.S. Patents 4,952,683, 5,110,987, 6,235,912 B1, 6,239,297 B1.

SUMMARY OF THE INVENTION

The present invention provides a derivative or analogue of sphingosine that is able to regulate the functions of sphingolipid, and pharmaceutical compositions comprising said derivative or analogue.

These compounds are represented by the formula I, each of which compounds may have sphingosine-1-phosphate receptor agonist and or antagonist biological activity:



I

wherein

X is selected from the group consisting of CR^3 and N;

Y is selected from the group consisting of CR^3 and N;

Z is selected from the group consisting of CR^3 and N;

and at least one of X, Y and Z is N;

W is NR^3 or O;

V is oxo or represents two H atoms;

provided that when V is two H atoms, z is 0;

R^1 is an aryl group and is selected, preferably, from the group consisting of phenyl and substituted derivatives thereof;

R^2 is an aryl group and is selected, preferably from the group consisting of phenyl, furanyl, thienyl, pyridyl, pyranyl and substituted derivatives thereof;

R^3 is a hydrocarbyl or substituted hydrocarbyl radical which is selected, preferably, from the group consisting of H and alkyl and more preferably, R^3 is selected from the group consisting of H and lower alkyl, e. g. C_1 to C_6 alkyl ;

R^4 is a hydrocarbyl or substituted hydrocarbyl radical which is selected, preferably, from the group consisting of H and alkyl and, more preferably, R^4 is selected from the group consisting of H and lower alkyl, e. g. C_1 to C_6 alkyl;

and 2 of said R^3 or R^4 may together form a cyclic alkyl ring having from 3 to 6 carbon atoms;

a is 0 or an integer of from 1 to 6, e. g. 0 or an integer of from 1 to 3;

b is 0 or 1;

c is 0 or an integer of from 1 to 6, e. g. 0 or an integer of from 1 to 5;

d is 0 or 1;

e is 0 or 1;

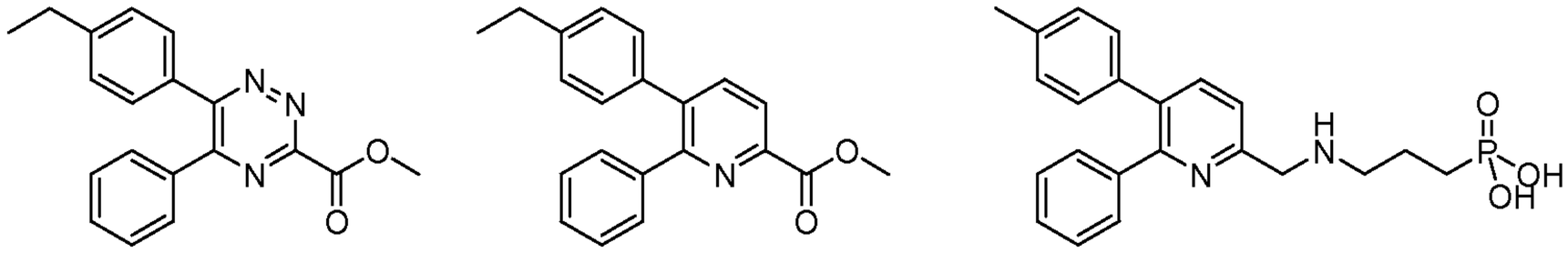
x is 1;

y is 0 or an integer of from 1 to 2;

z is 0 or an integer of from 1 to 2;

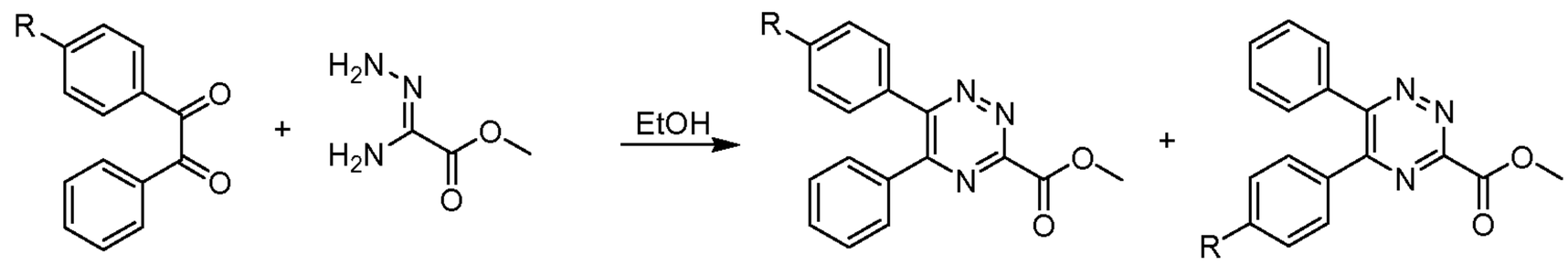
provided however that when d is 0, e is 1, and when e is 0, d is 1, and when y is 0, z is 1 and when z is 0, y is 1.

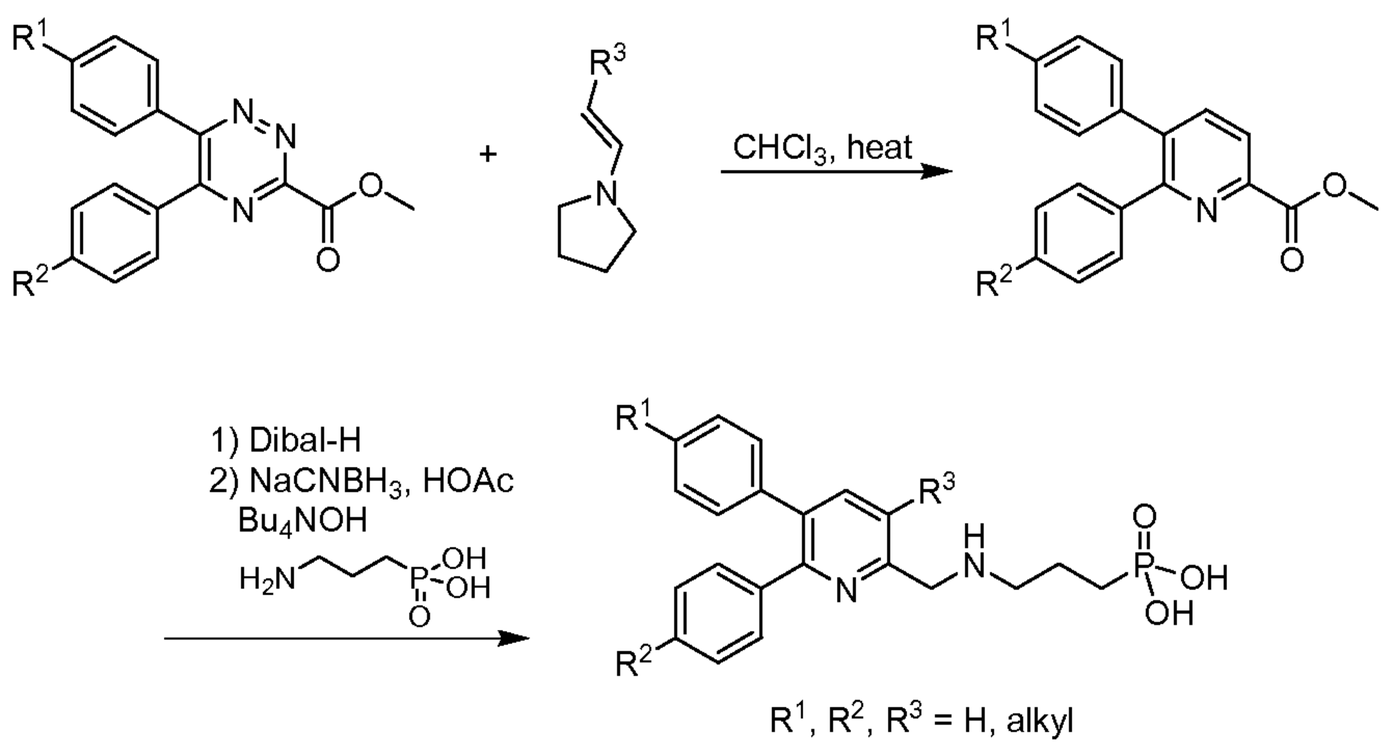
Specific Examples of the compounds of formula I include



These compounds may be synthesized as illustrated by the synthesis scheme below:

It is noted that, in the general synthetic schemes used throughout this patent application, the various substituents designated as R, R^1, R^2 etc. may represent substituents which differ from the substituents that R, R^1, R^2 etc. represent in the above formula I. However, it will be apparent to the skilled artisan that it is intended for the definition of the invention, as claimed, that the definition of the substituents in formula I control in defining the scope of the invention, while the substituents of the general synthetic scheme are for the purpose of showing the making of the claimed compounds





In general, a diphenylethyl-1,2-dione (e.g. benzil) is treated with methyl oxalamidrazonate in ethanol to produce a methyl 5,6-diphenyl-1,3,4-triazine-2-carboxylate (as a mixture of geometric isomers if the dione is asymmetrical). These triazines can undergo Diels-Aler reactions with a pyrrolidine enamine compound to give a methyl 5,6-diphenylpyridine-2-carboxylate derivative. These compounds can be reduced with diisobutylaluminum hydride to the corresponding aldehyde derivatives, which then can be converted into a number of homologs and derivatives. For instance, the aldehyde can be converted into a secondary amine by reacting it with a primary amine in the presence of a reducing agent, such as sodium cyanoborohydride. Alternatively, the aldehyde may be reduced to an alcohol and treated with an alkyl halide in the presence of a mild base to produce alkyl ethers. Those skilled in the art will recognize that these compounds may be used to prepare many other homologs, many of which are described in the Specific Examples section below.

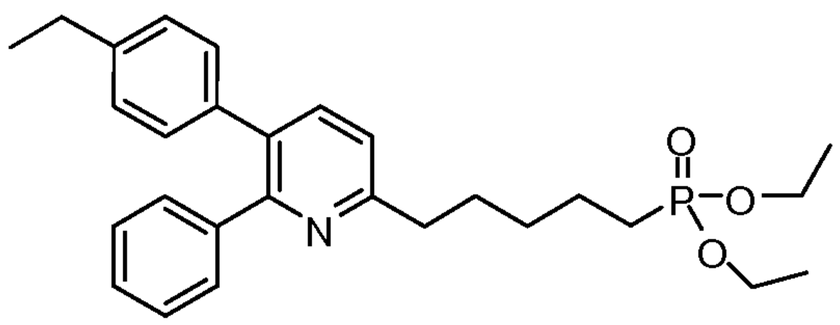
DETAILED DESCRIPTION OF THE INVENTION

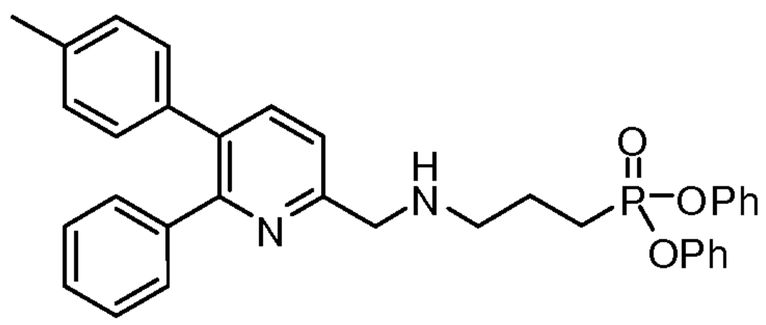
Unless otherwise indicated, reference to a compound should be construed broadly to include pharmaceutically acceptable salts, prodrugs, tautomers, alternate solid forms, non-covalent complexes, and combinations thereof, of a chemical entity of the depicted structure or chemical name.

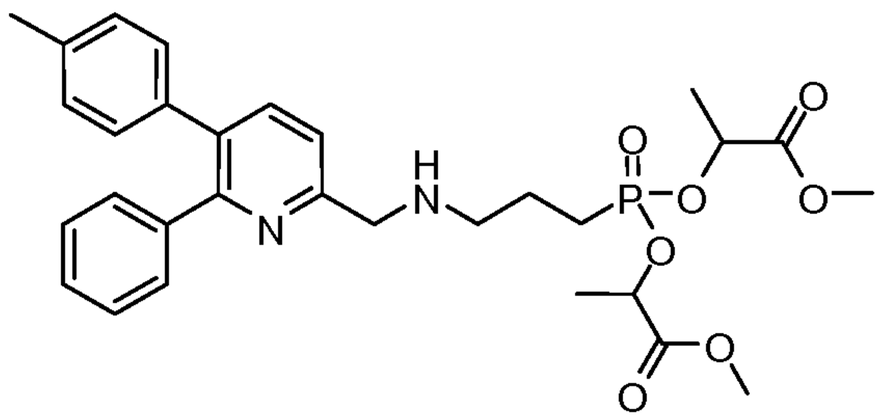
A pharmaceutically acceptable salt is any salt of the parent compound that is suitable for administration to an animal or human. A pharmaceutically acceptable salt also refers to any salt which may form *in vivo* as a result of administration of an acid, another salt, or a prodrug which is converted into an acid or salt. A salt comprises one or more ionic forms of the compound, such as a conjugate acid or base, associated with one or more corresponding counter-ions. Salts can form from or incorporate one or more deprotonated acidic groups (e.g. carboxylic acids), one or more protonated basic groups (e.g. amines), or both (e.g. zwitterions).

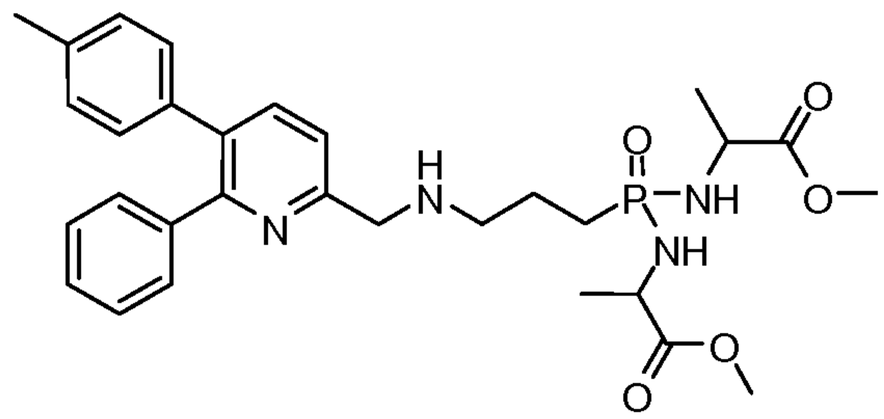
A prodrug is a compound which is converted to a therapeutically active compound after administration. For example, conversion may occur by hydrolysis of an ester group or some other biologically labile group. Prodrug preparation is well known in the art. For example, "Prodrugs and Drug Delivery Systems," which is a chapter in Richard B. Silverman, *Organic Chemistry of Drug Design and Drug Action*, 2d Ed., Elsevier Academic Press: Amsterdam, 2004, pp. 496-557, provides further detail on the subject. One example of useful prodrugs are compounds having a phosphonate ester or amide functional groups, such as mono- and di-alkyl phosphonate, mono- and di-diaryl phosphonate, mono- and bis- phosphoramidate, and the like. The structures shown below are typical examples. (See Mark D. Erion, et al. PNAS 2005, 102, 7970-7975; Mark D. Erion, et al. J. Am. Chem. Soc. 2004, 126, 5154-5163; Didier Saboulard, et al. Mol. Pharmacol. 1999, 56, 693-704; Jeffrey P. Krise, et al. Adv. Drug Deliver. Rev. 1996, 19, 287-310; Halina T.

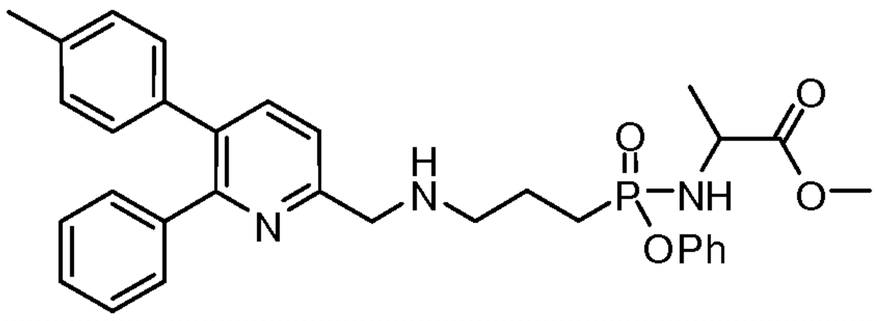
Serafinowska, et al. J. Med. Chem. 1995, 38, 1372-1379; Christopher McGuigan, et al. J. Med. Chem. 1993, 36, 1048-1052.)

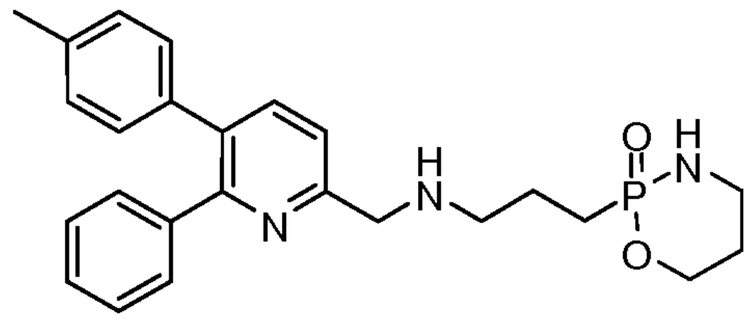












Tautomers are isomers that are in rapid equilibrium with one another. For example, tautomers may be related by transfer of a proton, hydrogen atom, or hydride ion.

Unless stereochemistry is explicitly depicted, a structure is intended to include every possible stereoisomer, both pure or in any possible mixture.

Alternate solid forms are different solid forms than those that may result from practicing the procedures described herein. For example, alternate solid forms may be polymorphs, different kinds of amorphous solid forms, glasses, and the like.

Non-covalent complexes are complexes that may form between the compound and one or more additional chemical species that do not involve a covalent bonding interaction between the compound and the additional chemical species. They may or may not have a specific ratio between the compound and the additional chemical

species. Examples might include solvates, hydrates, charge transfer complexes, and the like.

In the novel compounds of this invention R^3 and R^4 may be independently selected from the group consisting of hydrogen, straight or branched chain alkyl having 1 to 12 carbons, cycloalkyl having 3 to 6 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, aryl, preferably a carbocyclic aryl group having from 6 to 14 carbon atoms or a heterocyclic aryl group having from 2 to 14 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, halo, e.g. fluoro or chloro, C_1 to C_{12} haloalkyl, e.g. trifluoromethyl, hydroxyl, C_1 to C_{12} alkoxy, C_1 to C_{12} alkylcarbonyl, formyl, oxycarbonyl, carboxy, C_1 to C_{12} alkyl carboxylate, C_1 to C_{12} alkyl amide, aminocarbonyl, amino, cyano, diazo, nitro, thio, sulfoxyl, or sulfonyl groups.

R^1 and R^2 are aryl groups which may be any carbocyclic aryl or heterocyclic aryl group including but not limited to benzene, pyridine, pyrazine, pyridazine, pyrimidine, triazine, thiophene, furan, thiazole, thiadiazole, isothiazole, oxazole,oxadiazole, isooxazole, naphthalene, quinoline, tetralin, chroman, thiochroman, tetrahydroquinoline, dihydronaphthalene, tetrahydronaphthalen, chromene, thiochromene, dihydroquinoline, indan, dihydrobenzofuran, dihydrobenzothiophene, indene, benzofuran, benzothiophene, coumarin and coumarinone. Such aryl groups can be bonded to the above moiety at any position. Such aryl group may itself be substituted with any common organic functional group including but not limited to alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, hydroxyl, alkoxyl, alkylcarbonyl, formyl, oxycarbonyl, carboxyl, alkyl carboxylate, alkyl amide, aminocarbonyl, amino, cyano, diazo, nitro, thio, sulfoxyl, or sulfonyl groups.

Preferably, the carbocyclic aryl group will comprise from 6 to 14 carbon atoms, e.g. from 6 to 10 carbon atoms. Preferably the heterocyclic aryl group will comprise from 2 to 14 carbon atoms and one or more, e.g. from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur.

In one aspect of the invention wherein e is 0, the compounds have a side chain which terminates in a phosphonic acid or a phosphonic acid ester group.

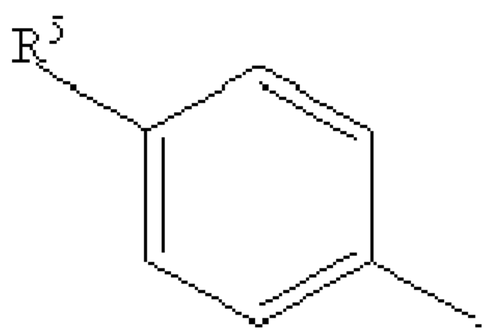
Preferably R^1 is selected from the group consisting of phenyl and substituted derivatives thereof.

Preferably R^2 is selected from the group consisting of phenyl, furanyl, thienyl, pyridyl, pyranyl and substituted derivatives thereof.

Preferably R^3 and R^4 are H or lower alkyl.

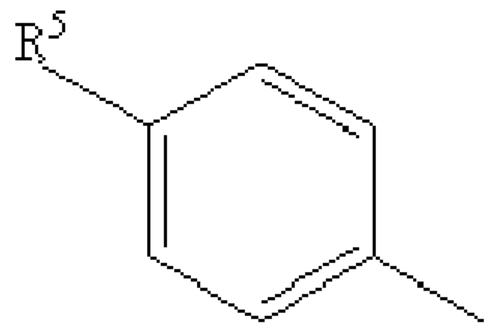
Preferably a is 0 or an integer of from 1 to 3 and c is 0 or an integer of from 1 to 5.

In these compounds, R^1 is represented, preferably, by the general formula



wherein R^5 is selected from the group consisting of H, alkyl, trifluoromethyl, trifluoromethyloxy, halo, e. g.chloro, and loweralkylthio.

In said phosphonic acid terminated compounds, preferably R^2 is selected from the group consisting of furanyl, thienyl, pyridyl and pyranyl or R^2 is

represented by the general formula 

wherein R^5 is selected from the group consisting of H, alkyl, trifluoromethyl, trifluoromethyloxy, halo, e. g. chloro, and loweralkylthio .

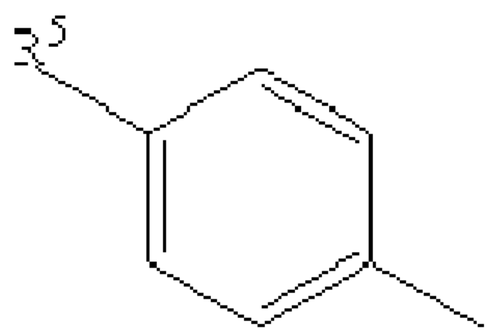
In these phosphonic acid terminated compounds, preferably R^3 is H, and

Furthermore, in said compounds, preferably c is 1, 2 or 3 and a is 1.

Finally, in said phosphonic acid-terminated compounds most preferably Z is N, X and Y are CR^3, W is NR^3, R^2 is phenyl and R^5 is selected from the group consisting of H and methyl or R^2 is pyridyl and R^5 is ethyl

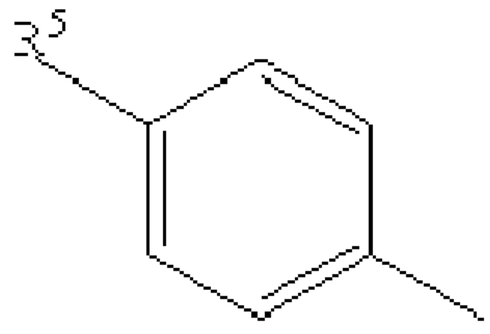
In another aspect of the present invention d is 0 and therefore the compounds have a side chain which terminates in a carbon-oxygen radical such as a carboxylic acid, an ester thereof, an ether, an alcohol, or an alkyl carboxy group.

In these carbon-oxygen terminated compounds, R^1 may be represented by the general formula



wherein R^5 is selected from the group consisting of H, alkyl, trifluoromethyl, trifluoromethyloxy, halo, e. g. chloro, and loweralkylthio

Furthermore R^2 may also be represented by the general formula



wherein R^5 is selected from the group consisting of H, lower alkyl, trifluoromethyl, trifluoromethyloxy, halo, e. g. chloro, and loweralkylthio or R^2 is selected from the group consisting of furanyl, thienyl, pyridyl and pyranyl.

In such compounds, preferably R^3 is H and more preferably, a is 1.
More preferably, in said compounds x is 1, z is 0 and R^4 is selected from the group consisting of H, methyl and ethyl.

Finally, in the carbon-oxygen compounds of this invention preferably is Z is N, X and Y are CR^3, R^2 is pyridyl, R^4 is selected from the group consisting of methyl and ethyl and R^5 is selected from the group consisting of H, methyl, ethyl, propyl and trifluoromethyl, or

X, Y and Z are N, R^4 is selected from the group consisting of methyl and ethyl and R^5 is selected from the group consisting of H, methyl, ethyl, propyl and trifluoromethyl, or

X and Z are N and Y is CR^3.

Unless otherwise indicated, the following terms as used throughout this specification have the following meanings:

"Me" refers to methyl.

"Et" refers to ethyl.

"tBu" refers to t-butyl.

"iPr" refers to i-propyl.

"Ph" refers to phenyl.

"Pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are obtained by reaction with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

"Alkyl" refers to a straight-chain, branched or cyclic saturated aliphatic hydrocarbon. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from 1 to 7 carbons, most preferably 1 to 4 carbons. Typical alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl and the like. The alkyl group may be optionally substituted with one or more substituents are selected from the group consisting of hydroxyl, cyano, alkoxy, .= O, .= S, NO_2, halogen, dimethyl amino, and SH.

"Alkenyl" refers to a straight-chain, branched or cyclic unsaturated hydrocarbon group containing at least one carbon--carbon double bond. Preferably, the alkenyl group has 2 to 12 carbons. More preferably it is a lower alkenyl of from 2 to 7 carbons, most preferably 2 to 4 carbons. The alkenyl group may be optionally substituted with one or more substituents selected from the group consisting of hydroxyl, cyano, alkoxy, O, S, NO_2, halogen, dimethyl amino, and SH.

"Alkynyl" refers to a straight-chain, branched or cyclic unsaturated hydrocarbon containing at least one carbon--carbon triple bond. Preferably, the alkynyl group has 2 to 12 carbons. More preferably it is a lower alkynyl of from 2 to 7 carbons, most preferably 1 to 4 carbons. The alkynyl group may be optionally substituted with one or more substituents selected from the group consisting of hydroxyl, cyano, alkoxy, O, S, NO_2, halogen, dimethyl amino, and SH.

"Alkoxyl" refers to an "O-alkyl" group.

"Aryl" refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups. The aryl group may be optionally substituted with one or more substituents selected from the group consisting of halogen, trihalomethyl, hydroxyl, SH, OH, NO_2, amine, thioether, cyano, alkoxy, alkyl, and amino.

"Alkaryl" refers to an alkyl that is covalently joined to an aryl group. Preferably, the alkyl is a lower alkyl.

"Carbocyclic aryl" refers to an aryl group wherein the ring atoms are carbon.

"Heterocyclic aryl" refers to an aryl group having from 1 to 3 heteroatoms as ring atoms, the remainder of the ring atoms being carbon. Heteroatoms include oxygen, sulfur, and nitrogen.

"Hydrocarbyl" refers to a hydrocarbon radical having only carbon and hydrogen atoms. Preferably, the hydrocarbyl radical has from 1 to 20 carbon atoms, more preferably from 1 to 12 carbon atoms and most preferably from 1 to 7 carbon atoms.

"Substituted hydrocarbyl" refers to a hydrocarbyl radical wherein one or more, but not all, of the hydrogen and/or the carbon atoms are replaced by a halogen, nitrogen, oxygen, sulfur or phosphorus atom or a radical including a halogen, nitrogen, oxygen, sulfur or phosphorus atom, e.g. fluoro, chloro, cyano, nitro, hydroxyl, phosphate, thiol, etc.

"Amide" refers to --C(O)--NH--R', wherein R' is alkyl, aryl, alkylaryl or hydrogen.

"Thioamide" refers to --C(S)--NH--R', wherein R' is alkyl, aryl, alkylaryl or hydrogen.

"Amine" refers to a --N(R")R'" group, wherein R" and R'" are independently selected from the group consisting of alkyl, aryl, and alkylaryl.

"Thioether" refers to --S--R", wherein R" is alkyl, aryl, or alkylaryl.

"Sulfonyl" refers to --$S(O)_2$ --R"", where R"" is aryl, C(CN)=C-aryl, CH_2 CN, alkyaryl, sulfonamide, NH-alkyl, NH-alkylaryl, or NH-aryl.

SPECIFIC EXAMPLES

Specific compounds of the invention and their activity at the sphingosine-1-phosphate receptors are reported in Table I, below.

Compounds were also assessed for their ability to activate or block activation of the human S1P3 receptor in T24 cells stably expressing the human S1P3 receptor. Ten thousand cells/well were plated into 384-well poly-D-lysine coated plates one day prior to use. The growth media for the S1P3 receptor expressing cell line was McCoy's 5A medium supplemented with 10% charcoal-treated fetal bovine serum (FBS), 1% antibiotic-antimycotic and 400 μg/ml geneticin. On the day of the

experiment, the cells were washed twice with Hank's Balanced Salt Solution supplemented with 20 mM HEPES (HBSS/Hepes buffer). The cells were then dye loaded with 2 uM Fluo-4 diluted in the HBSS/Hepes buffer with 1.25 mM Probenecid and incubated at 37°C for 40 minutes. Extracellular dye was removed by washing the cell plates four times prior to placing the plates in the FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices). Ligands were diluted in HBSS/Hepes buffer and prepared in 384-well microplates. The positive control, Sphingosine-1-Phosphate (S1P), was diluted in HBSS/Hepes buffer with 4 mg/ml fatty acid free bovine serum albumin. The FLIPR transferred 12.5 µl from the ligand microplate to the cell plate and took fluorescent measurements for 75 seconds, taking readings every second, and then for 2.5 minutes, taking readings every 10 seconds. Drugs were tested over the concentration range of 0.61 nM to 10,000 nM. Data for Ca^{+2} responses were obtained in arbitrary fluorescence units and not translated into Ca^{+2} concentrations. IC_{50} values were determined through a linear regression analysis using the Levenburg Marquardt algorithm. In Table 1, NA is defined as "Not Active," ND is defined as "Not Determined," % efficacy is defined as "percent of receptor activity induced by a test compound at the highest dose test (10 µM) relative to the receptor activity induced by 5 nM sphingosine-1-phosphate.," and % inhibition is defined as "percent of receptor activity induced by 5 nM sphingosine-1-phosphate that is inhibited by a test compound at the highest dose tested (10 µM)."

Table 1

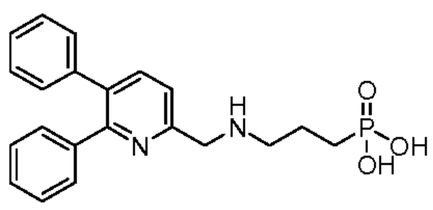
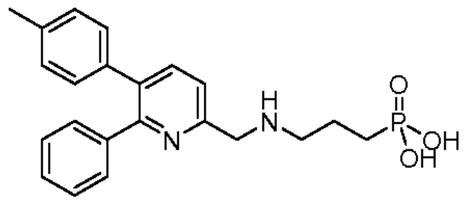
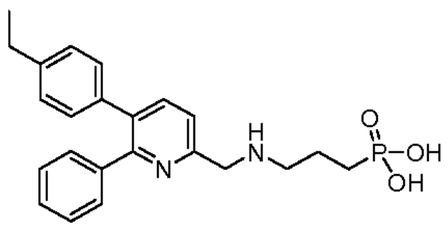
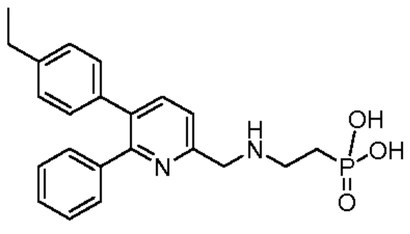
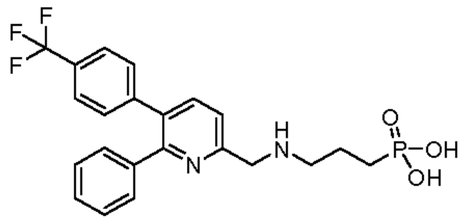
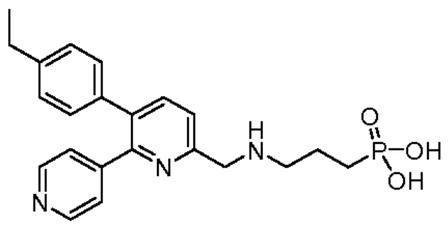
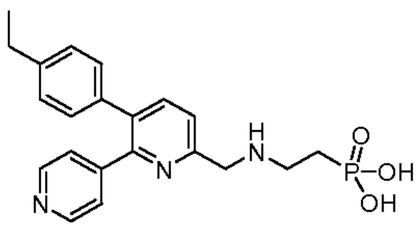
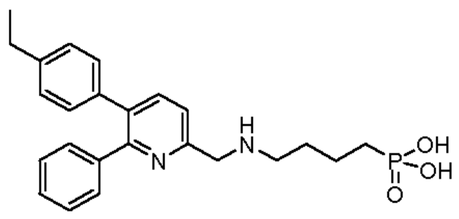
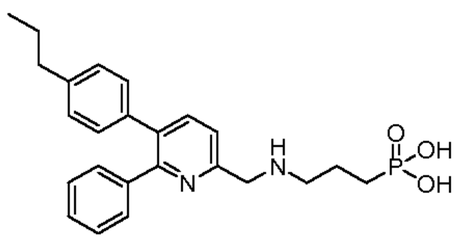
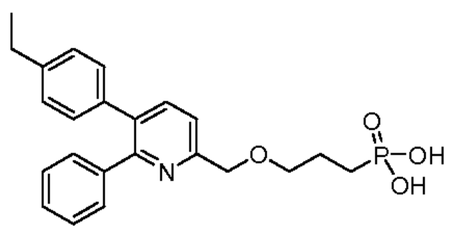
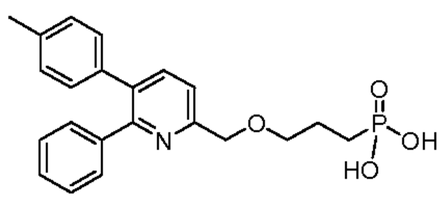
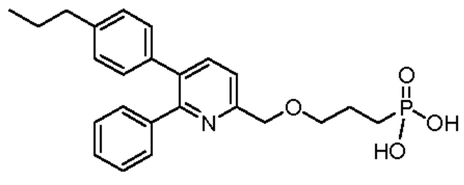
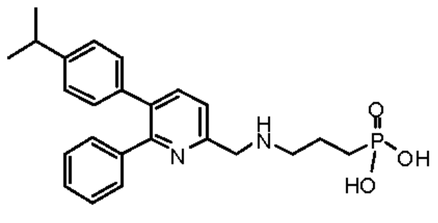
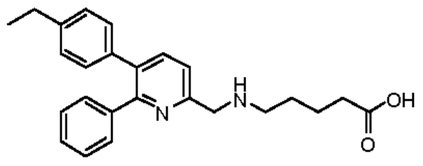
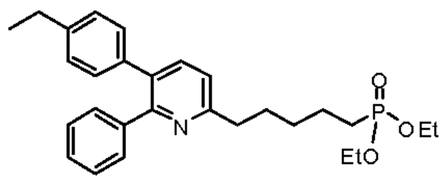
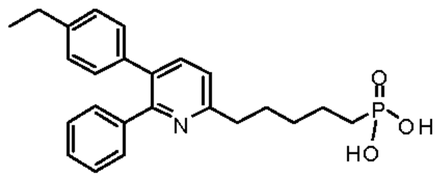
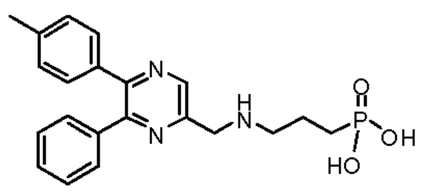
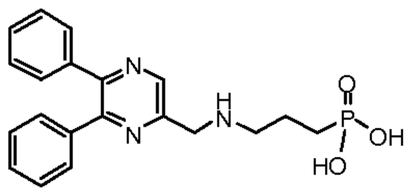
Example Number	Structure	S1P1 EC_{50} (% efficacy)	S1P3 IC_{50} (% inhibiton)
63		ND	1.6 μM (83)
64		121 nM (36)	231 nM (98)
65		170 nM (57)	319 nM (98)
66		NA	1.8 μM (99)
67		ND	ND (95)
68		NA	1.1 μM (95)
69		NA	1.8 μM (68)
70		NA	ND (30)
71		114 nM (69)	319 nM (98)

Table 1

Example Number	Structure	S1P1 EC_{50} (% efficacy)	S1P3 IC_{50} (% inhibiton)
72		NA	4.0 μM (27)
73		NA	1.9 μM (11)
74		NA	ND
75		NA	ND
76		NA	ND
77		NA	NA
78		NA	NA
79		NA	ND
80		NA	ND

As a result of the above activity of the compounds utilized in the method of the present invention, it is clear that such compounds may be used in treating the following diseases and conditions for the following reasons.

Pain

S1P increases capsaicin responsiveness of DRG neurons

S1P pathway, S1P3, S1P1 deregulated in multiple pain models (EHT/AGN)

Glaucoma

S1P1/3 subtypes expressed in primary HTM cells

S1P decreases outflow facility >30% in perfused porcine eyes (See IOVS 45, 2263; 2004)

Altered paracellular permeability

Dry Eye/Immunology

Induces lymphocyte sequestration without affecting T cell proliferation

Angiogenesis disorders

siRNA knockdown of S1P1 and S1P3 inhibits angiogenesis

S1P1/3 subtypes expressed in VEC

promote VEC migration

promote barrier assembly and integrity

Cardiovascular (S1P3)

S1P3 "knock out" mice lack S1P induced COPD

S1P3 agonism is dose limiting effect of FTY720

Wound Healing

S1P is released from activated platelets

The invention is further illustrated by the following examples which are illustrative of a specific mode of practicing the invention and are not intended as limiting the scope of the claims.

To assess the potential lymphopenic effect of a compound, male C57/Blk6 mice (Charles River, Wilmington, MA at 8 weeks of age and weighing ~30 grams)

received a single (IP) injection of vehicle or Compound 65 (3 mg/kg). Four hours post-injection animals were anesthetized with iso/O_2 mix, blood was collected by retro-orbital bleeding into a BD Biosciences Microtainer tube containing the anti-coagulant dipotassium-EDTA (~300-500 ul of blood collected). After blood collection, animals were humanely euthanized using Iso/0_2 mix overdose or cervical dislocation.Hematologic assessments of blood samples from treated animals was conducted using an automated Advia 120 hematology analyzer [Bayer Diagnostics, Tarrytown, NY]. The Advia 120 analyzes K-EDTA anticoagulated whole blood using cytochemical reactions and flow-cytometry measurements to enumerate and differentiate leukocytes (white blood cells), enumerate and characterize erythrocytes (red blood cells), thrombocytes (platelets), and reticulocytes (immature red blood cells). Leukocytes are enumerated and differentiated using a combination of two methods, a Peroxidase method and a Basophil Lobularity method, which generate relative and absolute counts for neutrophils, lymphocytes, monocytes, eosinophils, and basophils. In the Peroxidase method a cell suspension passes through the flowcell where the absorption (correlating to cytoplasmic peroxidase staining) and forward light-scattering (correlating to cell size) are measured. In the Basophil Lobularity method a suspension cell nuclei are passed though a flowcell where the low-angle light scatter and high-angle light scatter are measured correlating to nuclear size and complexity. When necessary leukocyte differentials may be performed manually from Romanowski stained blood smears. In addition, an adaptation of the classic cyan-methemoglobin spectrophotometric methodology was used to measure total hemoglobin concentration. Using the data obtained from direct measurements erythrocytic and thrombocytic indices were derived by the Advia 120 software. The results are summarized in Table 2.

Table 2

DRUG	DOSE/ROUTE	LYMPHOCYTE# x10^3/uL
VEHICLE	1 ml/kg IP	6.10±0.6
65	3 mg/kg IP	3.25±0.7**

****p<0.01 vs. Vehicle**

An art-accepted model or assay for measuring an analgesic effect of a compound in chronic pain (in particular peripheral neuropathy) is the model known as *Kim and Chung* 1992, Pain 150, pp 355-363 (*Chung* model). This model involves the surgical ligation of the L5 (and optionally the L6) spinal nerves on one side in experimental animals. Rats recovering from the surgery gain weight and display a level of general activity similar to that of normal rats. However, these rats develop abnormalities of the foot, wherein the hindpaw is moderately everted and the toes are held together. More importantly, the hindpaw on the side affected by the surgery appears to become sensitive to low-threshold mechanical stimuli and will perceive pain instead of the faint sensation of touch. This sensitivity to normally non-painful touch, called "tactile allodynia", develops within the first week after surgery and lasts for at least two months. The allodynia response includes lifting the affected hindpaw to escape from the stimulus, licking the paw and holding it in the air for many seconds. None of these responses is normally seen in the control group.

To produce the tactile allodynia, rats are anesthetized before surgery. The surgical site is shaved and prepared either with betadine or Novacaine. Incision is made from the thoracic vertebra Xlll down toward the sacrum. Muscle tissue is separated from the spinal vertebra (left side) at the L4 - S2 levels. The L6 vertebra is located and the transverse process is carefully removed with a small rongeur to expose the L4 - L6 spinal nerves. The L5 and L6 spinal nerves are isolated and

tightly ligated with 6-0 silk thread. The same procedure is done on the right side as a control, except no ligation of the spinal nerves is performed.

After a complete hemostasis is confirmed, the wounds are sutured. A small amount of antibiotic ointment is applied to the incised area, and the rat is transferred to the recovery plastic cage under a regulated heat-temperature lamp.

On the day of the experiment, at least seven days after the surgery, typically six rats per test group are administered the test drugs by intraperitoneal (i.p.) injection or oral gavage (p.o.). For i.p. administration, the compounds are formulated in H_2O and given in a volume of 1 ml/kg body weight by injecting into the intraperitoneal cavity. For p.o. administration, the compounds are formulated in H_2O and given in a volume of 1 ml/kg body weight using an 18-gauge, 3 inch gavage needle that is slowly inserted through the esophagus into the stomach.

Tactile allodynia is assessed via von Frey hairs, which are a series of fine hairs with incremental differences in stiffness. Rats are placed in a plastic cage with a wire mesh bottom and allowed to acclimate for approximately 30 minutes. To establish the pre-drug baseline, the von Frey hairs are applied perpendicularly through the mesh to the mid-plantar region of the rats' hindpaw with sufficient force to cause slight buckling and held for 6-8 seconds. The applied force has been calculated to range from 0.41 to 15.1 grams. If the paw is sharply withdrawn, it is considered a positive response. A normal animal will not respond to stimuli in this range, but a surgically ligated paw will be withdrawn in response to a 1-2 gram hair. The 50% paw withdrawal threshold is determined using the method of Dixon, W.J., *Ann. Rev. Pharmacol. Toxicol.* 20:441-462 (1980) hereby incorporated by reference. Tactile allodynia is measured prior to and 15, 30, and 60 minutes after drug administration. The post-drug threshold is compared to the pre-drug threshold and the percent reversal of tactile sensitivity is calculated based on a normal threshold of 15.1 grams.

Table 3 below indicates the degree of pain reversal obtained in the Chung model with exemplary compounds of the invention. The intraperitonial (i.p.)

and/or intravenous (iv) administration of the compounds was dosed (as indicated) and the peak percentage of reversal of allodynia was measured at 15, 30 or 60 minutes after administration, as is indicated in the table. Data are expressed as the highest % allodynia reversal (out of 3 time points: 15 min, 30 min, or 60 min. post-drug) with a minimum of a 20% allodynia reversal in the rat Chung model. Comparisons between groups (drug treated vs. saline treated) were made using a two-tailed, 2-sample, unpaired t-test.

Table 3

DRUG	DOSE/ ROUTE	% Allodynia Reversal		
		15 min. post	30 min. post	60 min. post
64	3.0 mg/kg IP	35.1±20.6	54.1±17.9*	91.7±5.3**
65	0.3 mg/kg IP	8.6±1.8	95.9±4.1**	80.8±14.5**

***p<0.05, **p<0.01 vs. Vehicle**

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims. Unless otherwise indicated, the following Chemical Abbreviations are used in the examples:

NH_4Cl: ammonium chloride

$CHCl_3$: chloroform

Et_2O: diethyl ether

DIBAL-H: diisobutylaluminum hydride

DME : 1,2-dimethoxyethane

DMF: *N,N*-dimethylformamide

DMSO: dimethylsulfoxide

EtOH: ethanol

EtOAc: ethyl acetate

HCl: hydrogen chloride or hydrochloric acid

NH_2OH-HCl: hydroxylamine hydrochloride

MeI: iodomethane

i-PrOH: isopropanol

$MgSO_4$: magnesium sulfate

MeOH: methanol

NH_2OMe-HCl: methoxylamine hydrochloride

CH_2Cl_2: methylene chloride

KOH: potassium hydroxide

K_2CO_3: potassium carbonate

PTLC: preparative thin layer chromatography

MPLC: medium pressure liquid chromatography

RuCl2(PPh3)4: Na: sodium

NaOEt: sodium ethoxide

NaOH: sodium hydroxide

Na_2SO_4: sodium sulfate

$NaHCO_3$: sodium bicarbonate

$NaBH_4$: sodium borohydride

$NaBH_3CN$: sodium cyanoborohydride

NaH: sodium hydride

H_2SO_4: sulfuric acid

Bu_4NOH: tetrabutylammonium hydroxide

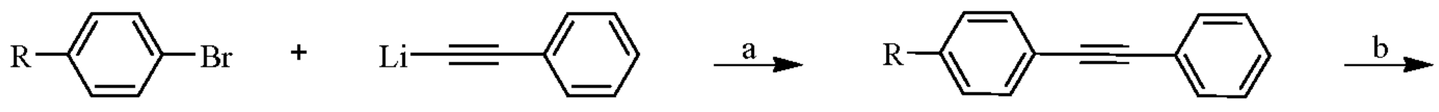
THF: tetrahydrofuran

$Pd(PPh_3)_4$: palladium tetrakis(tripenylphosphine)

TMSI: iodotrimethylsilane

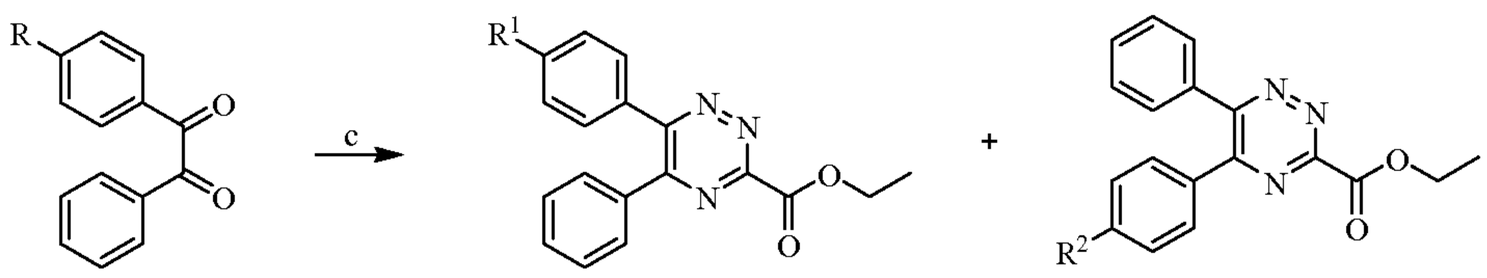
All other chemicals were purchased from Aldrich Chemical Company, and they were used as provided.

Scheme 1



R =Me
R =Et
R = *n*-Pr
R = CF_3
R = *n*-C_9H_{19}

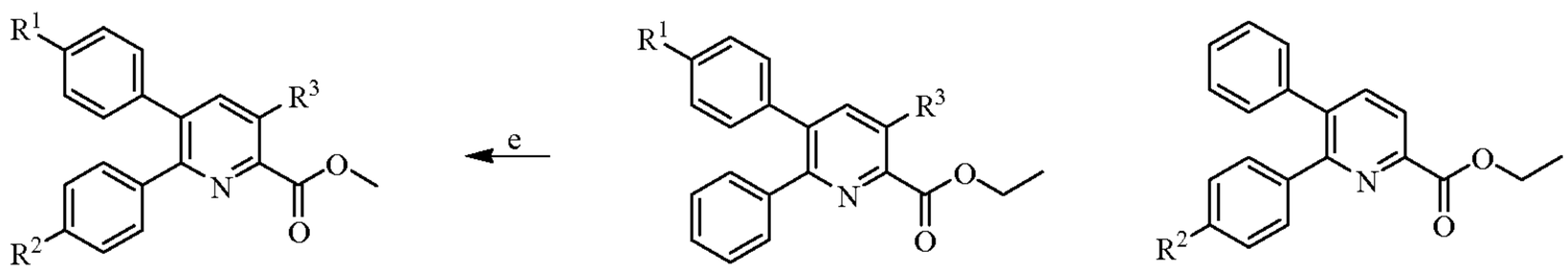
1 R = Me
2 R = Et
3 R = *n*-Pr
4 R = CF_3
5 R = *n*-C_9H_{19}



6 R =Me
7 R = Et
8 R = *n*-Pr
9 R = CF_3
10 R = *n*-C_9H_{19}

11 R^1 = H
12 R^1 =Me
13 R^1 = Et
14 R^1 = *n*-Pr
15 R^1 = CF_3
16 R^1 = *n*-C_9H_{19}

17 R^2 =Me
18 R^2 = Et
19 R^2 = CF_3
20 R^2 = *n*-C_9H_{19}



30 R^1 = H, R^2 = R^3 = H
31 R^1 = Me, R^2 = R^3 = H
32 R^1 = Et , R^2 = R^3 = H
33 R^1 = *n*-Pr, R^2 = R^3 = H
34 R^1 = CF_3 , R^2 = R^3 = H
35 R^1 =R^3 = H , R^2= CF_3
36 R^1 = Et , R^2 =H, R^3 = Me

21 R^1 = R^3 = H
22 R^1 =Me, R^3 = H
23 R^1 = Et, R^3 = H
24 R^1 = *n*-Pr, R^3 = H
25 R^1 = CF_3, R^3 = H
26 R^1 = Et, R^3 =Me

27 R^2 = Me
28 R^2 = Et
29 R^2 = CF_3

(a) $B(OiPr)_3$, $Pd(PPh_3)_4$, DME, THF, 90 °C, 2 hours; (b) $RuCl_2(PPH_3)_3$, PhIO, CH_2Cl_2; (c) ethyl oxalamidrazonate, ethanol; (d) i) pyrrolidine, CH_3CHO, K_2CO_3, toluene, ii) CHC_{l3}, 72 °C; (e) c. H_2SO_4, MeOH, 70 °C.

Example 1

1-(2-*p*-Tolylethynyl)benzene (Compound 1). General Procedure A. To a solution of lithium phenylacetylide (15.2 ml, 15.2 mmol) in DME (20 ml) under Argon at -78 °C was added triisopropoxylborane (3.5 ml, 15.2 mmol). The mixture was stirred at -78 °C for 1.5 hours. A solution of 1-bromo-4-methylbenzene (2 g, 11.7 mmol) in DME/THF (10 ml/10ml) was degassed with dry argon, $Pd(PPh_3)_4$

(405 mg, 0.35 mmol) was added and the solution was degassed for another 5 min. The degassed solution was cannulated into the first solution, and the mixture was heated under argon at 85 °C for 2 hours. The mixture was cooled to room temperature, and it was diluted with ethyl acetate, and washed with water. The separated organic layer was washed with water and brine, and dried over $MgSO_4$. The filtered solvent was concentrated in *vacuo,* and the residue was purified by column chromatography (silica, 5% ethyl acetate in hexane) to give the title compound as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3 H), 7.16 (d, J = 8.50 Hz, 2 H), 7.29 - 7.38 (m, 3 H), 7.43 (d, J = 7.92 Hz, 2 H), 7.48 - 7.56 (m, 2 H).

Example 2

1-(2-(4-Ethylphenyl)ethynyl)benzene (Compound 2) Following General Procedure A, lithium phenylacetylide (14.0 ml, 14.1 mmol), triisopropoxylborane (3.2 ml, 14.1 mmol), 1-bromo-4-ethylbenzene (2 g, 10.8 mmol) and $Pd(PPh_3)_4$ (375 mg, 0.32 mmol) in DME (30ml) and THF (10 ml) were reacted to obtain the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J = 7.62 Hz, 3 H), 2.66 (q, J = 7.62 Hz, 2 H), 7.18 (d, J = 8.21 Hz, 2 H), 7.28 - 7.39 (m, 3 H), 7.45 (d, J = 8.21 Hz, 2 H), 7.49 - 7.56 (m, 2 H).

Example 3

1-(2-(4-*n*-Proylphenyl)ethynyl)benzene (Compound 3) Following General Procedure A, lithium phenylacetylide (13.0 ml, 13.1 mmol), triisopropoxylborane (3.0 ml, 13.1 mmol), 1-bromo-4-*n*-propylbenzene (2 g, 10.1 mmol) and $Pd(PPh_3)_4$ (348 mg, 0.30 mmol) in DME (30 ml) and THF (10 ml) were reacted to obtain the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.33 Hz, 17 H), 1.57 - 1.73 (m, 2 H), 2.57 - 2.62 (m, 2 H), 7.16 (d, *J* = 8.50 Hz, 2 H), 7.29 - 7.40 (m, *J* = 2.05 Hz, 3 H), 7.44 (d, *J* = 8.50 Hz, 2 H), 7.49 - 7.55 (m, 2 H).

Example 4

1-(2-(4-Trifluoromethylphenyl)ethynyl)benzene (Compound 4) Following General Procedure A, lithium phenylacetylide (17.3 ml, 17.3 mmol), triisopropoxylborane (4.0 ml, 17.3 mmol), 1-bromo-4-trifluoromethyl-benzene (3 g, 13.3 mmol) and $Pd(PPh_3)_4$ (462 mg, 0.40 mmol) in DME (40 ml) and THF (15 ml) were reacted to obtain the title compound as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 - 7.42 (m, 3 H), 7.50 - 7.58 (m, 2 H), 7.57 - 7.68 (m, 4 H).

Example 5

1-(2-(4-*n*-Nonanylphenyl)ethynyl)benzene (Compound 5) Following General Procedure A, lithium phenylacetylide (12.4 ml, 12.4 mmol), triisopropoxylborane (2.8 ml, 12.4 mmol), 1-bromo-4-*n*-nonanylbenzene (2.7 g, 9.5 mmol) and $Pd(PPh_3)_4$ (331 mg, 0.40 mmol) in DME (30 ml) and THF (10 ml) were reacted to obtain the title compound as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.04 Hz, 3 H), 1.17 - 1.38 (m, 12 H), 1.54 - 1.68 (m, 2 H), 2.55 - 2.65 (m, 2 H), 7.15 (d, *J* = 8.21 Hz, 2 H), 7.28 - 7.39 (m, 3 H), 7.44 (d, *J* = 8.21 Hz, 2 H), 7.48 - 7.56 (m, 2 H).

Example 6

1-Phenyl-2-*p*-tolylethane-1,2-dione (Compound 6). General Procedure B. To a suspension of iodosobenzene (2.5 g, 11.3 mmol) in CH_2Cl_2 (30 ml) was added $RuCl_2(PPh_3)_4$ (45 mg, 0.04 mmol). A solution of 1-(2-p-tolylethynyl)benzene

(Compound 1, 835 mg, 4.3 mmol) in CH_2Cl_2 (10 ml) was cannulated into the suspension**.** The resulting mixture was stirred at room temperature overnight resulting in a homogeneous solution. The solvent was removed *in vacuo,* and the residue was purified by silica gel chromatography (10% ethyl acetate in hexane) to produce the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 7.31 (d, *J* = 7.92 Hz, 2 H), 7.51 (t, *J* = 7.62 Hz, 2 H), 7.59 - 7.71 (m, 1 H), 7.87 (d, *J* = 8.21 Hz, 2 H), 7.92 - 8.00 (m, 2 H).

Example 7

1-(4-Ethyl-phenyl)-2-phenyl-ethane-1,2-dione (Compound 7). Following General Procedure B, iodosobenzene (1.5g, 6.7 mmol), $RuCl_2(PPh_3)_4$ (21 mg, 0.02 mmol) and 1-(2-(4-ethylphenyl)ethynyl)benzene **(Compound 2,** 360 mg, 1.8 mmol) in CH_2Cl_2 (30 ml) were reacted to produce the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.62 Hz, 3 H), 2.73 (q, *J* = 7.62 Hz, 2 H), 7.34 (d, *J* = 8.50 Hz, 2 H), 7.45 - 7.56 (m, 2 H), 7.59 - 7.70 (m, 1 H), 7.90 (d, *J* = 8.21 Hz, 2 H), 7.93 - 8.01 (m, 2 H).

Example 8

1-(4-*n*-Propyl-phenyl)-2-phenyl-ethane-1,2-dione (Compound 8). Following General Procedure B, iodosobenzene (2.2 g, 10.0 mmol), $RuCl_2(PPh_3)_4$ (38 mg, 0.04 mmol) and 1-(2-(4-*n*-propylphenyl)ethynyl)benzene **(Compound 3,** 860 mg, 3.9 mmol) in CH_2Cl_2 (50 ml) were reacted to produce the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.62 Hz, 3 H), 1.58 - 1.76 (m, 2 H), 2.60 -2.69 (m, 2 H), 7.31 (d, *J* = 8.21 Hz, 2 H), 7.46 - 7.56 (m, 2 H), 7.61 - 7.70 (m, 1 H), 7.89 (d, *J* = 8.21 Hz, 2 H), 7.94 - 8.01 (m, 2 H).

Example 9

1-(4-Trifluoromethyl -phenyl)-2-phenyl-ethane-1,2-dione (Compound 9). Following General Procedure B, iodosobenzene (5.5g, 24.3 mmol), $RuCl_2(PPh_3)_4$ (96 mg, 0.10 mmol) and 1-(2-(4-trifluoromethyl phenyl)ethynyl)benzene **(Compound 4,** 1.9 g, 8.1 mmol) in CH_2Cl_2 (100 ml) were reacted to produce the title compound as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 - 7.59 (m, 2 H), 7.65 - 7.74 (m, 1 H), 7.79 (d, *J* = 8.21 Hz, 2 H), 7.94 - 8.02 (m, 2 H), 8.11 (d, *J* = 8.21 Hz, 2 H).

Example 10

1-(4-*n*-Nonanylphenyl)-2-phenylethane-1,2-dione (Compound 10). Following General Procedure B, iodosobenzene (744 mg, 3.39 mmol), $RuCl_2(PPh_3)_4$ (11 mg, 0.01 mmol) and 1-(2-(4-*n*-nonanylphenyl)ethynyl)benzene **(Compound 5**, 343 mg, 1.12 mmol) in CH_2Cl_2 (30 ml) were reacted to produce the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.74 Hz, 3 H), 1.14 - 1.40 (m, 12 H), 1.55 - 1.71 (m, 2 H), 7.48 - 7.53 (m, 2 H), 7.60 - 7.72 (m, 1 H), 7.88 (d, *J* = 8.21 Hz, 2 H), 7.94 - 8.02 (m, 2 H).

Example 11

Ethyl 5,6-Diphenyl-1,2,4-triazine-3-carboxylate (Compound 11). General Procedure C. A solution of ethyl oxalamidrazonate **(Compound 37**, 236 mg, 1.8 mmol) in ethanol (20 ml) was cannulated slowly into a stirring solution of benzil (500 mg, 2.4 mmol) in ethanol (20 ml) under argon at room temperature. After the addition was completed, the reaction was stirred at room temperature overnight (~16 hours). The mixture was then refluxed for 1 hour. The solvent was removed *in vacuo*, and the crude products was purified by column chromatography (silica gel, 20% ethyl acetate in hexane) to obtain the title compound as an oil.

^{1}H NMR (300 MHz, acetone-d_6) δ 1.45 (t, J = 7.04 Hz, 3 H), 4.54 (q, J = 7.13 Hz, 2 H), 7.38 - 7.58 (m, 6 H), 7.61 - 7.72 (m, 4 H).

Example 12 and Example 17

Ethyl 5-Phenyl-6-*p*-tolyl-[1,2,4]triazine-3-carboxylate (Compound 12), and Ethyl 6-Phenyl-5-p-tolyl-[1,2,4]triazine-3-carboxylate (Compound 17). Following General Procedure C, ethyl oxalamidrazonate **(Compound 37,** 121 mg, 0.9 mmol), 1-phenyl-2-*p*-tolylethane-1,2-dione **(Compound 6,** 268 mg, 1.2 mmol) in ethanol (10 ml) were reacted, and the products were separated by recrystalization from 5% ethyl acetate in hexane to produce **Compound 12** and **Compound 17** as yellow solids.

Compound 12: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (t, J = 7.33 Hz, 3 H), 2.39 (s, 3 H), 4.61 (q, J = 7.04 Hz, 2 H), 7.19 (d, J = 7.92 Hz, 2 H), 7.32 - 7.49 (m, 3 H), 7.52 (d, J = 8.21 Hz, 2 H), 7.63 - 7.69 (m, 2 H).

Compound 17: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (t, J = 7.04 Hz, 3 H), 2.37 (s, 3 H), 4.61 (q, J = 7.04 Hz, 2 H), 7.15 (d, J = 7.92 Hz, 2 H), 7.35 - 7.51 (m, 3 H), 7.56 (d, J = 8.50 Hz, 2 H), 7.60 - 7.66 (m, 2 H).

Example 13 and Example 18

Ethyl 6-(4-Ethylphenyl)-5-phenyl -[1,2,4]triazine-3-carboxylate (Compound 13), and Ethyl 5-(4-Ethylphenyl)-6-phenyl-[1,2,4]triazine-3-carboxylate (Compound 18). Following General Procedure C, ethyl oxalamidrazonate (**Compound 37,** 117 mg, 0.9 mmol) and 1-(4-Ethyl-phenyl)-2-phenyl-ethane-1,2-dione (**Compound 7,** 276 mg, 1.2 mmol) in ethanol (10 ml) were reacted, and the products were separated by recrystalization from 5% ethyl acetate in hexane to produce **Compound 13** and **Compound 18** as yellow solids.

Compound 13: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, J = 7.81 Hz, 3 H), 1.51 (t, J = 7.32 Hz, 3 H), 2.69 (q, J = 7.81 Hz, 2 H), 4.61 (q, J = 7.32 Hz, 2 H), 7.23 (d, J =

7.32 Hz, 2 H), 7.35 – 7.38 (m, 2 H), 7.45 – 7.47 (m, 1 H), 7.56 (d, *J* = 8.30 Hz, 2 H), 7.67 (d, *J* = 7.81 Hz, 2 H).

Compound 18: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.81 Hz, 3 H), 1.51 (t, *J* = 7.32 Hz, 3 H), 2.67 (q, *J* = 7.81 Hz, 2 H), 4.62 (q, *J* = 7.32 Hz, 2 H), 7.19 (d, *J* = 8.79 Hz, 2 H), 7.39 – 7.42 (m, 2 H), 7.45 – 7.48 (m, 1 H), 7.59 (d, *J* = 8.30 Hz, 2 H), 7.65 (d, *J* = 8.30 Hz, 2 H).

Example 14

Ethyl 5-Phenyl-6-(4-propylphenyl)-[1,2,4]triazine-3-carboxylate (Compound 14). Following General Procedure C, ethyl oxalamidrazonate (**Compound 37**, 460 mg, 1.5 mmol) and 1-(4-*n*-propylphenyl)-2-phenyl-ethane-1,2-dione (**Compound 8**, 588 mg, 2.3 mmol) in ethanol (40 ml) were reacted and the product was recrystalized from 5% ethyl acetate in hexane to produce the title compound as yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.33 Hz, 3 H), 1.51 (t, *J* = 7.04 Hz, 3 H), 1.62 - 1.74 (m, 2 H), 2.55 - 2.63 (m, 2 H), 4.61 (q, *J* = 7.13 Hz, 2 H), 7.20 (d, *J* = 8.50 Hz, 2 H), 7.32 - 7.49 (m, 3 H), 7.50 - 7.57 (m, 2 H), 7.62 - 7.70 (m, 2 H).

Example 15 and Example 19

Ethyl 6-(4-Trifluoromethyl -phenyl)-5-phenyl -[1,2,4]-triazine-3-carboxylate (Compound 15), and Ethyl 5-(4-Trifluoromethylphenyl)-6-phenyl-[1,2,4]-triazine-3-carboxylatate (Compound 19). Following General Procedure C, ethyl oxalamidrazonate (**Compound 37**, 1.2 g, 8.8 mmol) and 1-(4-tirfluoromethyl-phenyl)-2-phenyl-ethane-1,2-dione (**Compound 9**, 1.6 g, 5.9 mmol) in ethanol (40 ml) were reacted, and the products were separated by recrystalization from 5% ethyl acetate in hexane to produce **Compound 15** and **Compound 19** as yellow solids.

Compound 15: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (t, *J* = 7.18 Hz, 3 H), 4.63 (q, *J* = 7.04 Hz, 2 H), 7.38 - 7.54 (m, 3 H), 7.56 - 7.68 (m, 4 H), 7.78 (d, *J* = 8.21 Hz, 2 H).

Compound 19: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (t, *J* = 7.18 Hz, 3 H), 4.63 (q, *J* = 7.13 Hz, 2 H), 7.35 - 7.54 (m, 3 H), 7.59 - 7.70 (m, 4 H), 7.73 - 7.81 (m, 2 H).

Example 16 and Example 20

Ethyl 6-(4-nonylphenyl)-5-phenyl-1,2,4-triazine-3-carboxylate (Compound 16), and ethyl 5-(4-nonylphenyl)-6-phenyl-1,2,4-triazine-3-carboxylate (Compound 20). Following General Procedure C, ethyl oxalamidrazonate (**Compound 37**, 108 mg, 0.83 mmol) and 1-(4-nonylphenyl)-2-phenylethane-1,2-dione (**Compound 10**, 252 mg, 0.75 mmol) in ethanol (10 ml) were reacted and the mixture purified by MPLC to isolate **Compound 16** and **Compound 20** as yellow oils.

Compound 16: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.04 Hz, 3 H), 1.18 - 1.39 (m, 12 H), 1.51 (t, *J* = 7.18 Hz, 3 H), 1.56 - 1.72 (m, 2 H), 2.58 - 2.70 (m, 2 H), 4.61 (q, *J* = 7.23 Hz, 2 H), 7.20 (d, *J* = 8.21 Hz, 2 H), 7.31 - 7.41 (m, 2 H), 7.33 - 7.40 (m, 1 H), 7.53 (d, *J* = 8.21 Hz, 2 H), 7.61 - 7.70 (m, 2 H).

Compound 20: ^{1}H NMR (300 MHz, $CDCl_3$): 1H NMR (300 MHz, Solvent) δ 0.88 (t, *J* = 7.04 Hz, 3 H), 1.17 - 1.37 (m, 12 H), 1.52 (t, *J* = 7.04 Hz, 3 H), 1.55 - 1.66 (m, 2 H), 2.54 - 2.69 (m, 2 H), 4.62 (q, *J* = 7.04 Hz, 2 H), 7.16 (d, *J* = 8.21 Hz, 2 H), 7.33 - 7.53 (m, 3 H), 7.58 (d, *J* = 8.21 Hz, 2 H), 7.60 - 7.70 (m, 2 H).

Example 21

Ethyl 5,6-diphenylpyridine-2-carboxylate (Compound 21). General Procedure D. Ethyl 5,6-diphenyl-[1,2,4]-triazine-3-carboxylate (**Compound 11**, 200 mg, 0.66 mmol) and crude 1-vinylpyrrolidine (**Compound 38**, 2 g) in $CHCl_3$ (20 ml) was heated at 75 °C overnight under nitrogen. The solvent was removed *in vacuo*, and

the residue was purified by silica gel column chromatography (20 % ethyl acetate in hexane) to yield the title compound as a light yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, *J* = 7.18 Hz, 3 H), 4.50 (q, *J* = 7.13 Hz, 2 H), 7.13 - 7.33 (m, 8 H), 7.35 - 7.44 (m, 2 H), 7.84 (d, *J* = 7.92 Hz, 1 H), 8.12 (d, *J* = 7.92 Hz, 1 H).

Example 22

6-Phenyl-5-*p*-tolyl-pyridine-2-carboxylic acid ethyl ester (Compound 22). Following General Procedure D, ethyl 5-phenyl-6-*p*-tolyl-[1,2,4]-triazine-3-carboxylate (**Compound 12**, 177 mg, 0.56 mmol) and crude 1-vinylpyrrolidine (**Compound 38**, 730 mg) in $CHCl_3$ (10 ml) were reacted to produce the title compound as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, *J* = 7.18 Hz, 3 H), 2.34 (s, 3 H), 4.49 (q, *J* = 7.04 Hz, 2 H), 7.05 – 7.11 (m, 4 H), 7.17 - 7.28 (m, 3 H), 7.36 - 7.44 (m, 2 H), 7.82 (d, *J* = 7.92 Hz, 1 H), 8.10 (d, *J* = 7.92 Hz, 1 H).

Example 23

Ethyl 5-(4-Ethyl-phenyl)-6-phenyl-pyridine-2-carboxylate (Compound 23). Following General Procedure D, ethyl 6-(4-ethyl-phenyl)-5-phenyl-[1,2,4]triazine-3-carboxylate (**Compound 13**, 105 mg, 0.30 mmol) and crude 1-vinylpyrrolidine (**Compound 38**, 2 g) in $CHCl_3$ (10 ml) were reacted to produce the title compound as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.62 Hz, 3 H), 1.45 (t, *J* = 7.04 Hz, 3 H), 2.58 (q, *J* = 7.62 Hz, 2 H), 4.47 (q, *J* = 7.04 Hz, 2 H), 7.09 – 7.16 (m, 4 H), 7.22 - 7.30 (m, 3 H), 7.36 – 7.42 (m, 2 H), 7.83 (d, *J* = 7.92 Hz, 1 H), 8.10 (d, *J* = 7.91 Hz, 1 H).

Example 24

Ethyl 6-Phenyl-5-(4-propylphenyl)-pyridine-2-carboxylate (Compound 24). Following General Procedure D, ethyl 5-phenyl-6-(4-propyl-phenyl)-[1,2,4]-triazine-3-carboxylate (**Compound 14),** (153 mg, 0.46 mmol) and crude 1-vinylpyrrolidine (**Compound 38**, 2 g) in $CHCl_3$ (10 ml) were reacted to produce the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.33 Hz, 3 H), 1.45 (t, *J* = 7.04 Hz, 3 H), 1.56 - 1.72 (m, 2 H), 2.55 – 2.62 (m, 2 H), 4.49 (q, *J* = 7.23 Hz, 2 H), 7.09 (s, 4 H), 7.20 - 7.30 (m, 3 H), 7.36 - 7.45 (m, 2 H), 7.84 (d, *J* = 7.92 Hz, 1 H), 8.11 (d, *J* = 7.92 Hz, 1 H).

Example 25

Ethyl 6-Phenyl-5-(4-trifluoromethylphenyl)-pyridine-2-carboxylate (Compound 25). Following General Procedure D, ethyl 6-(4-tirfluoromethylphenyl)-5-phenyl -[1,2,4]triazine-3-carboxylate (**Compound 15**), (378 mg, 1.01 mmol) and crude 1-vinylpyrrolidine (**Compound 38**, 780 mg) in $CHCl_3$ (10 ml) were reacted to produce the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (t, *J* = 7.18 Hz, 3 H), 4.52 (q, *J* = 7.04 Hz, 2 H), 7.15 - 7.22 (m, 2 H), 7.30 - 7.36 (m, 3 H), 7.47 - 7.58 (m, 4 H), 8.18 (d, *J* = 7.92 Hz, 1 H).

Example 26

Ethyl 5-(4-Ethylphenyl)-3-methyl-6-phenyl-pyridine-2-carboxylate (Compound 26). Following General Procedure D, ethyl 6-(4-ethylphenyl)-5-phenyl-[1,2,4]-triazine-3-carboxylate (**Compound 13**, 200 mg, 0.60 mmol) and crude 1-propenyl-pyrrolidine (**Compound 39**, 2 g) in $CHCl_3$ (10 ml) were reacted to produce the title compound as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.81 Hz, 3 H), 1.45 (t, *J* = 7.08 Hz, 3 H), 2.56 - 2.69 (m, 5 H), 4.47 (q, *J* = 7.08 Hz, 2 H), 7.01 - 7.15 (m, 4 H), 7.16 - 7.30 (m, 3 H), 7.35 - 7.42 (m, 2 H), 7.60 (s, 1 H).

Example 27

Ethyl 5-Phenyl-6-*p*-tolyl-pyridine-2-carboxylate (Compound 27). Following General Procedure D, ethyl 6-phenyl-5-*p*-tolyl-[1,2,4]triazine-3-carboxylate (**Compound 17**, 361 mg, 1.13 mmol) and crude 1-vinylpyrrolidine (**Compound 38**, 806 mg) in $CHCl_3$ (10 ml) were reacted to produce the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, *J* = 7.18 Hz, 3 H), 2.30 (s, 3 H), 4.49 (q, *J* = 7.04 Hz, 2 H), 7.05 (d *J* = 7.92 Hz, 2 H), 7.14 - 7.24 (m, 2 H), 7.27 - 7.33 (m, 5 H), 7.82 (d, *J* = 7.92 Hz, 1 H), 8.09 (d, *J* = 7.91 Hz, 1 H).

Example 28

Ethyl 5-(4-Ethylphenyl)-6-phenyl-pyridine-2-carboxylic acid ethyl ester (Compound 28). Following General Procedure D, ethyl 5-(4-ethylphenyl)-6-phenyl-[1,2,4]triazine-3-carboxylate (**Compound 18**, 245 mg, 0.74 mmol) and crude 1-vinylpyrrolidine (**Compound 38**, 572 mg) in $CHCl_3$ (10 ml) were reacted to produce the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.62 Hz, 3 H), 1.45 (t, *J* = 7.18 Hz, 3 H), 2.60 (q, *J* = 7.62 Hz, 2 H), 4.49 (q, *J* = 7.04 Hz, 2 H), 7.06 (d, *J* = 7.92 Hz, 2 H), 7.27 - 7.36 (m, 5 H), 7.82 (d, *J* = 7.92 Hz, 1 H), 8.09 (d, *J* = 7.91 Hz, 1 H).

Example 29

Ethyl 5-Phenyl-6-(4-trifluoromethyl-phenyl)-pyridine-2-carboxylate (Compound 29). Following General Procedure D, ethyl 5-(4-

trifluoromethylphenyl)-6-phenyl-[1,2,4]-triazine-3-carboxylate (**Compound 19**, 1 g, 2.68 mmol) and crude 1-vinylpyrrolidine (**Compound 38**, 1.4 g) in $CHCl_3$ (20 ml) were reacted to produce the title compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, *J* = 7.18 Hz, 12 H), 4.51 (q, *J* = 7.23 Hz, 2 H), 7.21 - 7.42 (m, 5 H), 7.85 (d, *J* = 7.92 Hz, 1 H), 8.15 (d, *J* = 8.21 Hz, 1 H).

Example 30

Methyl 5,6-diphenylpyridine-2-carboxylate (Compound 30). General Procedure E. A solution of ethyl 5,6-diphenylpyridine-2-carboxylate **(Compound 21**, 30 mg, 0.1 mmol) and conc. H_2SO_4 (3 drops) in MeOH (5 ml) was heated at 50 °C overnight**.** The mixture was diluted with water, and the products were extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over Na_2SO_4. The filtered solvent was concentrated in *vacuo* and the residue was purified by column chromatography (20 % ethyl acetate in hexane) to obtain the title compound as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (s, 3 H), 7.15 - 7.31 (m, 8 H), 7.38 (d, *J* = 7.81 Hz, 2 H), 7.86 (d, *J* = 8.30 Hz, 1 H), 8.15 (d, *J* = 7.81 Hz, 1 H).

Example 31

Methyl 6-Phenyl-5-*p*-tolyl-pyridine-2-carboxylate (Compound 31).

Following General Procedure E, ethyl 6-phenyl-5-*p*-tolyl-pyridine-2-carboxylate (**Compound 22**, 70 mg, 0.22 mmol) and conc. H_2SO_4 (3 drops) in MeOH (3 ml) were reacted to produce the title compound as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 4.01 (s, 3 H), 7.05 – 7.11 (m, 4 H), 7.19 - 7.30 (m, 3 H), 7.35 - 7.44 (m, 2 H), 7.84 (d, *J* = 7.92 Hz, 1 H), 8.13 (d, *J* = 7.92 Hz, 1 H).

Example 32

Methyl 5-(4-Ethylphenyl)-6-phenyl-pyridine-2-carboxylate (Compound 32).

Following General Procedure E, ethyl 5-(4-ethylphenyl)- 6-phenylpyridine-2-carboxylate (**Compound 23**, 45 mg, 0.15 mmol) and conc. H_2SO_4 (3 drops) in MeOH (3 ml) were reacted to produce title compound as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.62 Hz, 3 H), 2.64 (q, *J* = 7.62 Hz, 2 H), 4.02 (s, 3 H), 7.05 - 7.16 (m, 4 H), 7.19 - 7.29 (m, 3 H), 7.34 - 7.44 (m, 2 H), 7.84 (d, *J* = 7.92 Hz, 1 H), 8.13 (d, *J* = 7.92 Hz, 1 H).

Example 33

Methyl 6-Phenyl-5-(4-propylphenyl)-pyridine-2-carboxylate (Compound 33).

Following General Procedure E, ethyl 6-phenyl-5-(4-propylphenyl)-pyridine-2-carboxylate (**Compound 24**, 67 mg, 0.19 mmol) and conc. H_2SO_4 (3 drops) in MeOH (3 ml) were reacted to produce the title compound as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.33 Hz, 3 H), 1.56 - 1.71 (m, 2 H), 2.51 - 2.63 (m, 2 H), 4.02 (s, 3 H), 7.01 - 7.13 (m, 4 H), 7.16 - 7.31 (m, 3 H), 7.34 - 7.43 (m, 2 H), 7.85 (d, *J* = 7.92 Hz, 1 H), 8.14 (d, *J* = 7.92 Hz, 1 H).

Example 34

Methyl 6-Phenyl-5-(4-trifluoromethylphenyl)-pyridine-2-carboxylate (Compound 34).

Following General Procedure E, ethyl 6-phenyl-5-(4-trifluoromethylphenyl)-pyridine-2-carboxylate (**Compound 25**, 110 mg, 0.29 mmol) and conc. H_2SO_4 (5 drops) in MeOH (5 ml) were reacted to produce the title compound as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (s, 3 H), 7.08 - 7.22 (m, 3 H), 7.29 - 7.37 (m, 2 H), 7.51 (s, 4 H), 7.90 (d, *J* = 7.92 Hz, 1 H), 8.20 (d, *J* = 7.92 Hz, 1 H).

Example 35

Methyl 5-Phenyl-6-(4-trifluoromethylphenyl)-pyridine-2-carboxylate (Compound 35). Following General Procedure E, ethyl 5-phenyl-6-(4-trifluoromethylphenyl)-pyridine-2-carboxylate (**Compound 29**, 103 mg, 0.28 mmol) and conc. H_2SO_4 (5 drops) in MeOH (5 ml) were reacted to produce the title compound as a white solid.

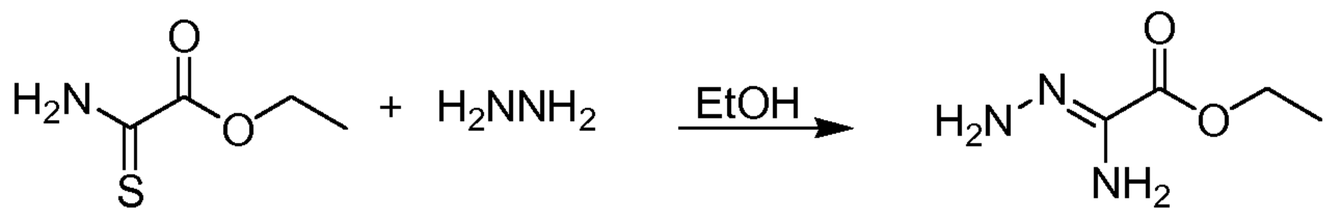
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (s, 3 H), 7.21 - 7.40 (m, 7 H), 7.55 (d, J = 8.50 Hz, 2 H), 7.86 (d, J = 7.92 Hz, 1 H), 8.18 (d, J = 7.92 Hz, 1 H).

Example 36

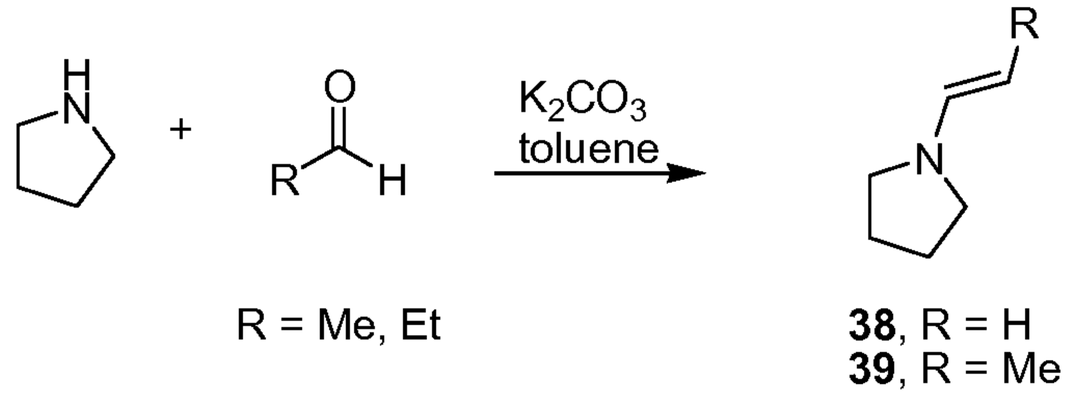
Methyl 5-(4-Ethylphenyl)-3-methyl-6-phenylpyridine-2-carboxylate (Compound 36). Following General Procedure E, ethyl 5-(4-ethylphenyl)-3-methyl-6-phenylpyridine-2-carboxylate (**Compound 26**, 29 mg, 0.08 mmol) and conc. H_2SO_4 (3 drops) in MeOH (5 ml) were reacted to produce the title compound as an oil.

^{1}H NMR (500 MHz,$CDCl_3$) δ 1.23 (t, J = 7.57 Hz, 3 H), 2.58 - 2.68 (m, 5 H), 3.99 (s, 3 H), 7.05 - 7.13 (m, 4 H), 7.18 - 7.25 (m, 3 H), 7.34 - 7.40 (m, 2 H), 7.61 (s, 1 H).

Scheme 2



37



38, R = H
39, R = Me

Example 37

Ethyl oxalamidrazonate (Compound 37). A solution of anhydrous hydrazine (0.5 ml, 15.0 mmol) in ethanol (5 ml) was added dropwise to a stirred solution of ethyl thiooxamate (2 g, 15.0 mmol) in ethanol (45 ml) under argon at room temperature. The mixture was stirred at room temperature for 1 hour, and the solvent was removed *in vacuo* and dried under high vacuum to get a white solid which was maintained in argon atmosphere after drying. The white solid was used in the next step without further purification.

Example 38

1-vinylpyrrolidine (Compound 38). General Procedure F. To a suspension of K_2CO_3 (3.8 g, 28.1 mmol) and pyrrolidine (1 g, 14.0 mmol) in toluene (10 ml) was added acetylaldehyde under argon at 0 °C. The mixture was stirred at room temperature overnight. After filtration, the filtrate was concentrated *in vacuo* to yield a crude oil which was used in the next reaction without further purification.

Example 39

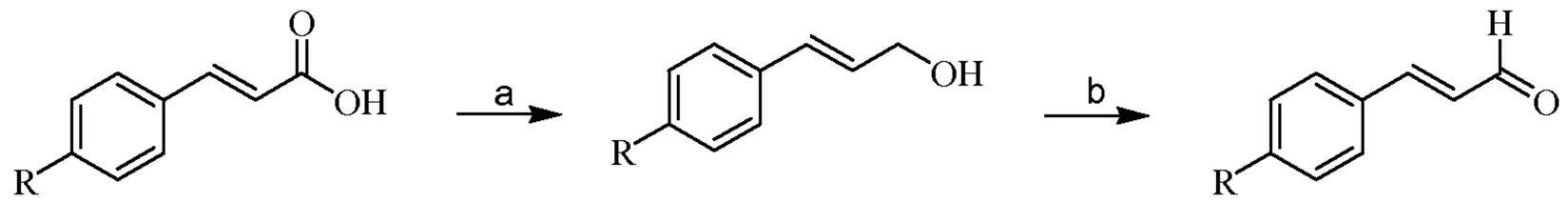
1-Propenylpyrrolidine (Compound 39). Following General Procedure F, K_2CO_3 (3.8 g, 28.1 mmol), pyrrolidine (1 g, 14.0 mmol) and propionaldehyde (1.6 g, 28.1 mmol) in toluene (10 ml) were reacted to produce the title compound as a brown oil.

Example 40

(*E*)-3-(4-ethylphenyl)prop-2-en-1-ol (Compound 40). General Procedure G. A solution of ethyl chloroformate (1.1 ml, 11.4 mmol) in THF (5 ml) was added to a solution of 4-ethylcinnamic acid (2 g, 11.4 mmol) and triethylamine (1.6 ml, 11.4 mmol) in THF (50 ml) at -5 °C to -10 °C, and the solution was stirred for 30 min. The resulting white precipitate was filtered off, rinsed with THF (10 ml), and the combined filtrates were added to a solution of $NaBH_4$ (945 mg, 24.9 mmol) in H_2O (20 ml) slowly in order to maintain an internal temperature of 10 °C to 15 °C. After the addition was completed, the reaction was stirred at room temperature for 4 hours, and then it was made acidic with HCl (20 %). The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with $NaHCO_3$ (aq), and water, and brine, and dried over Na_2SO_4. The filtered solution was concentrated in *vacuo,* and the residue was purified by column chromatography (20 % ethyl acetate in hexane) to yield a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 1.23 (t, J = 7.32 Hz, 3 H), 2.64 (q, J = 7.32 Hz, 2 H), 4.31 (s, 2 H), 6.30 – 6.39 (m, 1 H), 6.61 (d, J =16.11 Hz, 1 H), 7.16 (d, J = 8.30 Hz, 2 H), 7.32 (d, J = 8.30 Hz, 2 H).

Scheme 3



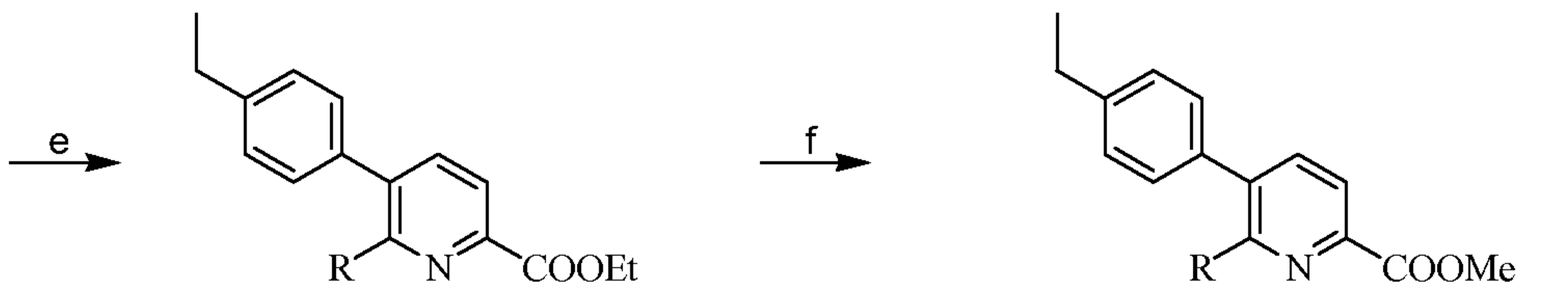
R = Et
R = Me

40 R = Et
41 R = Me

42 R = Et
43 R = Me

44 R = Et
45 R = Me

46 R = Et
47 R = Me



48 R = 4-(trifluoromethyl)phenyl
49 R = 4-pyridyl
50 R = 2-pyridyl

51 R = 4-(trifluoromethyl)phenyl
52 R = 4-pyridyl
53 R = 2-pyridyl

(a) i) Ethyl chloroformate, TEA, THF, ii) $NaBH_4$, H_2O, THF; (b) $(COCl)_2$, DMSO, TEA, -60°C;
(c) ethyl azidoacetate, NaOEt, EtOH; (d) PPh_3, ether; (e) R'CHO, CH_3CN, 60°C; (f) MeOH, c.H_2SO_4, 60°C.

Example 41

(*E*)-3-(4-methylphenyl)prop-2-en-1-ol (Compound 41). Following General Procedure G, ethyl chloroformate (1.2 ml, 12.3 mmol), 4-methylcinnamic acid (2 g, 12.3 mmol) and triethylamine (1.7 ml, 12.3 mmol) in THF (50 ml) were reacted to produce a mixed anhydride, which was then were reacted with $NaBH_4$ (1.02 g, 27.2 mmol) in H_2O (20 ml) to produce title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 2.34 (s, 3 H), 4.31 (t, *J* = 4.88 Hz, 2 H), 6.30 – 6.39 (m, 1 H), 6.61 (d, *J* =16.11 Hz, 1 H), 7.14 (d, *J* = 8.30 Hz, 2 H), 7.29 (d, *J* = 8.30 Hz, 2 H).

Example 42

(*E*)-3-(4-ethylphenyl)acrylaldehyde (Compound 42). General Procedure H. To a solution of oxalyl chloride (5.9 ml, 11.8 mmol, 2 M in CH_2Cl_2) in CH_2Cl_2 (20 ml) was added a solution of DMSO (1.1 ml, 15.7 mmol) in CH_2Cl_2 (3 ml) dropwise at -60 °C. A solution of (*E*)-3-(4-ethylphenyl)prop-2-en-1-ol (**Compound 40**, 1.3 g, 7.8 mmol) in CH_2Cl_2 (5 ml) was cannulated slowly into the above mixture at -60 °C. After the reaction was stirred at the same temperature for 1 hour, a solution of triethylamine (4.4 ml, 31.4 mmol) in CH_2Cl_2 (5 ml) was added into the reaction, which was stirred an additional 1 hour at -60 °C. The reaction was quenched with water, and the products were extracted with CH_2Cl_2. The organic layer was washed with 5% aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. The filtered solution was concentrated *in vacuo,* and the residue was purified by column chromatography (silica gel, 15% ethyl acetate in hexane) to obtain the title compound as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 1.26 (t, J = 7.32 Hz, 3 H), 2.70 (q, J = 7.32 Hz, 2 H), 6.72 (dd, J =7.81, 16.11 Hz, 1 H), 7.28 (d, J = 8.30 Hz, 2 H), 7.48 (d, J = 15.62 Hz, 1 H),7.50 (d, J = 8.30 Hz, 2 H), 9.70 (s, 1 H).

Example 43

(*E*)-3-(4-methylphenyl)acrylaldehyde (Compound 43). Following General Procedure H, oxalyl chloride (7.1 ml, 14.2 mmol, 2 M in CH_2Cl_2), DMSO (1.3 ml, 18.9 mmol), (*E*)-3-(4-methylphenyl)prop-2-en-1-ol (**Compound 41**, 1.4 g, 9.5 mmol) and triethylamine (4.4 ml, 31.4 mmol)in CH_2Cl_2 (5 ml) were reacted to obtain the title compound as an oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.40 (s, 3 H), 6.72 (dd, J =7.81, 16.11 Hz, 1 H), 7.25 (d, J = 7.81 Hz, 2 H), 7.44 (d, J = 16.11 Hz, 1 H),7.48 (d, J = 8.30 Hz, 2 H), 9.70 (s, 1 H).

Example 44

Ethyl (2*Z*,4*E*)-2-azido-5-(4-ethylphenyl)penta-2,4-dienoate (Compound 44).

General Procedure I. A solution of NaOEt in ethanol was prepared in situ by dissolving Na (948 mg, 41.3 mmol) in 30 ml of ethanol. To this solution was added a solution of (*E*)-3-(4-ethylphenyl)acrylaldehyde (**Compound 42**, 1.1g , 6.9 mmol) and ethyl azidoacetate (13 ml, 41.3 mmol) in EtOH (20 ml) dropwise at -10 °C. After the addition was complete, the solution was stirred for an additional 1 hour at -10 °C. The reaction was quenched by adding water, and the product was extracted with ethyl acetate. The organic phase was washed with water, and brine, and dried over Mg_2SO_4. The solvent was removed *in vacuo,* and the residue was purified by column chromatography (silica gel, 20% ethyl acetate in hexane) to obtain the title compound as a pale solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.81 Hz, 3 H), 1.37 (t, *J* = 7.32 Hz, 3 H), 2.66 (q, *J* = 7.81 Hz, 2 H), 4.34 (q, *J* = 7.32 Hz, 2 H), 6.76 (d, *J* =11.23 Hz, 1 H), 6.81 (d, *J* = 16.11 Hz, 1 H), 7.15 (dd, *J* = 11.23, 15.62 Hz, 1 H), 7.19 (d, *J* = 8.30 Hz, 2 H),7.39 (d, *J* = 8.30 Hz, 2 H).

Example 45

Ethyl (2*Z*,4*E*)-2-azido-5-(4-methylphenyl)penta-2,4-dienoate (Compound 45).

Following General Procedure I, a 1.38 M solution of NaOEt in ethanol (30 ml), (*E*)-3-(4-methylphenyl)acrylaldehyde (**Compound 43**, 1.1g , 7.5 mmol) and ethyl azidoacetate (12 ml, 37.5 mmol) in EtOH (20 ml) were reacted to produce the title compound as a solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.32 Hz, 3 H), 2.36 (s, 3 H), 4.34 (q, *J* = 7.32 Hz, 2 H), 6.76 (d, *J* =10.25 Hz, 1 H), 6.81 (d, *J* =15.62 Hz, 1 H), 7.11 (dd, *J* = 11.23, 15.62 Hz, 1 H), 7.17 (d, *J* = 8.30 Hz, 2 H),7.39 (d, *J* = 7.81 Hz, 2 H).

Example 46

3-Ethoxycarbonyl-1,1,1-triphenyl-6-(4-ethylphenyl)-2-aza-1λ^5-phosphahexa-1, 3,5-triene (Compound 46). General Procedure J. A solution of triphenylphosphine (1.2 g, 4.54 mmol) in diethyl ether (10 ml) was added dropwise to a solution of ethyl (2*Z*,4*E*)-2-azido-5-(4-ethylphenyl)penta-2,4-dienoate (**Compound 44**, 1.2 g, 4.54 mmol) in diethyl ether (20 ml) at 0 °C. The solution was stirred for 12 hours at room temperature. Evaporation of solvent afforded a crude yellow solid, which was purified by column chromatography (silica gel, 20 % ethyl acetate in hexane) to give the title compound.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (t, *J* = 7.81 Hz, 3 H), 1.23 (t, *J* = 7.32 Hz, 3 H), 2.62 (q, *J* = 7.81 Hz, 2 H), 3.89 (q, *J* = 7.32 Hz, 2 H), 6.60 (d, *J* =15.62 Hz, 1 H), 6.70 (dd, *J* = 3.91, 10.74 Hz, 1 H), 7.12 (d, *J* = 8.30 Hz, 2 H), 7.30 (d, *J* = 8.30 Hz, 2 H), 7.41 – 7.50 (m, 9 H), 7.66 (dd, *J* = 11.23, 15.62 Hz, 1 H),7.73 - 7.77 (m, 6 H).

Example 47

3-Ethoxycarbonyl-1,1,1-triphenyl-6-(4-methylphenyl)-2-aza-1λ^5-phosphahexa-1, 3,5-triene (Compound 47). Following General Procedure J, triphenylphosphine (1.5 g, 5.8 mmol) ethyl (2*Z*,4*E*)-2-azido-5-(4-methylphenyl)penta-2,4-dienoate (**Compound 45**, 1.5 g, 5.8 mmol) in diethyl ether (50 ml) were reacted to produce the title compound as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (t, *J* = 7.32 Hz, 3 H), 2.33 (s, 3 H), 3.89 (q, *J* = 7.32 Hz, 2 H), 6.60 (d, *J* =16.11 Hz, 1 H), 6.70 (dd, *J* = 3.91, 11.23 Hz, 1 H), 7.09 (d, *J* = 8.30 Hz, 2 H), 7.27 (d, *J* = 8.30 Hz, 2 H), 7.41 – 7.50 (m, 9 H), 7.66 (dd, *J* = 11.23, 16.11 Hz, 1 H), 7.73 - 7.77 (m, 6 H).

Example 48

Ethyl 5-(4-ethylphenyl)-6-(4-(trifluoromethyl)phenyl)pyridine-2-carboxylate (Compound 48). General Procedure K. 4-(trifluoromethyl)benzaldehyde (153

mg, 1.88 mmol) was added to a stirred solution of 3-ethoxycarbonyl-1,1,1-triphenyl-6-(4-ethylphenyl)-2-aza-1λ^5-phosphahexa-1, 3,5-triene (**Compound 46**, 444 mg, 0.88 mmol) in dry acetonitrile (10 ml) and the solution was heated to 60 °C for 18 hours. The solution was concentrated *in vacuo*, and the crude product was passed through a silica gel column with 15% ethyl acetate in hexane as eluant to give the title compound as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.81 Hz, 3 H), 1.46 (t, *J* = 7.32 Hz, 3 H), 2.67 (q, *J* = 7.81 Hz, 2 H), 4.51 (q, *J* = 7.32 Hz, 2 H), 7.09 (d, *J* = 8.30 Hz, 2 H), 7.16 (d, *J* = 8.30 Hz, 1 H), 7.49 – 7.55 (m, 4 H), 7.88 (d, *J* = 7.81 Hz, 1 H), 8.16 (d, *J* = 7.81 Hz, 1 H).

Example 49

Ethyl 3-(4-Ethylphenyl)-[2,4']-bipyridinyl-6-carboxylate (Compound 49).

Following General Procedure K, 4-pyridinecarboxaldehyde (92 mg, 0.86 mmol) and 3-ethoxycarbonyl-1,1,1-triphenyl-6-(4-ethylphenyl)-2-aza-1λ^5-phosphahexa-1, 3,5-triene (**Compound 46**, 434 mg, 0.86 mmol) in dry acetonitrile (10 ml) were reacted to produce the title compound as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.81 Hz, 3 H), 1.46 (t, *J* = 7.32 Hz, 3 H), 2.67 (q, *J* = 7.81 Hz, 2 H), 4.51 (q, *J* = 7.32 Hz, 2 H), 7.09 (d, *J* = 8.30 Hz, 2 H), 7.16 (d, *J* = 8.30 Hz, 1 H), 7.33 (dd, *J* = 1.46, 4.39 Hz, 2 H), 7.90 (d, *J* = 7.81 Hz, 1 H), 8.21 (d, *J* = 7.81 Hz, 1 H), 8.52 (dd, *J* = 1.46, 4.39 Hz, 2 H).

Example 50

Ethyl 3-(4-Ethylphenyl)-[2,2']-bipyridinyl-6-carboxylate (Compound 50).

Following General Procedure K, 2-pyridinecarboxaldehyde (41 mg, 0.38 mmol) and 3-ethoxycarbonyl-1,1,1-triphenyl-6-(4-ethylphenyl)-2-aza-1λ^5-phosphahexa-1, 3,5-triene (**Compound 46**, 193 mg, 0.38 mmol) in dry acetonitrile (5 ml) were reacted to produce the title compound as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.81 Hz, 3 H), 1.45 (t, *J* = 7.32 Hz, 3 H), 2.62 (q, *J* = 7.81 Hz, 2 H), 4.52 (q, *J* = 7.32 Hz, 2 H), 7.05 – 7.11 (m, 4 H), 7.17 – 7.20 (m, 1 H), 7.49 (dd, *J* =0.98, 7.81 Hz, 1 H), 7.58 -7.62 (m, 1 H), 7.92 (d, *J* = 7.81 Hz, 1 H), 8.20 (d, *J* = 7.81 Hz, 1 H), 8.50 - 8.55 (m, 1 H).

Example 51

Methyl 5-(4-ethylphenyl)-6-(4-(trifluoromethyl)phenyl)pyridine-2-carboxylate (Compound 51). Following General Procedure E, ethyl 5-(4-ethylphenyl)-6-(4-(trifluoromethyl)phenyl)pyridine-2-carboxylate (**Compound 48**, 60 mg, 0.15 mmol) and conc. H_2SO_4 (10 drops) in methanol were reacted to produce the title compound as a light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 1.24 (t, *J* = 7.81 Hz, 3 H), 2.67 (q, *J* = 7.81 Hz, 2 H), 4.03 (s, 3 H), 7.09 (d, *J* = 8.30 Hz, 2 H), 7.16 (d, *J* = 8.30 Hz, 1 H), 7.49 – 7.55 (m, 4 H), 7.89 (d, *J* = 7.81 Hz, 1 H), 8.18 (d, *J* = 7.81 Hz, 1 H).

Example 52

Methyl 5-(4-ethylphenyl)-6-(pyridin-4-yl)pyridine-2-carboxylate (Compound 52). Following General Procedure E, ethyl 5-(4-ethylphenyl)-6-(pyridine-4-yl)phenyl)pyridine-2-carboxylate (**Compound 49**, 48 mg, 0.14 mmol) and conc. H_2SO_4 (10 drops) in methanol were reacted to produce the title compound as a light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 1.24 (t, *J* = 7.81 Hz, 3 H), 2.65 (q, *J* = 7.81 Hz, 2 H), 4.03 (s, 3 H), 7.09 (d, *J* = 7.81 Hz, 2 H), 7.16 (d, *J* = 7.81 Hz, 1 H), 7.32 (dd, *J* = 1.46, 4.39 Hz, 2 H), 7.90 (d, *J* = 8.30 Hz, 1 H), 8.21 (d, *J* = 8.30 Hz, 1 H), 8.52 (dd, *J* = 1.46, 4.39 Hz, 2 H).

Example 53

Methyl 5-(4-ethylphenyl)-6-(pyridin-2-yl)pyridine-2-carboxylate (Compound 53). Following General Procedure E, ethyl 5-(4-ethylphenyl)-6-(pyridine-2-yl)phenyl)pyridine-2-carboxylate (**Compound 50**, 16 mg, 0.05 mmol) and conc. H_2SO_4 (10 drops) in methanol were reacted to produce the title compound as a light yellow solid.

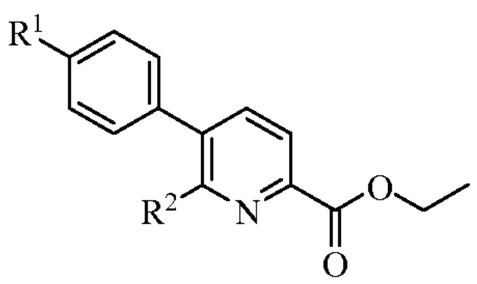
^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 1.22 (t, *J* = 7.81 Hz, 3 H), 2.63 (q, *J* = 7.81 Hz, 2 H), 4.02 (s, 3 H), 7.05 – 7.11 (m, 4 H), 7.18 – 7.22 (m, 1 H), 7.42 (dd, *J* =0.98, 7.81 Hz 1 H), 7.56 – 7.63 (m, 1 H), 7.93 (d, *J* = 8.30 Hz, 1 H), 8.23 (d, *J* = 8.30 Hz, 1 H), 8.55 -8.57 (m, 1 H).

Example 54

5, 6-diphenylpyridine-2-carbaldehyde (Compound 54). General Procedure L. To a solution of ethyl 5,6-diphenylpyridine-2-carboxylate (**Compound 21**, 145 mg, 0.48 mmol) in CH_2Cl_2 (5 ml) at -78 °C was added DIBAL-H (0.72 ml, 0.72 mmol, 1.0 M in Toluene) and the mixture was stirred between -78 °C and -60 °C for 1 hour under argon. The reaction was quenched with aq, NH_4Cl, diethyl ether and 400 mg Celite were added, and the mixture was stirred at room temperature 30 min. The solid was filtered off and rinsed with ether, and the combined filtrate was concentrated in *vacuo,* and the residue was purified by column chromatography (silica gel, 15% ethyl acetate in hexane) to produce the title compound.

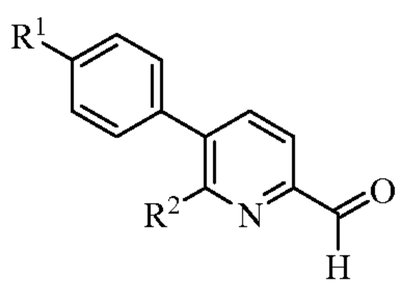
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.22 (m, 2 H), 7.27 – 7.32 (m, 6 H), 7.40 – 7.43 (m, 2 H), 7.92 (d, *J* = 7.91 Hz, 1 H), 8.01 (d, *J* = 7.91 Hz, 1 H), 10.19 (s, 1 H).

Scheme 4



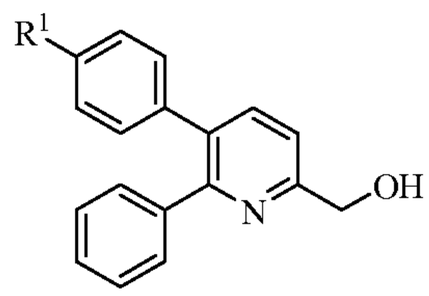
21 R^1 = H, R^2 = phenyl
22 R^1 = Me, R^2 = phenyl
23 R^1 = Et, R^2 = phenyl
25 R^1 =CF_3, R^2 = phenyl
49 R^1 = Et, R^2 = 4-pyridyl
24 R^1 = *n*-Pr, R^2 = phenyl

a



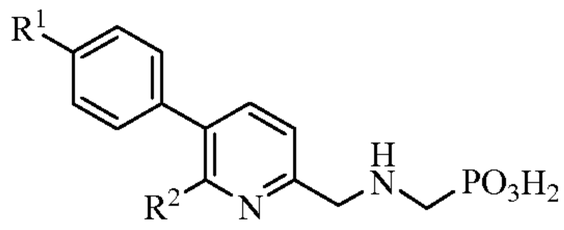
54 R^1 = H, R^2 = phenyl
55 R^1 = Me, R^2 = phenyl
56 R^1 = Et, R^2 = phenyl
57 R^1 =CF_3, R^2 = phenyl
58 R^1 = Et, R^2 = 4-pyridyl
59 R^1 = *n*-Pr, R^2 = phenyl

+



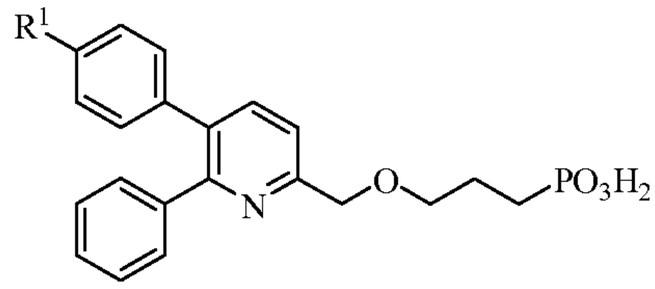
60 R^1 = Me
61R^1 = Et
62 R^1 = *n*-Pr

b



63 R_1 = H, R_2 = phenyl, n = 3
64 R_1 = Me, R_2 = phenyl, n = 3
65 R_1 = Et, R_2 = phenyl, n = 3
66 R_1 = Et, R_2 = phenyl, n = 2
67 R_1 =CF_3, R_2 = phenyl, n = 3
68 R_1 = Et, R_2 = 4-pyridyl, n = 3
69 R_1 = Et, R_2 = 4-pyridyl, n = 2
70 R_1 =Et, R_2 = phenyl, n = 4
71 R_1 = *n*-Pr, R_2 = phenyl, n = 3

c



72 R_1 = Et
73 R_1 = Me
74 R_1 = *n*-Pr

(a) DiBAL-H, CH_2Cl_2, -78 °C to -60 °C; (b) n-Bu_4NOH, $NH_2(CH_2)_nPO_3H_2$, MeOH, $Na(BH_3)CN$, 50 °C; (c)i) NaH, $Br(CH_2)_3PO(OEt)_2$, DMF, 110 °C; ii) TMSI, $CHCl_3$.

Example 55 and Example 60

6-Phenyl-5-*p*-tolylpyridine-2-carbaldehyde (Compound 55) and (6-phenyl-5-*p*-tolylpyridin-2-yl)methanol (Compound 60). Following General Procedure L, ethyl 6-phenyl-5-p-tolylpyridine-2-carboxylate (**Compound 22**, 1.1 g, 3.47 mmol) and DIBAL-H (5.2 ml, 5.21 mmol, 1.0M in cyclohexane) in CH_2Cl_2 (30 ml) were reacted to produce **Compound 55** and **Compound 60** after separation by column chromatography (silica gel, 15% ethyl acetate in hexane).

Compound 55: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3 H), 7.08 - 7.18 (m, 4 H), 7.29 - 7.38 (m, 3 H, 7.42 - 7.52 (m, 2 H), 7.94 (d, *J* = 7.32 Hz, 1 H), 8.03 (d, *J* = 7.81 Hz, 1 H), 10.27 (s, 1 H).

Compound 60: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3 H), 4.84 (s, 2 H), 7.02 - 7.13 (m, 4 H), 7.21 - 7.31 (m, 4 H), 7.35 - 7.42 (m, 2 H), 7.71 (d, *J* = 7.62 Hz, 1 H).

Example 56 and Example 61

5-(4-Ethylphenyl)-6-phenylpyridine-2-carbaldehyde (Compound 56) and [5-(4-Ethylphenyl)-6-phenylpyridin-2-yl]-methanol (Compound 61). Following General Procedure L, ethyl 5-(4-ethylphenyl)-6-phenylpyridine-2-carboxylate (**Compound 23**, 200 mg, 0.60 mmol) and DIBAL-H (1.2 ml, 1.20 mmol, 1.0 M in CH_2Cl_2) in CH_2Cl_2 (5 ml) were reacted to produce **Compound 56** and **Compound 61** after separation by column chromatography (silica gel, 15% ethyl acetate in hexane).

Compound 56: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.81 Hz, 3 H), 2.67 (q, *J* = 7.81 Hz, 2 H), 7.13 – 7.17 (m, 4H), 7.30 – 7.34 (m, 3 H), 7.44 – 7.47 (m, 2 H), 7.93 (d, *J* = 7.81 Hz, 1 H), 8.02 (d, *J* = 7.81 Hz, 1 H), 10.23 (s, 1 H).

Compound 61: ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.24 (t, *J* = 7.81 Hz, 3 H), 2.66 (q, *J* = 7.81 Hz, 2 H), 4.85 (d, *J* = 3.42 Hz, 2 H), 7.08 – 7.13 (m, 4H), 7.25 – 7.28 (m, 5 H), 7.39 (d, *J* = 7.81 Hz, 1 H), 7.74 (d, *J* = 7.81 Hz, 1 H).

Example 57

5-(4-Trifluoromethylphenyl)-6-phenylpyridine-2-carbaldehyde (Compound 57). Following General Procedure L, ethyl 5-(4-trifluoromethylphenyl)-6-phenylpyridine-2-carboxylate (**Compound 25**, 74 mg, 0.20 mmol) and DIBAL-H (0.3 ml, 0.30 mmol, 1.0 M in hexane) in CH_2Cl_2 (3 ml) were reacted to produce the title compound after purification by column chromatography (silica gel, 15% ethyl acetate in hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 - 7.39 (m, 2 H), 7.45 - 7.62 (m, 4 H), 7.95 (d, *J* = 7.92 Hz, 1 H), 8.05 (d, *J* = 7.92 Hz, 1 H), 10.19 (s, 1 H).

Example 58

3-(4-Ethylphenyl)-[2,4']-bipyridinyl-6-carbaldehyde (Compound 58)

Following General Procedure L, ethyl 3-(4-ethylphenyl)-[2,4']-bipyridinyl-6-carboxylate (**Compound 49**, 164 mg, 0.49 mmol) and DIBAL-H (0.75 ml, 0.75 mmol, 1.0 M in CH_2Cl_2) in CH_2Cl_2 (5 ml) were reacted to produce the title compound after purification by column chromatography (silica gel, 15% ethyl acetate in hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.81 Hz, 3 H), 2.68 (q, *J* = 7.81 Hz, 2 H), 7.11 ((d, *J* = 8.30 Hz, 2 H), 7.18 (d, *J* = 7.81 Hz, 1 H), 7.34 (dd, *J* = 1.95, 4.39 Hz, 2 H), 7.94 (d, *J* = 7.32 Hz, 1 H), 8.06 (d, *J* = 7.81 Hz, 1 H), 8.56 (dd, *J* = 1.95, 4.39 Hz, 2 H), 10.17 (s, 1 H).

Example 59 and Example 62

6-Phenyl-5-(4-propylphenyl)pyridine-2-carbaldehyde (Compound 59) and (6-Phenyl-5-(4-propylphenyl)pyridin-2-yl)methanol (Compound 62). Following General Procedure L, ethyl 6-phenyl-5-(4-propyl-phenyl)-pyridine-2-carboxylate (**Compound 24**, 370 mg, 0.49 mmol) and DIBAL-H (2.1 ml, 2.1 mmol, 1.0 M in cyclohexane) in CH_2Cl_2 (5 ml) were reacted to produce **Compound 59** and **Compound 62** after separation by column chromatography (silica gel, 15% ethyl acetate in hexane).

Compound 59: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.32 Hz, 3 H) ,1.59 - 1.71 (m, 2 H), 2.54 - 2.62 (m, 2 H), 7.11 (s, 4 H), 7.26 - 7.35 (m, 3 H), 7.40 - 7.45 (m, 2 H), 7.91 (d, *J* = 7.81 Hz, 1 H), 7.99 (d, *J* = 7.81 Hz, 1 H), 10.19 (s, 1 H).

Compound 62: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.32 Hz, 3 H), 1.60 - 1.70 (m, 2 H), 2.54 - 2.62 (m, 2 H), 4.87 (s, 2 H), 7.04 - 7.13 (m, 4 H), 7.22 - 7.32 (m, 4 H), 7.40 (d, *J* = 7.32 Hz, 2 H), 7.77 (d, *J* = 7.81 Hz, 1 H).

Example 63

{3-[(5,6-Diphenylpyridin-2-ylmethyl)-amino]-propyl}-phosphonic Acid (Compound 63). General Procedure M. To a solution of 5,6-diphenylpyridine-2-carbaldehyde (**Compound 54**, 95 mg, 0.37 mmol) and (3-amino-propyl)-phosphonic acid (51 mg, 0.37 mmol) in MeOH (3 ml) was added Bu_4NOH (0.4 ml, 0.37 mmol, 1M in MeOH) under argon. The mixture was stirred at 50 °C for 30 min. before adding $NaCNBH_3$ (23 mg, 0.37 mmol) to the mixture. The solution was stirred at 50 °C for 3 hours, and then it was concentrated *in vacuo*. The resulting crude solid was purified MPLC column chromatography (silica gel, 0 – 100% MeOH in ethyl acetate) to obtain the title compound as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 – 1.76 (m, 2 H), 2.00 – 2.08 (m, 2 H), 3.09 (t, J = 6.95 Hz, 2 H), 4.19 (s, 2 H), 7.02 – 7.09 (m, 2 H), 7.19 – 7.26 (m, 5 H), 7.30 – 7.36 (m, 3 H), 7.60 – 7.72 (m, 2 H).

Example 64

{3-[(6-Phenyl-5-p-tolylpyridin-2-ylmethyl)-amino]-propyl}-phosphonic Acid (Compound 64). Following General Procedure M, 6-phenyl-5-*p*-tolylpyridine-2-carbaldehyde (**Compound 55**, 67 mg, 0.25 mmol), (3-aminopropyl)-phosphonic acid (34 mg, 0.25 mmol), Bu_4NOH (0.2 ml, 0.25 mmol, 1 M in MeOH) and $NaCNBH_3$ (15 mg, 0.25 mmol) in MeOH (3 ml) were reacted to produce the title compound as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ 1.69 – 1.76 (m, 2 H), 2.00 – 2.08 (m, 2 H), 2.34 (s, 3 H), 3.19 (t, J = 6.80 Hz, 2 H), 4.39 (s, 2 H), 7.08 – 7.16 (m, 4 H), 7.25 – 7.31 (m, 3 H), 7.39 – 7.42 (m, 2 H), 7.54 (d, J = 7.80 Hz, 1 H), 7.89 (d, J = 7.81 Hz, 1 H).

Example 65

3-{[5-(4-Ethylphenyl)-6-phenylpyridin-2-ylmethyl]-amino}-propyl)-phosphonic Acid (Compound 65). Following General Procedure M, 5-(4-

ethylphenyl)-6-phenylpyridine-2-carbaldehyde (**Compound 56**, 43 mg, 0.15 mmol), (3-aminopropyl)-phosphonic acid (21 mg, 0.15 mmol), Bu_4NOH (0.15 ml, 0.15 mmol, 1 M in MeOH) and $NaCNBH_3$ (9 mg, 0.15 mmol) in MeOH (3 ml) were reacted to produce the title compound as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ 1.24 (t, J = 7.81 Hz, 3 H), 1.69 – 1.75 (m, 2 H), 2.00 – 2.08 (m, 2 H), 2.66 (q, J = 7.81 Hz, 2 H), 3.19 (t, J = 6.35 Hz, 2 H), 4.36 (s, 2 H), 7.10 – 7.16 (m, 4 H), 7.25 – 7.31 (m, 3 H), 7.39 – 7.42 (m, 2 H), 7.54 (d, J = 8.30 Hz, 1 H), 7.88 (d, J = 7.81 Hz, 1 H).

Example 66

(2-{[5-(4-Ethyl-phenyl)-6-phenyl-pyridin-2-ylmethyl]-amino}-ethyl)-phosphonic Acid (Compound 66). Following General Procedure M, 5-(4-ethyl-phenyl)-6-phenyl-pyridine-2-carbaldehyde (**Compound 56**, 31 mg, 0.11 mmol), (3-amino-ethyl)-phosphonic acid (14 mg, 0.11 mmol), Bu_4NOH (0.11 ml, 0.11 mmol, 1 M in MeOH) and $NaCNBH_3$ (7 mg, 0.11 mmol) in MeOH (2 ml) were reacted to produce the title compound as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ 1.23 (t, J = 7.81 Hz, 3 H), 1.90 – 1.96 (m, 2 H), 2.66 (q, J = 7.81 Hz, 2 H), 3.19 (t, J = 6.35 Hz, 2 H), 4.34 (s, 2 H), 7.09 – 7.16 (m, 4 H), 7.25 – 7.29 (m, 3 H), 7.39 – 7.42 (m, 2 H), 7.53 (d, J = 7.81 Hz, 1 H), 7.87 (d, J = 8.30 Hz, 1 H).

Example 67

(3-{[6-Phenyl-5-(4-trifluoromethylphenyl)-pyridin-2-ylmethyl]-amino}-propyl)-phosphonic Acid (Compound 67). Following General Procedure M, 5-(4-trifluoromethylphenyl)-6-phenyl-pyridine-2-carbaldehyde (**Compound 57**, 58 mg, 0.18 mmol), (3-amino-propyl)-phosphonic acid (25 mg, 0.18 mmol), Bu_4NOH (0.18 ml, 0.18 mmol, 1 M in MeOH) and $NaCNBH_3$ (11 mg, 0.18 mmol) in MeOH (3 ml) were reacted to produce the title compound as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ 1.02 (t, *J* = 7.33 Hz, 3 H), 1.65 – 1.75 (m, 2 H), 1.95 – 2.08 (m, 2 H), 3.16 (t, *J* = 6.35 Hz, 2 H), 4.36 (s, 2 H), 7.16 – 7.21 (m, 2 H), 7.29 – 7.31 (m, 3 H), 7.52 – 7.59 (m, 5 H), 7.91 (d, *J* = 7.92 Hz, 1 H).

Example 68

(3-{[3-(4-Ethylphenyl)-[2,4']-bipyridin-6-ylmethyl]-amino}-propyl)-phosphonic Acid (Compound 68). Following General Procedure M, 3-(4-ethyl-phenyl)-[2,4']-bipyridinyl-6-carbaldehyde (**Compound 58**, 50 mg, 0.17 mmol), (3-amino-propyl)-phosphonic acid (24 mg, 0.17 mmol), Bu_4NOH (0.17 ml, 0.17 mmol, 1 M in MeOH) and $NaCNBH_3$ (11 mg, 0.17 mmol) in MeOH (3 ml) were reacted to produce the title compound as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ1.25 (t, *J* = 7.81 Hz, 3 H), 1.69 -1.79 (m, 2 H), 2.00 – 2.09 (m, 2 H), 2.66 (q, *J* = 7.81 Hz, 2 H), 3.17 (t, *J* = 6.83 Hz, 2 H), 4.37 (s, 2 H), 7.16 (d, *J* = 8.30 Hz, 2 H), 7.22 (d, *J* = 8.30 Hz, 2 H), 7.49 (dd, *J* = 1.95, 4.88 Hz, 2 H), 7.64 (d, *J* = 7.81 Hz, 1 H), 7.94 (d, *J* = 7.81 Hz, 1 H), 8.45 (dd, *J* = 1.46, 4.39 Hz, 2 H).

Example 69

(2-{[3-(4-Ethyl-phenyl)-[2,4']-bipyridinyl-6-ylmethyl]-amino}-ethyl)-phosphonic Acid (Compound 69). Following General Procedure M, 3-(4-ethyl-phenyl)-[2,4']-bipyridinyl-6-carbaldehyde (**Compound 58**, 39 mg, 0.14 mmol), (3-amino-ethyl)-phosphonic acid (17 mg, 0.14 mmol), Bu_4NOH (0.14 ml, 0.14 mmol, 1 M in MeOH) and $NaCNBH_3$ (9 mg, 0.14 mmol) in MeOH (3 ml) were reacted to produce the title compound as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ 1.25 (t, *J* = 7.81 Hz, 3 H), 1.90 -1.99 (m, 2 H), 2.69 (q, *J* = 7.81 Hz, 2 H), 3.30 (t, *J* = 6.83 Hz, 2 H), 4.39 (s, 2 H), 7.14 (d, *J* = 8.30 Hz, 2 H), 7.20 (d, *J* = 8.30 Hz, 2 H), 7.48 (dd, *J* = 1.46, 4.39 Hz, 2 H), 7.62 (d, *J* = 7.81 Hz, 1 H), 7.93 (d, *J* = 7.81 Hz, 1 H), 8.45 (dd, *J* = 1.95, 4.88 Hz, 2 H).

Example 70

4-((5-(4-Ethylphenyl)-6-phenylpyridin-2-yl)methylamino)butylphosphonic Acid (Compound 70). Following General Procedure M, 5-(4-ethyl-phenyl)-6-phenyl-pyridine-2-carbaldehyde (**Compound 56**, 58 mg, 0.18 mmol), 4-aminobutylphosphonic acid (21 mg, 0.18 mmol), Bu_4NOH (0.18 ml, 0.18 mmol, 1 M in MeOH) and $NaCNBH_3$ (9 mg, 0.18 mmol) in MeOH (2 ml) were reacted to produce the title compound as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ 1.23 (t, *J* = 7.81 Hz, 3 H), 1.56 – 1.70 (m, 6 H), 2.61 – 2.71 (m. 4 H), 3.85 (s, 2 H), 7.07 – 7.12 (m, 4 H), 7.25 – 7.33 (m, 5 H), 7.66 (d, *J* = 8.30 Hz, 1 H), 7.83 (d, *J* = 8.30 Hz, 1 H).

Example 71

3-((6-Phenyl-5-(4-propylphenyl)pyridin-2-yl)methylamino)propylphosphonic Acid (Compound 71). Following General Procedure M, 6-phenyl-5-(4-propylphenyl)pyridine-2-carbaldehyde (**Compound 59**, 74 mg, 0.25 mmol), (3-amino-propyl) phosphonic acid (34 mg, 0.25 mmol), Bu_4NOH (0.25 ml, 0.25 mmol, 1M in MeOH) and $NaCNBH_3$ (15 mg, 0.25 mmol) in MeOH (5 ml) were reacted to produce the title compound as a white solid.

^{1}H NMR (500 MHz, CD_3OD) δ 0.94 (t, *J* = 7.32 Hz, 3 H), 1.58 - 1.78 (m, 4 H), 1.92 - 2.09 (m, 2 H), 2.51 - 2.66 (m, 2 H), 3.05 (t, *J* = 6.59 Hz, 2 H), 4.23 (s, 2 H), 7.03 - 7.16 (m, 4 H), 7.19 - 7.32 (m, 3 H), 7.36 - 7.38 (m, 2 H), 7.55 (d, *J* = 7.81 Hz, 1 H), 7.85 (d, *J* = 8.30 Hz, 1 H).

Example 72

{3-[5-(4-Ethyl-phenyl)-6-phenyl-pyridin-2-ylmethoxy]-propyl}-phosphonic Acid (Compound 72). General Procedure N. To a suspension of NaH (11 mg, 0.48 mmol) in DMF (1 ml) was added a solution of [5-(4-ethyl-phenyl)-6-phenyl-

pyridin-2-yl]-methanol (**Compound 61**, 69 mg, 0.24 mmol) at 0 °C under argon. After the mixture was stirred for 30 min., a solution of (3-bromo-propyl)-phosphonic acid diethyl ester (123 mg, 0.48 mmol) was added into the mixture and the reaction was heated to 110 °C overnight. The reaction was quenched with water, and the products were extracted with ethyl acetate. The combined organic layers were washed with water, and brine, and dried over Na_2SO_4. The filtered solvents were concentrated *in vacuo,* and the residue was purified by MPLC on silica gel (0 – 100 % ethyl acetate in hexane) to produce a crude mixture containing {3-[5-(4-Ethyl-phenyl)-6-phenyl-pyridin-2-ylmethoxy]-propyl}-phosphonic acid diethyl ester.

To a solution of crude {3-[5-(4-ethyl-phenyl)-6-phenyl-pyridin-2-ylmethoxy]-propyl}-phosphonic acid diethyl ester (18 mg, 0.039 mmol) in $CHCl_3$ (2 ml) at room temperature was added TMSI (77 mg, 0.39 mmol) dropwise. After the mixture was stirred for 1 hour, the solvent was removed *in vacuo* to recover a yellow oily residue. The residue was taken-up in THF/H_2O (4:1) and stirred at room temperature overnight. The mixture was extracted with ethyl acetate. The combined organic layers were washed with $NaHSO_3$, and water, and brine, and dried over Na_2SO_4. The filtered solvents were concentrated *in vacuo* and the residue was purified by MPLC on silica gel (0 – 100% MeOH in ethyl acetate) to give the title compound as a white solid..

^{1}H NMR (500 MHz, CD_3OD): δ1.20 (t, J = 7.81 Hz, 3 H), 1.67 – 1.73 (m, 2 H), 1.90 – 2.01 (m, 2 H), 2.61 (q, J = 7.81 Hz, 2 H), 3.67 (t, J = 6.35 Hz, 2 H), 4.69 (s, 2 H), 7.04 – 7.10 (m, 4 H), 7.23 – 7.29 (m, 5 H), 7.59 (d, J = 7.81 Hz, 1 H), 7.84 (d, J = 7.81 Hz, 1 H).

Example 73

3-((6-Phenyl-5-p-tolylpyridin-2-yl)methoxy)propylphosphonic Acid (Compound 73). Following General Procedure N, NaH (17 mg, 0.67 mmol), [5-(4-methyl-phenyl)-6-phenyl-pyridin-2-yl]-methanol (**Compound 60**, 91 mg, 0.33

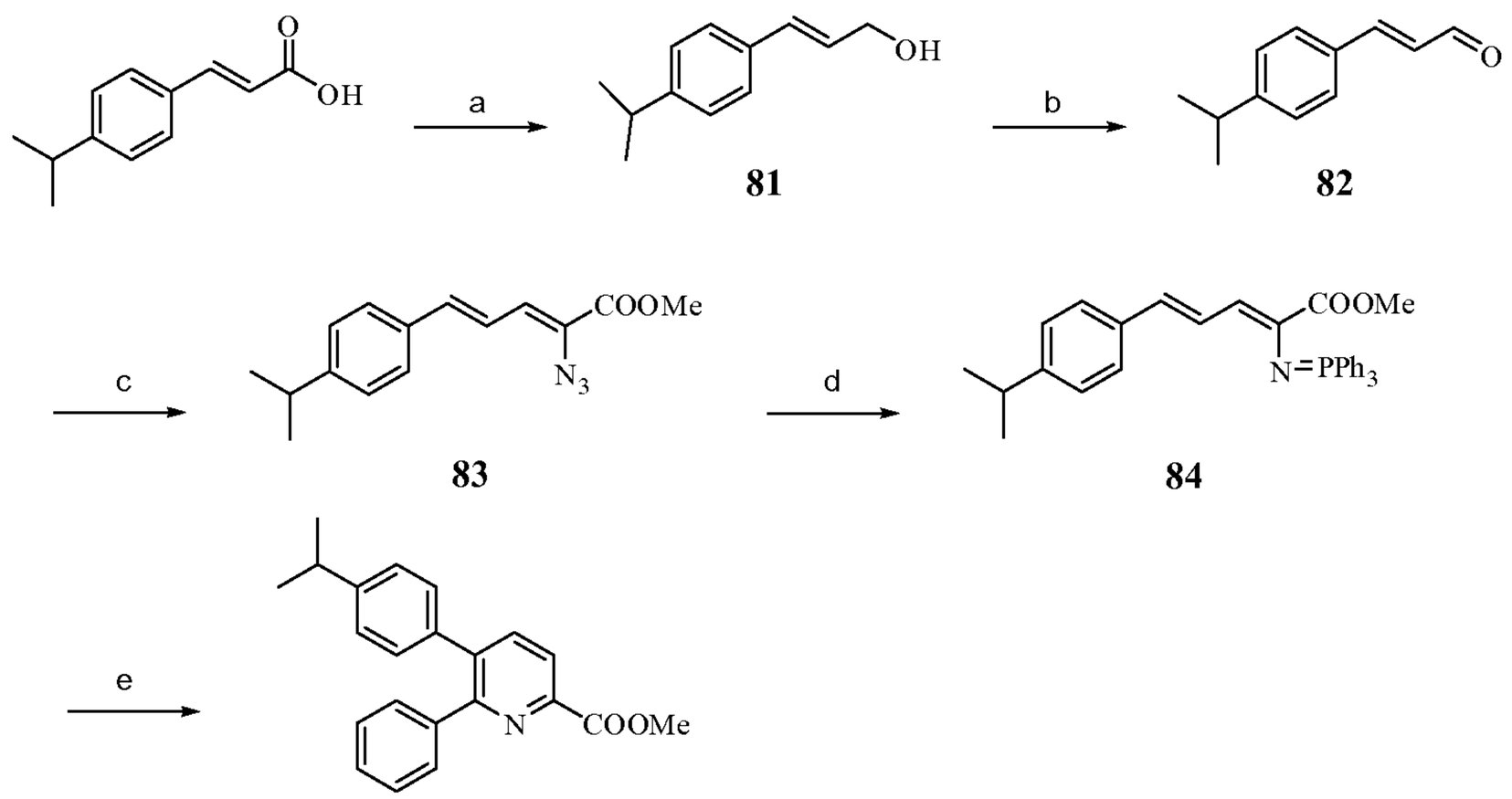
mmol) in DMF (3 ml) was refluxed to produce crude {3-[5-(4-methyl-phenyl)-6-phenyl-pyridin-2-ylmethoxy]-propyl}-phosphonic acid diethyl ester, which was then reacted with TMSI (0.13 ml, 0.09 mmol) in $CHCl_3$ (3 ml) to obtain the title compound as an oil.

^{1}H NMR (500 MHz, CD_3OD) δ 1.73 - 1.88 (m, 2 H), 1.90 - 2.05 (m, 2 H), 2.30 (s, 3 H), 3.69 (t, *J* = 6.35 Hz, 2 H), 4.69 (s, 2 H), 6.97 - 7.12 (m, 4 H), 7.20 - 7.34 (m, 5 H), 7.58 (d, *J* = 8.30 Hz, 1 H), 7.86 (d, *J* = 8.30 Hz, 1 H).

Example 74

3-((6-Phenyl-5-(4-propylphenyl)pyridin-2-yl)methoxy)propylphosphonic Acid (Compound 74). Following General Procedure N, NaH (17 mg, 0.67 mmol), [5-(4-methyl-phenyl)-6-phenyl-pyridin-2-yl]-methanol (**Compound 62**, 105mg, 0.35 mmol) in DMF (3 ml) was refluxed to produce crude {3-[5-(4-n-propyl-phenyl)-6-phenyl-pyridin-2-ylmethoxy]-propyl}-phosphonic acid diethyl ester, which was then reacted with TMSI (0.13 ml, 0.09 mmol) in $CHCl_3$ (3 ml) to obtain the title compound as an oil.

Scheme 5



(a) i) Ethyl chloroformate, TEA, THF, ii) $NaBH_4$, H_2O, THF; (b) $(COCl)_2$, DMSO, TEA, -60°C; (c) ethyl azidoacetate, NaOMe, MeOH; (d) PPh_3, ether; (e) PhCHO, CH_3CN, 60°C.

Example 81

(*E*)-3-(4-Isopropylphenyl)prop-2-en-1-ol (Compound 81). Following General Procedure G, 4-iso-propylcinnamic acid (3 g, 15.8 mmol), ethyl chloroformate (1.6 ml, 15.8 mmol) and triethylamine (2.2 ml, 15.8 mmol) in THF (100ml) were reacted to produce a mixed anhydride, which was then were reacted with $NaBH_4$ (1.3 g, 34.7 mmol) in H_2O (30 ml) to produce title compound as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 (d, *J*=7.04 Hz, 6 H), 2.86 - 2.97 (m, 1 H), 4.32 (dd, *J*=5.86, 1.17 Hz, 2 H), 6.29 - 6.38 (m, 1H), 6.61 (d, *J*=16.12 Hz, 1 H), 7.16 - 7.24 (d, *J*=8.21 Hz, 2 H), 7.33 (d, *J*=8.21 Hz, 2 H)

Example 82

(*E*)-3-(4-Isopropylphenyl)acrylaldehyde (Compound 82). Following General Procedure H, oxalyl chloride (9.5 ml, 19.0 mmol, 2M in CH_2Cl_2), DMSO (1.8 ml, 25.3 mmol), (*E*)-3-(4-isopropylphenyl)prop-2-en-1-ol **(Compound 81,** 2.2g, 12.6

mmol) and triethylamine (7.1 ml, 50.7 mmol) in CH_2Cl_2 (100 ml) were reacted to obtain the title compound as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.28 (d, *J*=7.04 Hz, 6 H), 2.77 - 3.11 (m, 1 H), 6.70 (dd, *J*=15.83, 7.62 Hz, 1 H), 7.31 (d, *J*=8.21 Hz, 1 H), 7.45 - 7.59 (m, 3 H), 9.70 (d, *J*=7.62 Hz, 1 H)

Example 83

Methyl (*2Z,4E*)- 2-Azido-5-(4-isopropylphenyl)penta-2,4-dienoate (Compound 111). Following General Procedure I, a 1.34 M solution of NaOMe in methanol (30 ml), (*E*)-3-(4-isopropylphenyl)acrylaldehyde **(Compound 82,**1.4 g, 8.0 mmol) and ethyl azidoacetate (12 ml, 40.2 mmol) in MeOH (20 ml) were reacted to produce the title compound as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 (d, *J*=6.74 Hz, 6 H), 2.80 - 3.02 (m, 1 H), 3.88 (s, 3 H), 6.70 - 6.87 (m, 2 H), 7.13 (dd, *J*=15.54, 11.43 Hz, 1 H), 7.22 (d, *J*=8.21 Hz, 2 H), 7.43 (d, 2 H)

Example 84

3-Methoxycarbonyl-1,1,1-triphenyl-6-(4-isopropylphenyl)-2-aza-1λ^5-phosphahexa-1,3,5-triene (Compound 84). Following General Procedure J, triphenylphosphine (1.4g, 5.2 mmol), methyl (*2Z,4E*)- 2-azido-5-(4-isopropylphenyl)penta-2,4-dienoate (**Compound 83,** 1.4 g, 5.2 mmol) in diethyl ether (50 ml) were reacted to produce the title compound as a yellow solid.

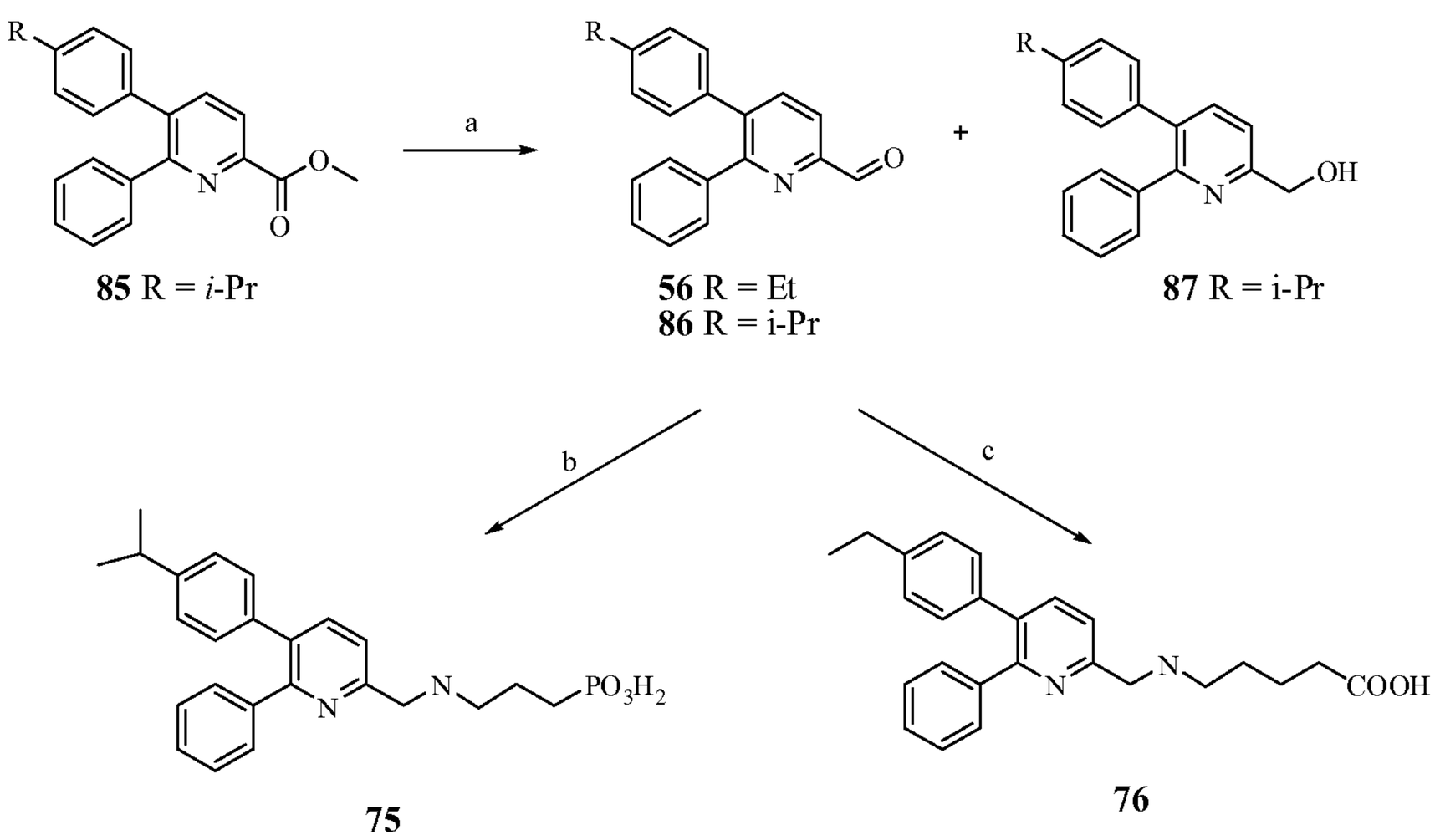
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 (d, *J*=6.74 Hz, 6 H), 2.81 - 2.98 (m, 1 H), 3.44 (s, 3 H), 6.58 - 6.76 (m, 2 H), 7.15 (d, *J*=8.21 Hz, 2 H), 7.32 (d, *J*=8.50 Hz, 2 H), 7.37 - 7.57 (m, 9 H), 7.76 (ddd, *J*=12.09, 7.99, 1.32 Hz, 7 H)

Example 85

Methyl 5-(4-Isopropyl-phenyl)-6-phenyl-pyridine-2-carboxylate (Compound 85). Following General Procedure K, Benzaldehyde (0.48 g, 4.6 mmol) and 3-Methoxycarbonyl-1,1,1-triphenyl-6-(4-isopropylphenyl)-2-aza-1λ^5-phosphahexa-1,3,5-triene (**Compound 84**, 2.3 g, 4.6 mmol) in dry acetonitrile (100 ml) were reacted to produce the title compound as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 (d, *J*=7.04 Hz, 6 H), 2.78 - 3.00 (m, 1 H), 4.03 (s, 3 H), 7.06 - 7.19 (m, 4 H), 7.21 - 7.32 (m, 3 H), 7.35 - 7.46 (m, 2 H), 7.86 (d, *J*=7.92 Hz, 1 H), 8.14 (d, *J*=7.92, 1 H)

Scheme 6



(a) DiBAL-H, CH_2Cl_2, -78 °C to -60 °C; (b) *n*-Bu_4NOH, $NH_2(CH_2)_3PO_3H_2$, MeOH, $Na(BH_3)CN$, 50 °C; (c) $NH_2(CH_2)_4CO_2H$, MeOH, $Na(BH_3)CN$, AcOH.

Example 86 and Example 87

5-(4-Isopropyl-phenyl)-6-phenyl-pyridine-2-carbaldehyde (Compound 86) and (5-(4-Isopropylphenyl)-6-phenylpyridin-2-yl)methanol (Compound 87). Following General Procedure L, methyl 5-(4-isopropyl-phenyl)-6-phenyl-pyridine-2-carboxylate (**Compound 85**, 283 mg, 0.86 mmol) and DIBAL-H (0.9 ml, 1.72 mmol, 1.0 M in cyclohexane) in CH_2Cl_2 (10 ml) were reacted to produce **Compound 86** and **compound 87** after separation by column chromatography (silica gel, 15% ethyl acetate in hexane).

Compound 86: ^{1}H NMR (300 MHz, CDCl3) δ ppm 1.26 (d, *J*=6.74 Hz, 6 H), 2.81 - 3.00 (m, 1 H), 7.08 - 7.21 (m, 4 H), 7.28 - 7.35 (m, 3 H), 7.38 - 7.48 (m, 2 H), 7.90 (d, *J*=7.92 Hz, 1 H), 7.99 (d, *J*=7.92 Hz, 1 H), 10.19 (s, 1 H)

Compound 87: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 (d, *J*=6.74 Hz, 6 H), 2.77 - 3.01 (m, 1 H), 4.85 (d, *J*=3.52 Hz, 2 H), 7.03 - 7.19 (m, 4 H), 7.19 - 7.33 (m, 4 H), 7.32 - 7.46 (m, 2 H), 7.74 (d, *J*=7.92 Hz, 1 H)

Example 75

3-{[5-(4-Isopropylphenyl)-6-phenylpyridin-2-ylmethyl]amino}-propyl-phosphonic Acid (Compound 75). Following General Procedure M, 5-(4-isopropyl-phenyl)-6-phenyl-pyridine-2-carbaldehyde (**Compound 86**, 150 mg, 0.5 mmol), (3-aminopropyl)-phosphonic acid (69 mg, 0.5 mmol), Bu_4NOH (0.5 ml, 0.5 mmol, 1 M in MeOH) and $NaCNBH_3$ (31 mg, 0.5 mmol) in MeOH (5 ml) were reacted to obtain the title compound as a white solid.

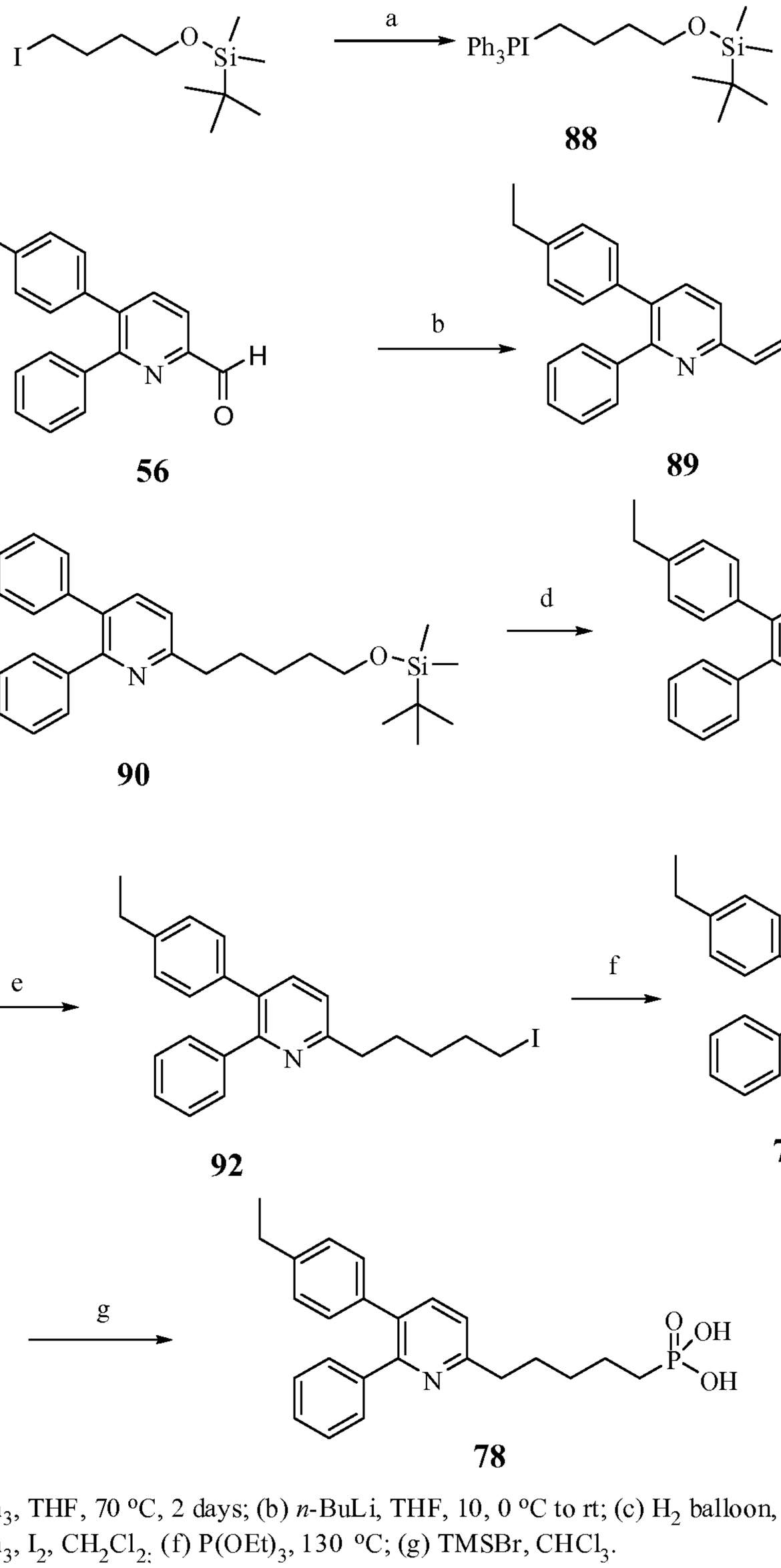
^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.23 (d, *J*=6.74 Hz, 6 H), 1.60 - 1.81 (m, 2 H), 1.90 - 2.13 (m, 2 H), 2.79 - 2.99 (m, 1 H), 3.19 (t, *J*=6.74 Hz, 2 H), 4.36 (s, 2 H), 7.04 - 7.21 (m, 4 H), 7.21 - 7.33 (m, 3 H), 7.33 - 7.44 (m, 2 H), 7.51 (d, *J*=7.92 Hz, 1 H), 7.86 (d, *J*=7.92 Hz, 1 H)

Example 76

4-{[5-(4-Ethyl-phenyl)-6-phenyl-pyridin-2-ylmethyl]-amino}-butyric Acid (Compound 76). 5-(4-Ethyl-phenyl)-6-phenyl-pyridine-2-carbaldehyde (**Compound 56**, 20 mg, 0.07 mmol), 5-amino-pentanoic acid (17 mg, 0.14 mmol), $NaCNBH_3$ (4 mg, 0.07 mmol) and HOAc (1drop) in MeOH (2 ml) were reacted overnight. The solvent was removed and the resulting crude solid was purified by MPLC column chromatography (silica gel, 0 – 100 % ethyl acetate in hexane) to obtain the title compound as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.21 (t, *J*=7.62 Hz, 3 H), 1.60 - 1.82 (m, 4 H), 2.20 (t, *J*=6.30 Hz, 2 H), 2.62 (q, *J*=7.62 Hz, 2 H), 3.02 (t, *J*=7.15 Hz, 2 H), 4.30 (s, 2 H), 7.03 - 7.16 (m, 4 H), 7.20 - 7.30 (m, 3 H), 7.33 – 7.37 (m, 2 H), 7.49 (d, *J*=7.92 Hz, 1 H), 7.86 (d, *J*=7.33 Hz, 1 H)

Scheme 7



(a) PPh_3, THF, 70 °C, 2 days; (b) *n*-BuLi, THF, 10, 0 °C to rt; (c) H_2 balloon, MeOH, EtOAc; (d) TBAF, THF; (e) PPh_3, I_2, CH_2Cl_2; (f) $P(OEt)_3$, 130 °C; (g) TMSBr, $CHCl_3$.

Example 88

[4-(Tert-butyl-dimethyl-silanyloxy)-butyl]-triphenyl-λ^5-phosphane Iodide Salt (Compound 88). Tert-butyl(4-iodobutoxy)dimethylsilane (2 g, 6.4 mmol) was treated with triphenylphosphine (2.2 g, 8.3 mmol) in THF (30 ml). After heating at 70 °C for 2 hours, the solution was cooled to room temperature and then diluted with pentane (50 ml), whereupon the product precipitated as a white solid, which was filtered and washed with an additional 50 ml of pentane to afford a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm -0.03 (s, 6 H), 0.78 (s, 9 H), 1.71 - 1.85 (m, 2 H), 1.86 - 2.01 (m, 2 H), 3.68 (t, *J*=5.42 Hz, 2 H), 3.72 - 3.88 (m, 2 H), 7.41 - 7.90 (m, 15 H)

Example 89

6-(5-(Tert-butyldimethylsilyloxy)pent-1-enyl)-3-(4-ethylphenyl)-2-phenylpyridine (Compound 89). To a solution of [4-(tert-butyl-dimethyl-silanyloxy)-butyl]-triphenyl-λ^5-phosphane iodide salt (**Compound 88**, 451 mg, 0.8 mmol) in THF (2 ml) was added *n*-BuLi (0.3 ml, 0.8 mmol, 2.5 M in hexane) at 0 °C. The solution was warmed to room temperature and allowed to stir for an additional 45 min. A solution of 5-(4-ethyl-phenyl)-6-phenyl-pyridine-2-carbaldehyde (**Compound 56**, 174 mg, 0.6 mmol) in THF (3 ml) was cannulated into the first solution, and the reaction was stirred at room temperature overnight. The reaction was quenched with water, and the products were extracted with ethyl acetate. The organic layer was washed with brine, and dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 15 % ethyl acetate in hexane) to give the title compound as a oil. ^{1}H NMR shows it is a mixture of cis/tran isomers. MS (ES+) M+1: 458

Example 90

6-(5-(Tert-butyldimethylsilyloxy)pentyl)-3-(4-ethylphenyl)-2-phenylpyridine (Compound 90). A solution of 6-(5-(tert-butyldimethylsilyloxy)pent-1-enyl)-3-(4-

ethylphenyl)-2-phenylpyridine (**Compound 89**, 45 mg, 0.1 mmol) and Pd-C (2 mg, 10% wt) in MeOH (5 ml) was hydrogenated under H_2 balloon atmosphere overnight. The catalyst was filtered away and the filtrate was concentrated *in vacuo* and purified by MPLC column chromatography (silica gel, 15 % ethyl acetate in hexane) to obtain the title compound as a oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.06 (s, 6 H), 0.90 (s, 9 H), 1.23 (t, *J*=7.62 Hz, 3 H), 1.61 - 1.93 (m, 4 H), 2.63 (q, *J*=7.82 Hz, 2 H), 2.89 (d, *J*=7.62 Hz, 2 H), 3.53 - 3.71 (m, 2 H), 4.23 (dd, *J*=5.86, 3.52 Hz, 2 H), 7.02 - 7.14 (m, 4 H), 7.17 (d, *J*=7.92 Hz, 1 H), 7.23 (dd, *J*=3.37, 1.61 Hz, 2 H), 7.32 - 7.40 (m, 1 H), 7.53 (t, *J*=2.78 Hz, 1 H), 7.62 (d, *J*=7.92 Hz, 1 H), 7.72 (dd, *J*=5.57, 3.22 Hz, 1 H)

Example 91

5-(5-(4-Ethylphenyl)-6-phenylpyridin-2-yl)pentan-1-ol (Compound 91). To a solution of 6-(5-(tert-butyldimethylsilyloxy)pentyl)-3-(4-ethylphenyl)-2-phenylpyridine (**Compound 90**, 44 mg, 0.1 mmol) in THF (2 ml) was added TBAF (0.2 ml, 1.0 M in THF) at room temperature. The reaction was completed after stirring overnight at room temperature. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, and dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 20 % ethyl acetate in hexane) to give the title compound as a oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 (t, *J*=7.62 Hz, 3 H), 1.43 - 1.58 (m, 2 H), 1.59 - 1.74 (m, 2 H), 1.74 - 1.94 (m, 2 H), 2.64 (q, *J*=7.62 Hz, 2 H), 2.90 (d, *J*=7.92 Hz, 2 H), 3.67 (t, *J*=6.45 Hz, 2 H), 7.01 - 7.14 (m, 4 H), 7.17 (d, *J*=7.92 Hz, 1 H), 7.25 (t, *J*=6.30 Hz, 3 H), 7.30 - 7.44 (m, 2 H), 7.63 (d, 1 H)

Example 92

3-(4-Ethylphenyl)-6-(5-iodopentyl)-2-phenylpyridine (Compound 92). Iodine (31 mg, 0.12 mmol) was added into a solution of triphenylphosphine (32 mg, 0.12 mmol) in CH_2Cl_2 at 0 °C and allowed the mixture to stir for 5 mins. To the resulting yellow slurry was added dropwise a solution of 5-(5-(4-ethylphenyl)-6-phenylpyridin-2-yl)pentan-1-ol (**Compound 91,** 28 mg, 0.08 mmol) and imidazol in CH_2Cl_2. The mixture was stirred overnight and then diluted with CH_2Cl_2, washed with $NaHSO_3$, and water, and brine, and dried over Na_2SO_4. The filtrate was concentrated *in vacuo*, and the residue was purified by MPLC (silica gel, 20 % ethyl acetate in hexane) to produce the title compound as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.15 (t, *J*=7.48 Hz, 3 H), 1.38 - 1.59 (m, 3 H), 1.69 - 1.92 (m, 3 H), 2.56 (q, *J*=7.62 Hz, 2 H), 2.81 (d, *J*=7.62 Hz, 2 H), 3.15 (t, *J*=7.04 Hz, 2 H), 6.95 - 7.05 (m, 4 H), 7.09 (d, *J*=7.62 Hz, 1 H), 7.12 - 7.21 (m, 3 H), 7.29 (dd, *J*=3.81, 2.64 Hz, 2 H), 7.55 (d, 1 H)

Example 93

Diethyl 5-(5-(4-ethylphenyl)-6-phenylpyridin-2-yl)pentylphosphonate (Compound 77). A solution of 3-(4-ethylphenyl)-6-(5-iodopentyl)-2-phenylpyridine (**Compound 92,** 28 mg, 0.06 mmol) and triethyl phosphate (1.5 ml) was heated at 130 °C overnight. Triethyl phosphate was removed under vacuum to give the crude oil. The crude material was purified by MPLC (silica gel, 20% ethyl acetate in hexane) to obtain the title compound as a white solid.

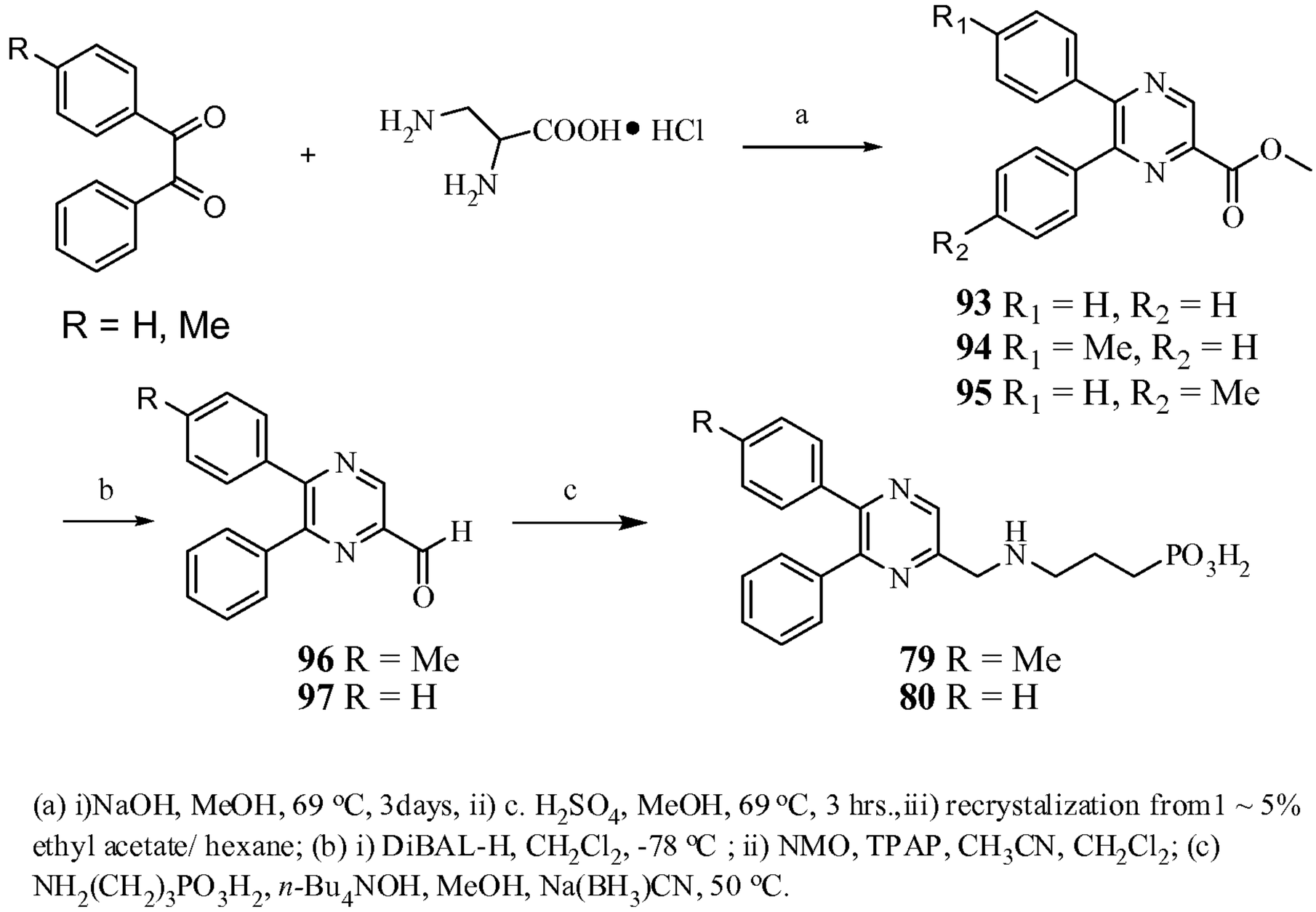
^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.20 (t, *J*=7.62 Hz, 3 H), 1.31 (t, *J*=7.04 Hz, 6 H), 1.45 - 1.90 (m, 8 H), 2.60 (q, *J*=7.43 Hz, 2 H), 2.86 (t, *J*=7.92 Hz, 2 H), 4.07 (qd, *J*=7.23, 7.04 Hz, 4 H), 7.06 (q, *J*=8.31 Hz, 4 H), 7.27 (d, *J*=2.05 Hz, 5 H), 7.33 (d, *J*=7.92 Hz, 1 H), 7.74 (d, 1 H)

Example 78

5-(5-(4-Ethylphenyl)-6-phenylpyridin-2-yl)pentylphosphonic Acid (Compound 78). To a solution of diethyl 5-(5-(4-ethylphenyl)-6-phenylpyridin-2-yl)pentylphosphonate (**Compound 77**, 20 mg, 0.04 mmol) in $CHCl_3$ under argon was added bromotrimethylsilane (0.03 ml, 0.22 mmol) at room temperature. After the reaction was stirred for 4 hours at room temperature, excess TMSBr was removed under high vacuum. The residue was then treated with MeOH for 10 min at room temperature, and the solvent was removed *in vacuo*. Trituation of the residue several times with diethyl ether followed by removal of the final traces of diethyl ether under high vacuum yielded the title compound as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.20 (t, *J*=7.48 Hz, 3 H), 1.53 - 1.99 (m, 8 H), 2.63 (q, *J*=7.72 Hz, 2 H), 3.15 (d, *J*=8.21 Hz, 2 H), 7.08 - 7.24 (m, 4 H), 7.37 - 7.63 (m, 5 H), 8.01 (d, *J*=8.21 Hz, 1 H), 8.54 (d, 1 H)

Scheme 8



(a) i)NaOH, MeOH, 69 °C, 3days, ii) c. H_2SO_4, MeOH, 69 °C, 3 hrs.,iii) recrystalization from1 ~ 5% ethyl acetate/ hexane; (b) i) DiBAL-H, CH_2Cl_2, -78 °C ; ii) NMO, TPAP, CH_3CN, CH_2Cl_2; (c) $NH_2(CH_2)_3PO_3H_2$, *n*-Bu_4NOH, MeOH, $Na(BH_3)CN$, 50 °C.

Example 93

Methyl 5,6-Diphenyl-pyrazine-2-carboxylate (93). General Procedure O. To a solution of benzyl (500 mg, 2.38 mmol) and 2,3 –diaminopropionic acid monohydro chloride (334 mg, 2.38 mmol) in MeOH (10 ml) was added NaOH (380 mg, 9.51 mmol) at room temperature. After the mixture was refluxed for 6 hours, it was cooled down in an ice-bath, and conc. H_2SO_4 (1 ml) was added dropwise, and the reaction mixture was stirred under reflux for 3 hours. MeOH was removed under vacuum, and the residue was dissolved in water, and extracted with ethyl acetate. The separated organic layer was washed with $NaHCO_3$ (sat.), and water, and brine, and dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (15% ethyl acetate in hexane) to give the title compound as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.06 (s, 3 H), 7.27 - 7.40 (m, 6 H), 7.45 - 7.54 (m, 4 H), 9.28 (s, 1 H).

Example 94 and Example 95

Methyl 6-Phenyl-5-p-tolylpyrazine-2-carboxylate (Compound 94) and Methyl 5-Phenyl-6-*p*-tolylpyrazine-2-carboxylate (Compound 95). Followin General Procedure O, 1-phenyl-2-*p*-tolylethane-1,2-dione (287 mg, 1.3 mmol) and 2,3-diaminopropionic acid monohydro chloride (180 mg, 1.3 mmol) NaOH (205 mg, 5.2 mmol) in MeOH (10 ml) was refluxed for 48 hours. Then it was cooled down in an ice-bath, and conc. H_2SO_4 (1ml) was added dropwise and the reaction mixture mixture was stirred under refluxed for 3 hours. Recrystalization from 3 to 5% ethyl acetate in hexane was used to isolate isomer the two isomers, **Compound 94** and **Compound 95**. The structure of **Compound 95** was confirmed by x-ray crystalography.

Compound 94: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.36 (s, 3 H), 4.06 (s, 3 H), 7.13 (d, *J*=7.92 Hz, 2 H), 7.30 - 7.45 (m, 5 H), 7.52 (dd, *J*=7.48, 2.20 Hz, 2 H), 9.27 (s, 1 H)

Compound 95: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.36 (s, 3 H), 4.06 (s, 3 H), 7.12 (d, *J*=7.92 Hz, 2 H), 7.37 (dd, *J*=16.86, 7.77 Hz, 5 H), 7.52 (dd, *J*=7.92, 1.76 Hz, 2 H), 9.26 (s, 1 H)

Example 96

6-Phenyl-5-*p*-tolylpyrazine-2-carbaldehyde (Compound 96). Following General Procedure L, methyl 6-phenyl-5-*p*-tolylpyrazine-2-carboxylate (**Compound 94**, 60 mg, 0.2mmol) and DiBAL-H (0.4 ml, 0.4 mmol, 1 M in cyclohexane) in CH_2Cl_2 (2 ml) were reacted to produce the title compound as a oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.37 (s, 3 H), 7.14 (d, *J*=7.92 Hz, 2 H), 7.33 - 7.47 (m, 5 H), 7.54 (dd, *J*=7.77, 1.91 Hz, 2 H), 9.15 (s, 1 H), 10.26 (s, 1 H)

Example 79

3-((6-Phenyl-5-*p*-tolylpyrazin-2-yl)methylamino)propylphosphonic Acid (Compound 79). Following General Procedure M, 6-phenyl-5-*p*-tolylpyrazine-2-carbaldehyde (**Compound 96**, 37 mg, 0.14 mmol), (3-aminopropyl)-phosphonic acid (19 mg, 0.14 mmol), Bu_4NOH (0.14 ml, 0.14 mmol, 1 M in MeOH) and $NaCNBH_3$ (8 mg, 0.14 mmol) in MeOH (2 ml) were reacted to obtain the title compound as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.74 (dd, *J*=17.15, 7.18 Hz, 2 H), 2.05 (dd, *J*=11.73, 6.45 Hz, 2 H), 2.34 (s, 3 H), 3.21 - 3.35 (m, 2 H), 4.49 (s, 2 H), 7.14 (d, *J*=7.92 Hz, 4 H), 7.25 - 7.40 (m, 3 H), 7.50 (dd, *J*=7.92, 1.76 Hz, 2 H), 8.70 (s, 1 H)

Example 97

5,6-Diphenylpyrazine-2-carbaldehyde (Compound 97). Following General Procedure L, methyl 5,6-diphenyl-pyrazine-2-carboxylate (**Compound 93**, 408 mg, 1.5 mmol) and DiBAL-H (3.3 ml, 3.3 mmol, 1 M in cyclohexane) in CH_2Cl_2 (5 ml) were reacted to produce title compound as a oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.29 - 7.46 (m, 6 H), 7.53 (d, *J*=6.74 Hz, 4 H), 9.17 (s, 1 H), 10.27 (s, 1 H)

Example 80

3-((5,6-Diphenylpyrazin-2-yl)methylamino)propylphosphonic Acid (Compound 80). Following General Procedure M, 5,6-diphenylpyrazine-2-carbaldehyde (**Compound 97**, 44 mg, 0.14 mmol), (3-aminopropyl)-phosphonic acid (28 mg, 0.14 mmol), Bu_4NOH (0.14 ml, 0.14 mmol, 1 M in MeOH) and $NaCNBH_3$ (12 mg, 0.14 mmol) in MeOH (5 ml) were reacted to obtain the title compound as a white solid.

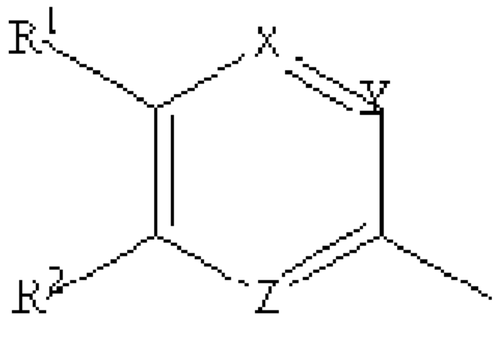
^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.60 - 1.83 (m, 2 H), 1.98 - 2.17 (m, 2 H), 3.23 - 3.40 (m, 2 H), 4.51 (s, 2 H), 7.20 - 7.62 (m, 10 H), 8.73 (s, 1 H)

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims. In particular, the present invention contemplates and includes a compound comprising a 6-membered heteroaromatic ring including one, two or three enchained nitrogen atoms at the 1, or 1 and 3 or 1, 3 and 4 positions, respectively, and the remaining ring atoms being carbon, an aryl radical directly bonded to said 6-membered heteroaromatic ring at both of the 5 and 6 positions and a side chain at the 2 position of said 6-membered heteroaromatic ring, wherein said side chain terminates with an end group selected from the group consisting of a phosphonic acid, a lower alkyl ester thereof, a carboxylic acid, a lower alkyl ester thereof, a

lower alkyl ether and a lower alkylcarboxy and a compound comprising a 6-membered heteroaromatic ring including one, two or three enchained nitrogen atoms and the remaining ring atoms being carbon, an aryl radical directly bonded to said 6-membered heteroaromatic ring at both of the 5 and 6 positions and a side chain at the 2 position of said 6-membered heteroaromatic ring, wherein said side chain terminates with an end group selected from the group consisting of a phosphonic acid, a lower alkyl ester thereof, a carboxylic acid, a lower alkyl ester thereof, a lower alkyl ether and a lower alkylcarboxy.

What is claimed is:

Claim 1. A novel compound having antagonist activity at the $S1P_3$ receptor which is represented by the formula I



$[C(O)_u(R^3)_v]_a(W)_b[C(R^4)_2]_c[P(O)(OR^3)_2]_d[C(O)_x(OR^3)_y(R^3)_z]_e$

I

wherein

X is selected from the group consisting of CR^3 and N;

Y is selected from the group consisting of CR^3 and N;

Z is selected from the group consisting of CR^3 and N;

and at least one of X, Y and Z is N;

W is NR^3 or O;

R^1 is an aryl group;

R^2 is an aryl group;

R^3 is selected from the group consisting of H and alkyl; and 2 of said R^3 groups together with N may form a heterocylic ring having from 2 to 6 carbon atoms;

R^4 is selected from the group consisting of H, alkyl, OR^3, and $N(R^3)_2$;

a is 0 or an integer of from 1 to 6;

b is 0 or 1;

c is 0 or an integer of from 1 to 6;

d is 0 or 1;

e is 0 or 1;

u is 0 or 1;

v is 0 or an integer of from 1 to 2;

x is 0 or 1;

y is 0 or an integer of from 1 to 3;

z is 0 or an integer of from 1 to 3;

provided however that when d is 0, e is 1, and when e is 0, d is 1.

Claim 2. The compound of claim 1 wherein R^1 is selected, from the group consisting of phenyl and substituted derivatives thereof;

R^2 is selected, preferably from the group consisting of phenyl, furanyl, thienyl, pyridyl, pyranyl and substituted derivatives thereof;

R^3 is selected from the group consisting of H and lower alkyl;

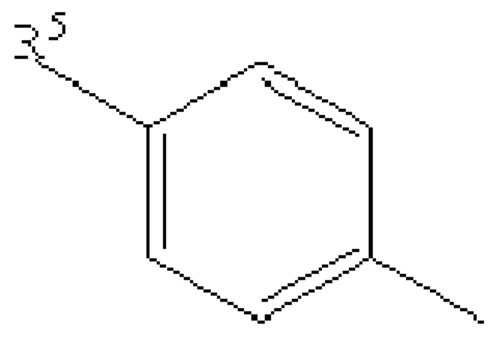
R^4 is selected from the group consisting of H and lower alkyl;

a is 0 or an integer of from 1 to 3;

c is 0 or an integer of from 1 to 5;

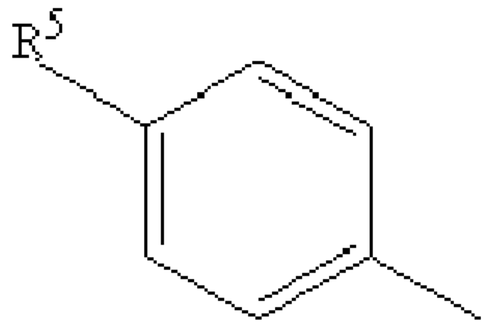
Claim 3. The compound of claim 2, wherein e is 0.

Claim 4. The compound of claim 3, wherein R^1 is represented by the general formula



wherein R^5 is selected from the group consisting of H, alkyl, trifluoromethyl, trifluoromethyloxy, halo and lower alkylthio.

Claim 5. The compound of claim 4, wherein R^2 is selected from the group consisting of furanyl, thienyl, pyridyl and pyranyl or R^2 is

represented by the general formula 

wherein R^5 is selected from the group consisting of H, alkyl, trifluoromethyl, trifluoromethyloxy, halo, and lower alkylthio .

Claim 6. The compound of claim 5 wherein R^3 is H.

Claim 7. The compound of claim 6, wherein c is 1, 2 or 3.

Claim 8. The compound of claim 7, wherein a is 1.

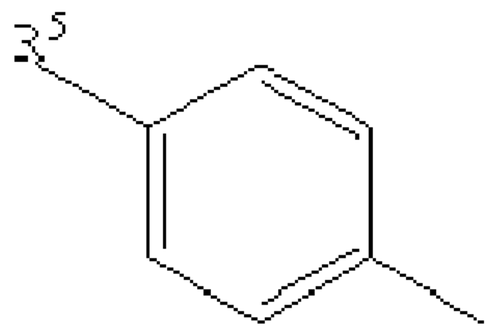
Claim 9. The compound of claim 8, wherein Z is N and X and Y are CR^3.

Claim 10. The compound of claim 9, wherein W is NR^3, R^2 is phenyl and R^5 is selected from the group consisting of H and methyl.

Claim 11. The compound of claim 9, wherein R^2 is pyridyl and R^5 is ethyl, and W is NR^3.

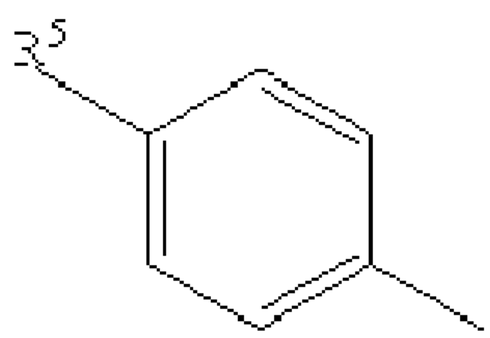
Claim 12. The compound of claim 2, wherein d is 0.

Claim 13. The compound of claim 12, wherein R^1 is represented by the general formula



wherein R^5 is selected from the group consisting of H, alkyl, trifluoromethyl, trifluoromethyloxy, halo, and loweralkylthio

Claim 14. The compound of claim 13, wherein R^2 is represented by the general formula



wherein R^5 is selected from the group consisting of H, lower alkyl, trifluoromethyl, trifluoromethyloxy, halo, and lower alkylthio or R^2 is selected from the group consisting of furanyl, thienyl, pyridyl and pyranyl.

Claim 15. The compound of claim 14 wherein R^3 is H.

Claim 16. The compound of claim 15 wherein a is 1.

Claim 17. The compound of claim 15 wherein x is 1 and z is 0.

Claim 18. The compound of claim 17 wherein R^4 is selected from the group consisting of H, methyl and ethyl,

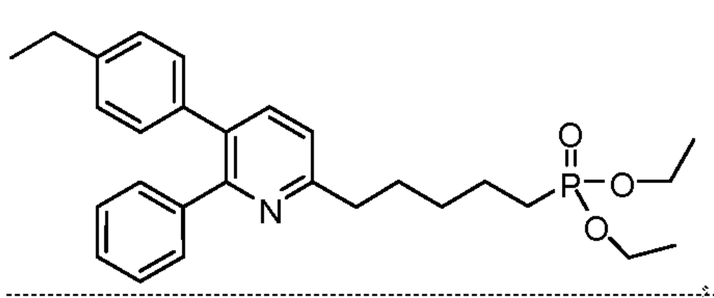
Claim 19. The compound of claim 18 wherein Z is N, X and Y are CR^3, R^2 is pyridyl, and R^5 is selected from the group consisting of H, methyl, ethyl, propyl and trifluoromethyl.

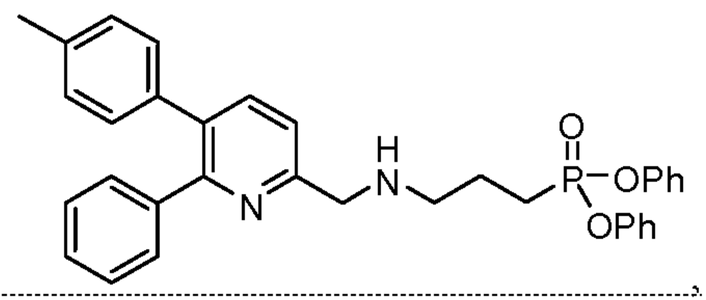
Claim 20. The compound of claim 18 wherein X, Y and Z are N, R^5 is selected from the group consisting of H, methyl, ethyl, propyl and trifluoromethyl.

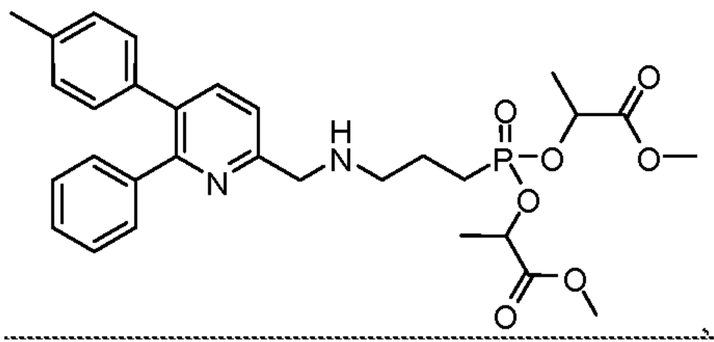
Claim 21. The compound of claim 18 wherein X and Z are N and Y is CR^3.

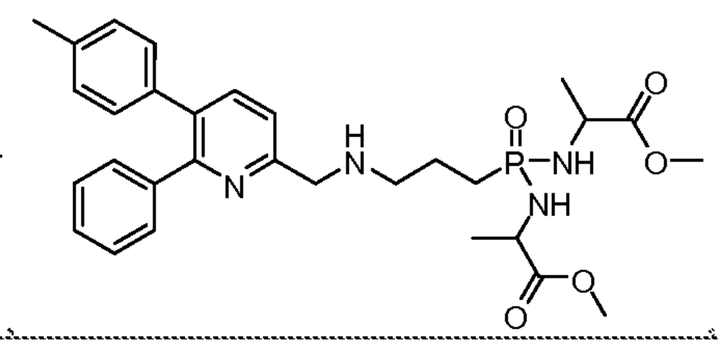
Claim 22. The compound of claim 15 wherein y is 0.

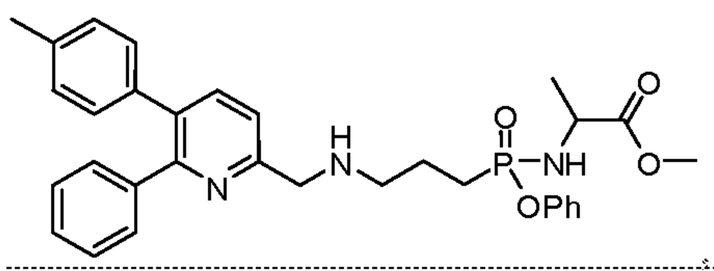
Claim 23. The compound of claim 1 selected from the group consisting of

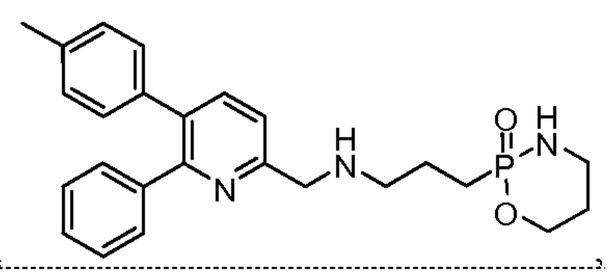


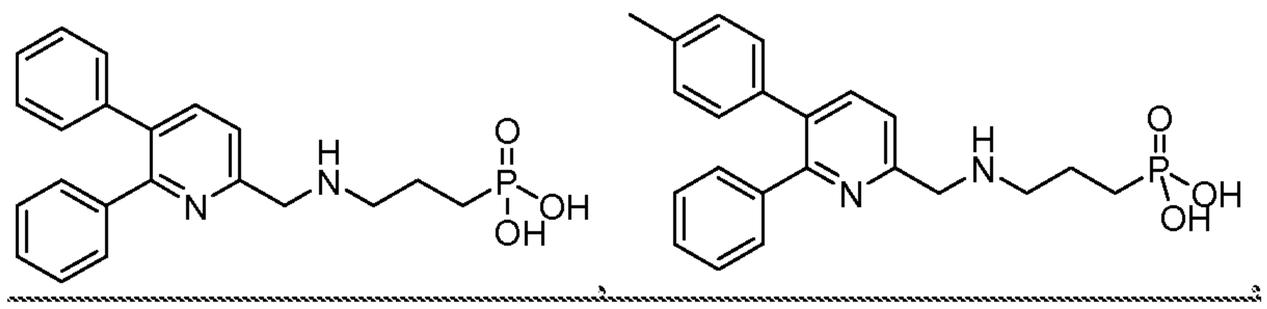


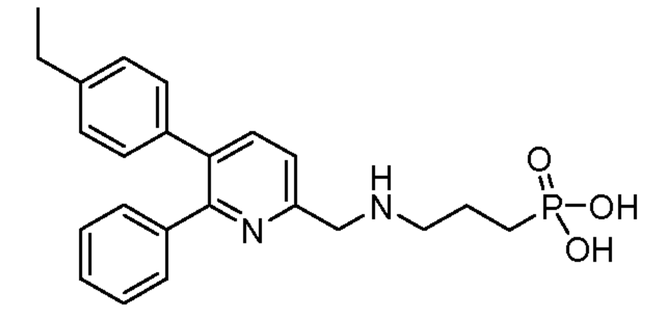


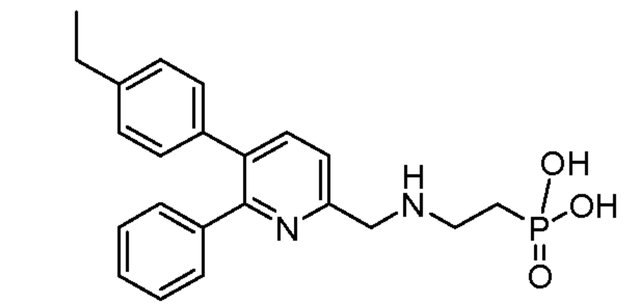


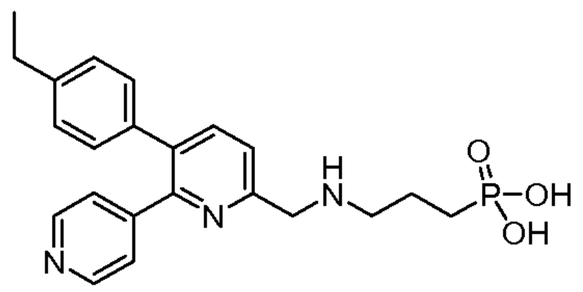


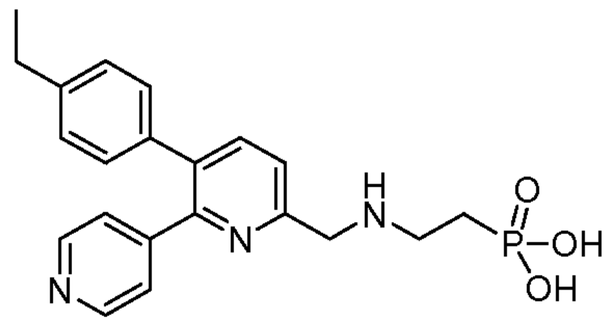


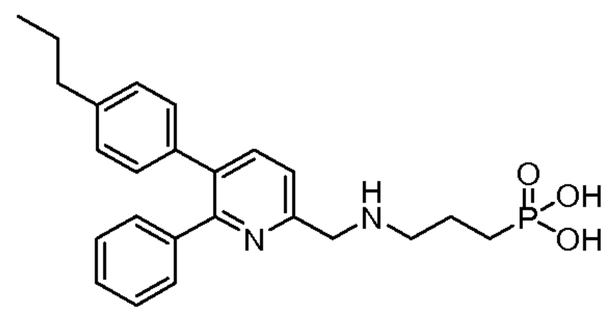


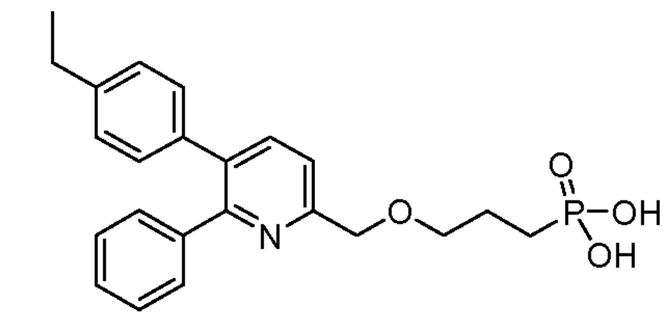


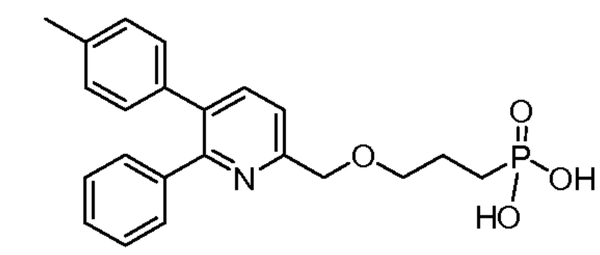












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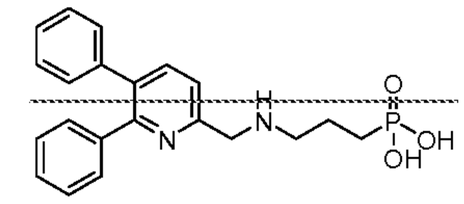
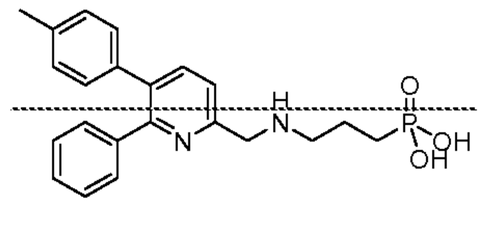
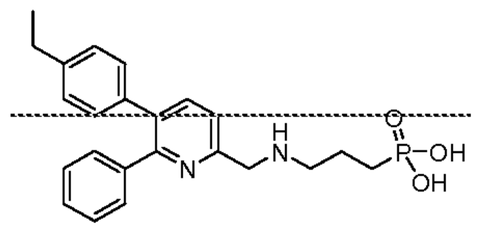
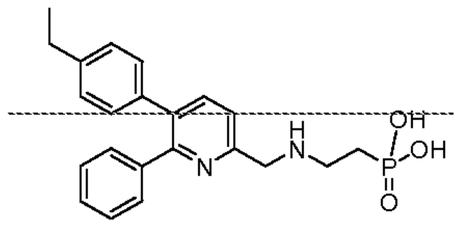
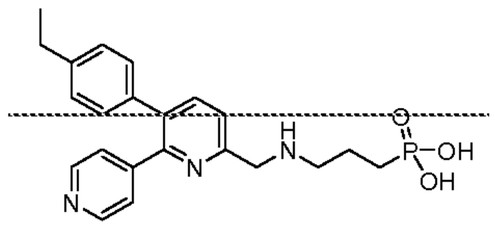
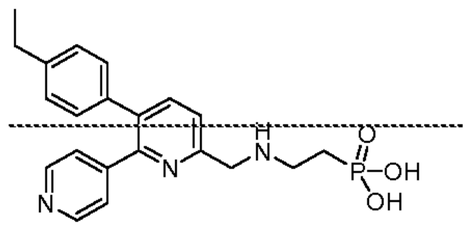


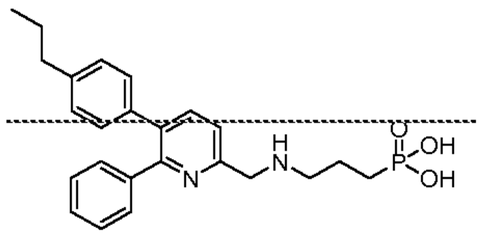


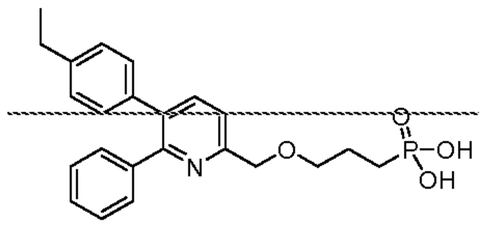


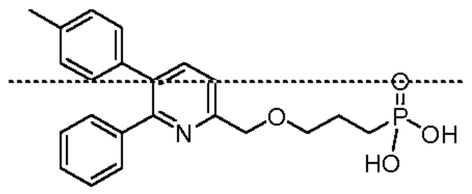


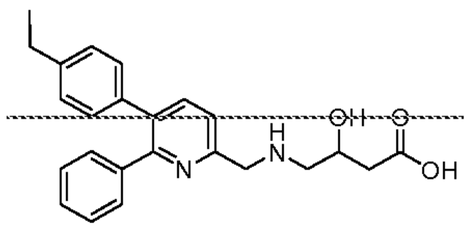




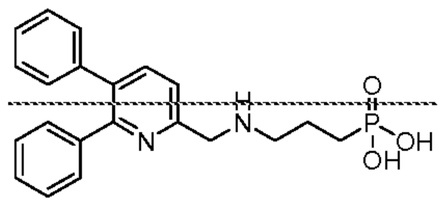


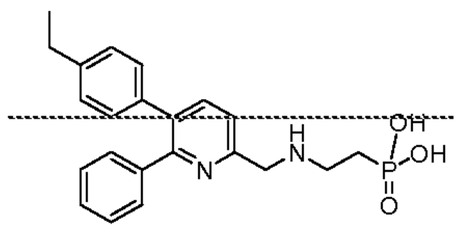


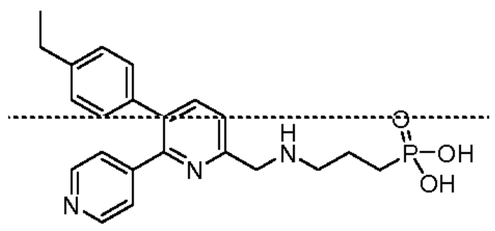


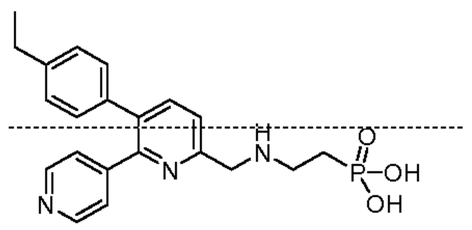


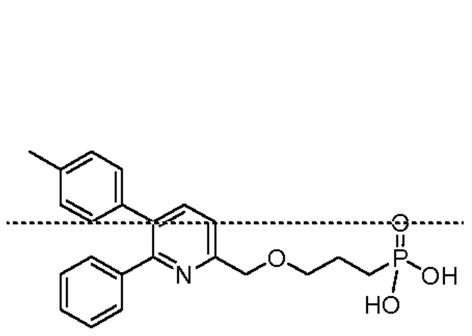
Claim 24. The compound of claim 23 selected from the group consisting of

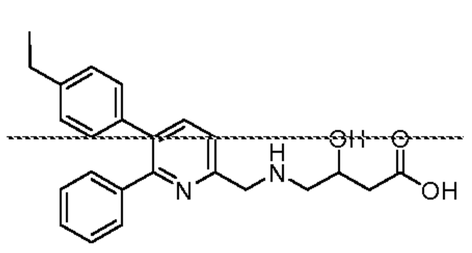








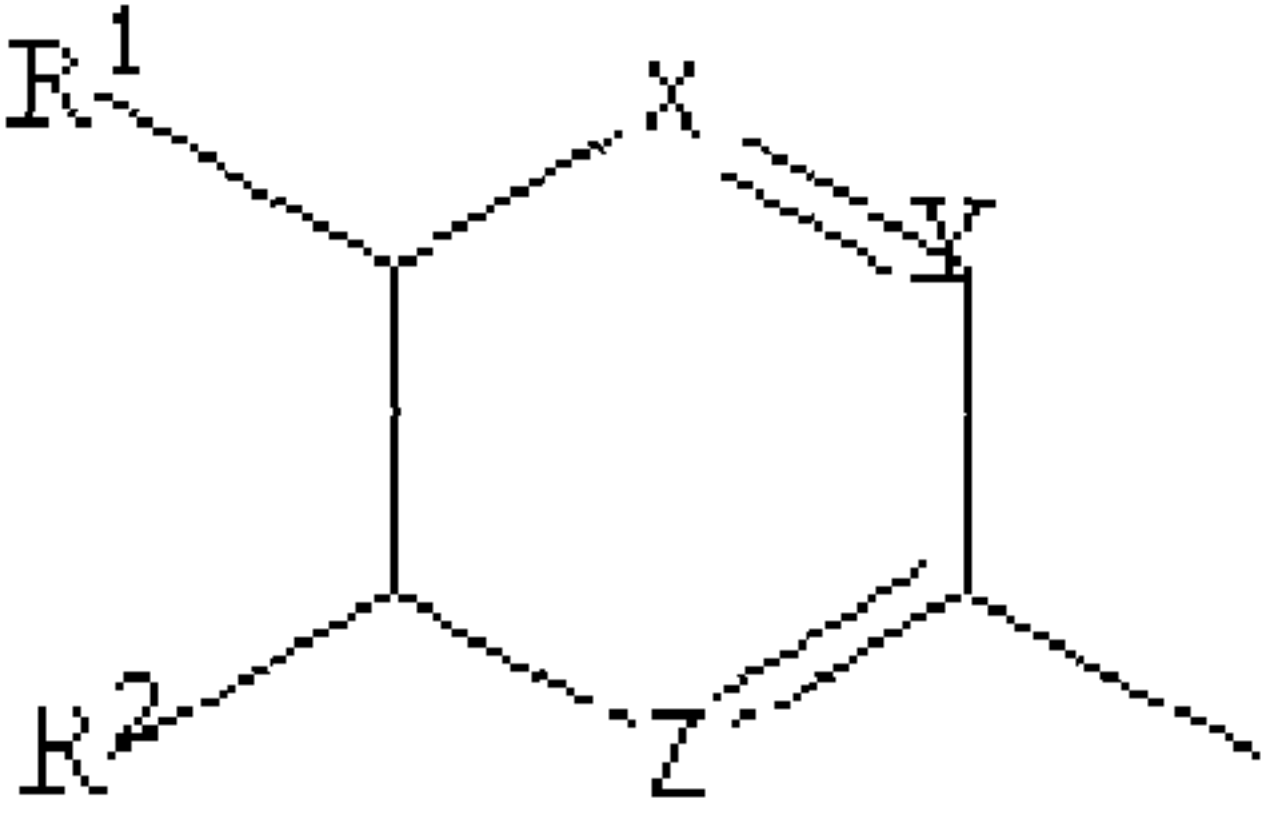




Claim ~~25~~24. A compound having antagonist activity at the $S1P_3$ receptor comprising a 6-membered heteroaromatic ring including one, two or three enchained nitrogen atoms and the remaining ring atoms being carbon, an aryl radical directly bonded to said 6-membered heteroaromatic ring at both of the 5 and 6 positions and a side chain at the 2 position of said 6-membered heteroaromatic ring, wherein said side chain terminates with an end group selected from the group consisting of a phosphonic acid, a lower alkyl ester thereof, a carboxylic acid, a

lower alkyl ester thereof, a lower alkyl ether and a lower alkylcarboxy, and any pharmaceutically acceptable salt thereof.

Claim 2625. The compound of claim 25 wherein said one, two or three enchained nitrogen atoms are at the 1, or 1 and 3, or 1 and 4, or 1, 3 and 4 positions, respectively.


R1
X
Y
R2
Z