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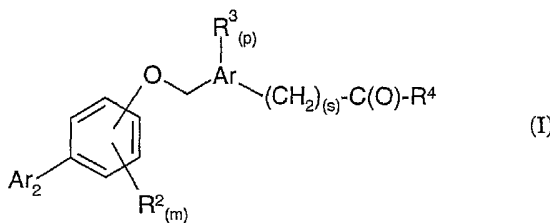
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(54) Title: BIARYLOXYMETHYLARENE CARBOXYLIC ACIDS



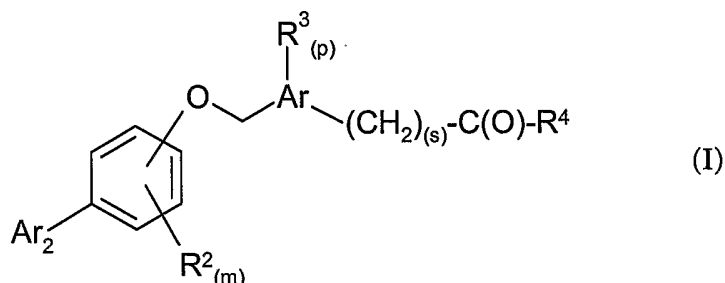
(57) Abstract: The present invention relates to compounds of Formula (I) wherein Ar, Ar₂, R², R³, R⁴, m, p and s are as defined in the description and claims, and pharmaceutically acceptable salts thereof. The compounds are useful for the treatment and/or prophylaxis of diseases that are associated with the activation of the glycogen synthase enzyme, such as diabetes.

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Biaryloxymethylarene-carboxylic acids

The present invention is concerned with novel biaryloxymethylarene-carboxylic acids and their pharmaceutically acceptable salts, their manufacture and their use as medicaments. The present invention further relates to pharmaceutical compositions containing these compounds.

5 In detail, the present invention relates to compounds of the formula (I)



wherein

Ar is an aromatic carbocyclic or heterocyclic ring;

10 Ar₂ is a substituted or unsubstituted cyclic ring selected from the group consisting of benzo[1,3]dioxol-5-yl, furan-2-yl, isoquinolin-5-yl, isoxazol-4-yl, 1-naphthyl, pyrazol-1-yl, pyrazol-4-yl, pyridin-3-yl, thiophen-2-yl, thiophen-3-yl and phenyl, and where substituted the substituents are selected from the group consisting of acetamido, aminocarbonyl, benzyl, benzyloxy, halogen, hydroxyl-lower alkyl, lower alkyl, lower alkoxy-lower alkyl, phenoxy, phenyl, lower alkoxy and trifluoro-methoxy;

15 R² and R³ are independently selected from the group consisting of lower alkyl, lower alkoxy, trifluoromethyl, halogen, hydroxy, amino, alkylamino, dialkylamino, cyano and nitro;

R⁴ is hydroxy or an amino acid attached through a nitrogen atom of the amino acid;

20 m is 0, 1, 2, 3 or 4;

p is 0, 1 or 2, and

s is 0, 1 or 2,

or a pharmaceutically acceptable salt thereof,

provided that when Ar₂ is phenyl, the phenyl ring is substituted by at least one substituent selected from the group consisting of acetamido, aminocarbonyl, benzloxy, hydroxyl-lower alkyl, lower-alkoxy-lower alkyl, phenoxy, phenyl, pyrazol-1-yl and trifluoromethoxy, and

when Ar₂ is phenyl, there are not two lower alkyl substituents ortho to the point of attachment of the Ar₂ ring.

It has been found that compounds of formula I are useful in the treatment and prevention of diabetes, especially type 2 diabetes.

Diabetes mellitus is a common and serious disorder, affecting 10 million people in the U.S. [Harris, M. I. *Diabetes Care* 1998 21 (3S) Supplement, 11C], putting them at increased risk of stroke, heart disease, kidney damage, blindness, and amputation. Diabetes is characterized by decreased insulin secretion and/or an impaired ability of peripheral tissues to respond to insulin, resulting in increased plasma glucose levels. The incidence of diabetes is increasing, and the increase has been associated with increasing obesity and a sedentary life. There are two forms of diabetes: insulin-dependent and non-insulin-dependent, with the great majority of diabetics suffering from the non-insulin-dependent form of the disease, known as type 2 diabetes or non-insulin-dependent diabetes mellitus (NIDDM). Because of the serious consequences, there is an urgent need to control diabetes.

Treatment of NIDDM generally starts with weight loss, a healthy diet and an exercise program. However, these factors are often unable to control the disease, and there are a number of drug treatments available, including insulin, metformin, sulfonylureas, acarbose, and thiazolidinediones. Each of these treatments has disadvantages and there is an ongoing need for new drugs to treat diabetes.

Metformin is an effective agent that reduces fasting plasma glucose levels and enhances the insulin sensitivity of peripheral tissue, mainly through an increase in glycogen synthesis [De Fronzo, R. A. *Drugs* 1999, 58 Suppl. 1, 29]. Metformin also leads to reductions in the levels of LDL cholesterol and triglycerides [Inzucchi, S. E. *JAMA* 2002, 287, 360]. However, it loses its effectiveness over a period of years [Turner, R. C. et al. *JAMA* 1999, 281, 2005].

Thiazolidinediones are activators of the nuclear receptor peroxisome-proliferator activated receptor-gamma. They are effective in reducing blood glucose levels, and their efficacy has been attributed primarily to decreasing insulin resistance in skeletal muscle [Tadayyon, M. and Smith, S.A. *Expert Opin. Investig. Drugs* 2003, 12, 307]. One
5 disadvantage associated with the use of thiazolidinediones is weight gain.

Sulfonylureas bind to the sulfonylurea receptor on pancreatic beta cells, stimulate insulin secretion, and consequently reduce blood glucose levels. Weight gain is also associated with the use of sulfonylureas [Inzucchi, S. E. *JAMA* 2002, 287, 360] and, like metformin, they lose efficacy over time [Turner, R. C. et al. *JAMA* 1999, 281, 2005]. A
10 further problem often encountered in patients treated with sulfonylureas is hypoglycemia [Salas, M. and Caro, J. J. *Adv. Drug React. Tox. Rev.* 2002, 21, 205-217].

Acarbose is an inhibitor of the enzyme alpha-glucosidase which breaks down disaccharides and complex carbohydrates in the intestine. It has lower efficacy than metformin or the sulfonylureas, and it causes intestinal discomfort and diarrhea which
15 often lead to the discontinuation of its use [Inzucchi, S. E. *JAMA* 2002, 287, 360].

Because none of these treatments is effective over the long term without serious side effects, there is a need for new drugs with improved properties for the treatment of type 2 diabetes.

In skeletal muscle and liver, there are two major pathways of glucose utilization:
20 glycolysis, or oxidative metabolism, where glucose is oxidized to pyruvate; and glycogenesis, or glucose storage, where glucose is stored in the polymeric form glycogen. The key step in the synthesis of glycogen is the addition of the glucose derivative UDP-glucose to the growing glycogen chain, and this step is catalyzed by the enzyme glycogen synthase [Cid, E. et al. *J. Biol. Chem.* 2000, 275, 33614]. There are two isoforms of
25 glycogen synthase, found in liver [Bai, G. et al. *J. Biol. Chem.* 1990, 265, 7843] and in other peripheral tissues including muscle [Browner, M. F. et al. *Proc. Nat. Acad. Sci. U. S. A.* 1989, 86, 1443]. There is clinical and genetic evidence implicating glycogen synthase in type 2 diabetes. Both basal and insulin-stimulated glycogen synthase activity in muscle cells from diabetic subjects were significantly lower than in cells from lean non-diabetic
30 subjects [Henry, R. R. et al. *J. Clin. Invest.* 1996, 98, 1231-1236; Nikoulina, S. E. et al. *J. Clin. Endocrinol. Metab.* 2001, 86, 4307-4314]. Furthermore, several studies have shown that levels of glycogen are lower in diabetic patients than in control subjects [Eriksson, J. et al. *N. Engl. J. Med.* 1989, 331, 337; Schulman, R. G. et al. *N. Engl. J. Med.* 1990, 332, 223; Thorburn, A. W. et al. *J. Clin. Invest.* 1991, 87, 489], and in addition, genetic studies
35 have shown associations in several populations between type 2 diabetes and mutation in

the GYS1 gene encoding the muscle isoform of glycogen synthase [Orhu-Melander, M. et al. *Diabetes* 1999, 48, 918].

Glycogen synthase is subject to complex regulation, involving phosphorylation at at least nine sites [Lawrence, J. C., Jr. and Roach, P. J. *Diabetes* 1997, 46, 541]. The
5 dephosphorylated form of the enzyme is active. Glycogen synthase is phosphorylated by a number of enzymes of which glycogen synthase kinase 3 β (GSK3 β) is the best understood [Tadayyon, M. and Smith, S.A. *Expert Opin. Investig. Drugs* 2003, 12, 307], and glycogen synthase is dephosphorylated by protein phosphatase type I (PP1) and protein phosphatase type 2A (PP2A). In addition, glycogen synthase is regulated by an
10 endogenous ligand, glucose-6-phosphate which allosterically stimulates the activity of glycogen synthase by causing a change in the conformation of the enzyme that renders it more susceptible to dephosphorylation by the protein phosphatases to the active form of the enzyme [Gomis, R. R. et al. *J. Biol. Chem.* 2002, 277, 23246].

Several mechanisms have been proposed for the effect of insulin in reducing blood
15 glucose levels, each resulting in an increase in the storage of glucose as glycogen. First, glucose uptake is increased through recruitment of the glucose transporter GLUT4 to the plasma membrane [Holman, G. D. and Kasuga, M. *Diabetologia* 1997, 40, 991]. Second, there is an increase in the concentration of glucose-6-phosphate, the allosteric activator of glycogen synthase [Villar-Palasi, C. and Guinovart, J. J. *FASEB J.* 1997, 11, 544]. Third,
20 a kinase cascade beginning with the tyrosine kinase activity of the insulin receptor results in the phosphorylation and inactivation of GSK3 β , thereby preventing the deactivation of glycogen synthase [Cohen, P. *Biochem. Soc. Trans.* 1993, 21, 555; Yeaman, S. J. *Biochem. Soc. Trans.* 2001, 29, 537].

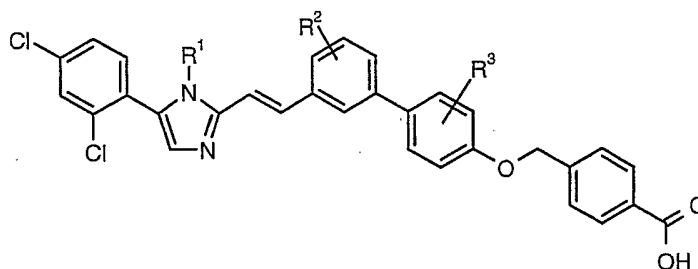
Because a significant decrease in the activity of glycogen synthase has been found in
25 diabetic patients, and because of its key role in glucose utilization, the activation of the enzyme glycogen synthase holds therapeutic promise for the treatment of type 2 diabetes. The only known allosteric activators of the enzyme are glucose-6-phosphate [Leloir, L. F. et al. *Arch. Biochem. Biophys.* 1959, 81, 508] and glucosamine-6-phosphate [Virkamaki, A. and Yki-Jarvinen, H. *Diabetes* 1999, 48, 1101].

30 Briefly stated, biaryloxymethylarene-carboxylic acids as described herein have been found to be glycogen synthase activators. Consequently, the compounds of the present invention are useful for the treatment and/or prophylaxis of type 2 diabetes, and/or impaired glucose tolerance, as well as other conditions wherein the activation of the glycogen synthase enzyme gives a therapeutic benefit.

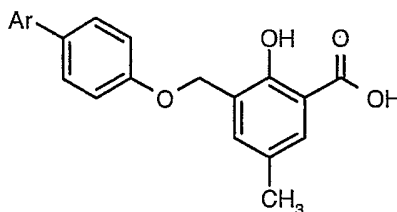
Some biaryloxymethylarene-carboxylic acids are known in the art. However, none of these known compounds have been associated with either the treatment of diseases mediated by the activation of the glycogen synthase enzyme or to any pharmaceutical composition for the treatment of diseases mediated by the activation of the glycogen synthase enzyme.

H. S. Andersen et al. (PCT Int. Appl. WO 9740017) disclose the structure and synthetic route to 3-(biphenyl-4-yloxymethyl)-benzoic acid as an intermediate in the synthesis of SH2 inhibitors. E. Winkelmann et al. (DE 2842243) disclose 5-(biphenyl-4-yloxymethyl)-thiophene-2-carboxylic acid as a hypolipemic agent.

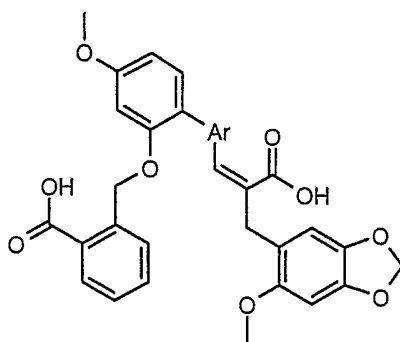
M. M. Mjalli et al. (Transtech Pharma Inc., PCT Int. Appl. WO 2004071447) disclose 375 compounds as inhibitors of protein tyrosine phosphatase for the treatment of diabetes. Eleven of these compounds have the following general structure.



S. S. Ghosh et al. (Mitokor, Inc., PCT Int. Appl. WO 2004058679) disclose compounds with the following general structure as ligands of adenine nucleotide translocase for the treatment of a variety of diseases including Alzheimer's disease, diabetes and obesity.

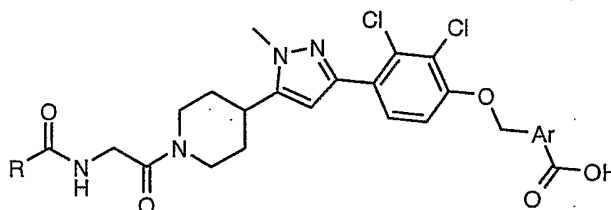


A number of patents and patent applications from SmithKline Beecham and The University of Illinois disclose compounds with the general structure shown below as endothelin receptor antagonists for the treatment of renal failure, cerebrovascular disease, congestive heart failure, etc. or for the treatment of Alzheimer's disease. Among these patents and patent applications are the following: PCT Int. Appl. WO 9704773, US 5985886, PCT Int. Appl. WO 9704781, PCT Int. Appl. WO 9704774, PCT Int. Appl. WO 9607653, US 2003004202, PCT Int. Appl. WO 9630358, and PCT Int. Appl. WO 2004028634.

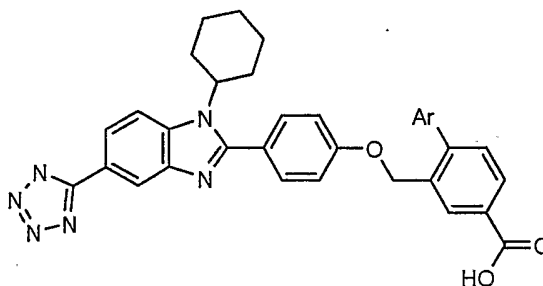


T. Inaba et al (Japan Tobacco, Inc., PCT Int. Appl. WO 2003048140) disclose 4-[[4-[4-[(4-carboxyphenyl)methoxy]phenyl]-2-thiazolyl]methyl]-benzoic acid (CAS Number 540734-96-1) as an inhibitor of protein tyrosine phosphatase 1B.

- 5 C. Braisted et al., *J. Am. Chem. Soc.* 2003, 125, 3714-3715, disclose compounds with the following general structure as IL-2 inhibitors useful for the treatment of inflammation.



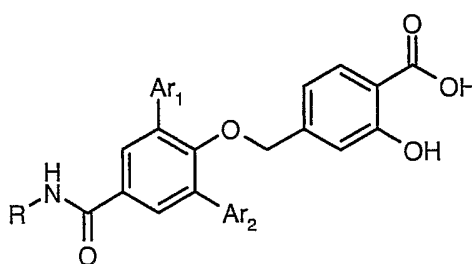
- 10 E. S. Priestley et al. (Bristol-Myers Squibb Company, USA, PCT Int. Appl. WO 2003026587) and H. Hashimoto et al. (Japan Tobacco, Inc., PCT Int. Appl. WO 2003000254) disclose compounds with the following general structure for the treatment of Hepatitis C.



- 15 H. Shinkai et al. (Japan Tobacco Inc., PCT Int. Appl. WO 2001027088) disclose 2-[[2-chloro-5-[5-(1,1-dimethylethyl)-1H-benzimidazol-2-yl]phenoxy]methyl]-benzoic acid (CAS Number 335014-96-5) as a lipoprotein lipase enhancer for the treatment of arteriosclerosis.

P. Lacombe et al. (Merck Frosst Canada & Co., PCT Int. Appl. WO 2001019814) and T. P. Broten et al. (Merck Frosst Canada & Co., PCT Int. Appl. WO 2002015902) disclose 3-[3-[2-[(4-carboxyphenyl)methoxy]-5-chlorophenyl]-2-thienyl]-benzoic acid (CAS Number 330811-34-2) and 4-[3-[2-[(4-carboxyphenyl)methoxy]-5-chlorophenyl]-2-thienyl]-benzoic acid (CAS Number 330811-33-1) for the treatment of prostaglandin-mediated diseases such as urinary incontinence.

J. Butera et al. (American Home Products Corporation, US 6214877 and PCT Int. Appl. WO 9961410) disclose compounds of the following general structure as inhibitors of protein tyrosine phosphatase for the treatment of diabetes.



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T. Mueller et al. (DE 4142514) disclose 2-(biphenyl-3-yloxymethyl)-benzoic acid and 3-(biphenyl-3-yloxymethyl)-benzoic acid as fungicides.

Marfat et al. (Pfizer Inc., US 5322847 and PCT Int. Appl. WO 9117163) disclose 3-[[4-(2-methyl-1H-imidazo[4,5-c]pyridin-1-yl)phenoxy]methyl]-benzoic acid as a platelet activating factor blocker and leukotriene D4 receptor blocker useful in the treatment of illnesses including myocardial infarction and stroke.

F. J. Brown et al., *J. Med. Chem.* 1989, 32, 807-826 disclose 4-[[3-hydroxy-2-propyl-4-(2-quinolinyl)phenoxy]methyl]-3-methoxy-benzoic acid (CAS Number 118683-37-7) as a compound tested in a assay for leukotriene D4 antagonist activity.

M. Isogai et al. (Hitachi, Ltd., Eur. Par. Appl. EP 110299) disclose 4-[[[4'-(octyloxy)[1,1'-biphenyl]-4-yl]oxy]methyl]-benzoic acid as an intermediate useful in the preparation of liquid crystal compositions.

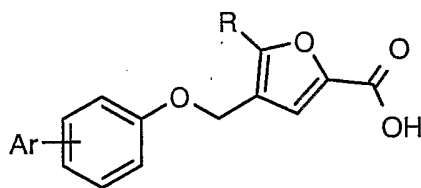
G. L. Araldi et al. (Applied Research Systems Ars Holding N.V., PCT Int. Appl. WO 2004012656) disclose 5-[[4-(2-benzoxazolyl)phenoxy]methyl]-2-furancarboxylic acid, (CAS Number 654665-86-8), 5-[[4-(1,3,4-oxadiazol-2-yl)phenoxy]methyl]-2-furancarboxylic acid (CAS Number 654665-84-6), and 5-[[[1,1'-biphenyl]-4-yloxy]methyl]-2-furan-carboxylic acid (CAS Number 327990-68-1) as prostaglandin EP2 agonists, useful for the treatment of illnesses such as asthma, inflammatory diseases, infertility, and osteoporosis. One of these compounds, 5-[[[1,1'-biphenyl]-4-

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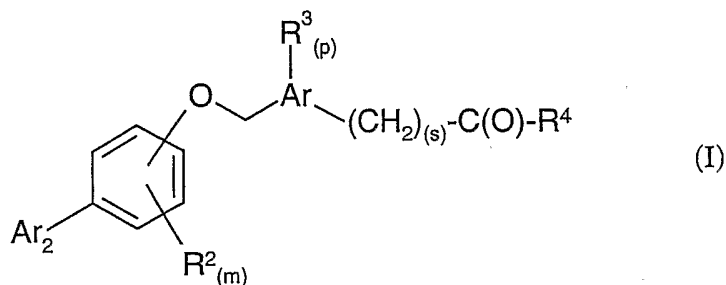
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oxy)methyl]-2-furan-carboxylic acid, is commercially available from ChemDiv, Inc., San Diego, CA, and Ambinter SARL, Paris, France.

D. E. Clark et al. (Pharmagene Laboratories Ltd., PCT Int. Appl. WO 2004067524) disclose compounds with the following general structure as prostaglandin EP4 receptor antagonists useful for the treatment of pain, including migraine. One of these compounds (4-(biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid) is commercially available from ChemBridge Corporation, San Diego, CA, and TimTec, Inc. Newark, DE.



10 According to one aspect of the present invention, there are provided compounds of formula (I)



wherein Ar, Ar₂, R², R³, R⁴, m, p and s are as defined below.

15 According to another aspect of the present invention, there are provided pharmaceutical compositions comprising a compound of formula (I), or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier and/or adjuvant.

20 According to a further aspect of the present invention, there are provided uses for the preparation of medicaments for treating or preventing diseases which are associated with activation of the glycogen synthase enzyme, comprising a therapeutically effective amount of a compound of formula (I).

These and other features, aspects and advantages of the present invention will become better understood with reference to the following description and claims.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this application, the term "lower" is used to mean a group consisting of one to seven, preferably of one to four carbon atom(s).

5 The term "halogen" refers to fluorine, chlorine, bromine and iodine, preferably to fluorine and chlorine.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon
10 atoms.

Alkyl groups can optionally be substituted e.g. with halogen, hydroxy, lower-alkoxy, lower-alkoxy-carbonyl, NH_2 , N(H, lower-alkyl) and/or N(lower-alkyl)_2 . Unsubstituted alkyl groups are preferred.

The term "lower-alkyl", alone or in combination with other groups, refers to a
15 branched or straight-chain monovalent alkyl radical of one to seven carbon atoms, preferably one to four carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl and the like. A lower-alkyl group may optionally have a substitution pattern as described earlier in connection with the term "alkyl". Unsubstituted lower-alkyl groups are preferred.

20 The term "alkoxy" refers to the group $\text{R}'\text{-O-}$, wherein R' is alkyl. The term "lower-alkoxy" refers to the group $\text{R}'\text{-O-}$, wherein R' is lower-alkyl. Examples of lower-alkoxy groups are e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and hexyloxy. Alkoxy and lower-alkoxy groups may optionally have a substitution pattern as described earlier in connection with the term "alkyl". Unsubstituted alkoxy and lower-alkoxy
25 groups are preferred.

The term "amino acid" refers to both natural amino acids, to their enantiomers, and to unnatural amino acids. Natural amino acids include alanine (Ala), arginine (Arg), asparagine (Asn), aspartic acid (Asp), cysteine (Cys), glutamine (Gln), glutamic acid (Glu), glycine (Gly), histidine (His), isoleucine (Ile), leucine (Leu), lysine (Lys),
30 methionine (Met), phenylalanine (Phe), proline (Pro), serine (Ser), threonine (Thr), tryptophan (Trp), tyrosine (Tyr) and valine (Val). Unnatural amino acids include, but are not limited to azetidinedicarboxylic acid, 2-aminoadipic acid, 3-aminoadipic acid, beta-alanine, 2-aminobutyric acid, 4-aminobutyric acid, 6-aminocaproic acid, 2-aminoheptanoic acid, 2-aminoisobutyric acid, 3-aminoisobutyric acid, 2-aminopimelic

acid, 2,4 diaminoisobutyric acid, 2,2'-diaminopimelic acid, 2,3-diaminopropionic acid, N-ethylglycine, N-ethylasparagine, hydroxylysine, allo-hydroxylysine, 3-hydroxyproline, 4-hydroxyproline, allo-isoleucine, N-methylglycine, N-methylisoleucine, N-methylvaline, norvaline, norleucine, ornithine and pipercolic acid.

5 The term "aryl" relates to an aromatic carbocyclic or heterocyclic ring or ring system, preferably having from 5 to 6 carbon atoms. Examples of aryl groups include phenyl, furanyl, thiophenyl, pyridinyl, thiazolyl and oxazolyl, which can optionally be mono- or multiply-substituted by lower-alkyl, lower-alkoxy, halogen, CN, CF₃, hydroxy, NO₂, NH₂, N(H, lower-alkyl) and/or N(lower-alkyl)₂. Preferred substituents are lower-
10 alkyl, lower-alkoxy, halogen, and/or NO₂.

 The term "carbocyclic ring" refers to a substituted or unsubstituted monocyclic or bicyclic aromatic hydrocarbon ring system of 5 to 10 members, preferably 5 or 6 members. Preferred groups include phenyl, naphthyl, tolyl, xylyl, etc., especially preferred are phenyl or naphthyl.

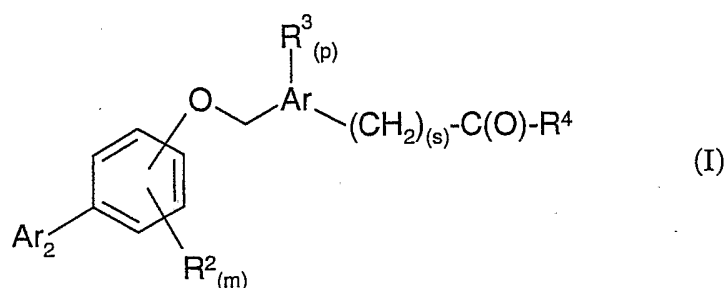
15 The term "heterocyclic ring" refers to a 5- or 6-membered ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulfur such as tetrahydropyridine, dihydrofuran, dihydropyran, furyl, pyrrolyl, pyridyl, 1,2-, 1,3- and 1,4-diazinyl, thienyl, oxazolyl, oxadiazolyl, isoxazolyl, thiazolyl, isothiazolyl or imidazolyl. The heterocyclic ring may be optionally substituted with an aryl group or have a substitution pattern as
20 described earlier in connection with the term "aryl".

 The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, fumaric acid, succinic acid, tartaric acid, methanesulfonic acid, p-toluenesulfonic acid
25 and the like, which are non toxic to living organisms. Preferred salts with acids are formates, maleates, citrates, hydrochlorides, hydrobromides and methanesulfonic acid salts.

 This term also encompasses carboxylate salts having organic and inorganic cations, such as alkali and alkaline earth metal cations (for example, lithium, sodium, potassium,
30 magnesium, barium and calcium); ammonium; or organic cations, for example, dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl) ammonium, phenylethylbenzylammonium, and the like. Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, and the protonated forms of basic amino acids such as glycine,
35 ornithine, histidine, phenylglycine, lysine, and arginine.

The term "leaving group" relates to a group which is removed or replaced during a reaction. Examples of leaving groups are halogen, mesylate and tosylate.

In detail, the present invention relates to compounds of formula (I)



5 wherein

Ar is an aromatic carbocyclic or heterocyclic ring;

Ar₂ is a substituted or unsubstituted cyclic ring selected from the group consisting of benzo[1,3]dioxol-5-yl, furan-2-yl, isoquinolin-5-yl, isoxazol-4-yl, 1-naphthyl, pyrazol-1-yl, pyrazol-4-yl, pyridin-3-yl, thiophen-2-yl, thiophen-3-yl and phenyl, and where
 10 substituted the substituents are selected from the group consisting of acetamido, aminocarbonyl, benzyl, benzyloxy, halogen, hydroxyl-lower alkyl, lower alkyl, lower alkoxy-lower alkyl, phenoxy, phenyl, lower alkoxy and trifluoro-methoxy;

R² and R³ are independently selected from the group consisting of lower alkyl, lower alkoxy, trifluoromethyl, halogen, hydroxy, amino, alkylamino, dialkylamino, cyano
 15 and nitro;

R⁴ is hydroxy or an amino acid attached through a nitrogen atom of the amino acid;

m is 0, 1, 2, 3 or 4;

p is 0, 1 or 2, and

20 s is 0, 1 or 2,

or a pharmaceutically acceptable salt thereof,

provided that when Ar₂ is phenyl, the phenyl ring is substituted by at least one substituent selected from the group consisting of acetamido, aminocarbonyl, benzloxy, hydroxyl-lower alkyl, lower-alkoxy-lower alkyl, phenoxy, phenyl, pyrazol-1-yl and
 25 trifluoromethoxy, and

when Ar₂ is phenyl, there are not two lower alkyl substituents ortho to the point of attachment of the Ar₂ ring.

Compounds of formula (I) represent a preferred embodiment of the present invention and pharmaceutically acceptable salts of compounds of formula (I)
5 individually also represent a preferred embodiment of the present invention.

Some preferred compounds of formula (I) are those, wherein Ar₂ is a substituted or unsubstituted cyclic ring selected from the group consisting of benzo[1,3]dioxol-5-yl, furan-2-yl, isoquinolin-5-yl, isoxazol-4-yl, 1-naphthyl, pyrazol-1-yl, pyrazol-4-yl, pyridin-3-yl, thiophen-2-yl, and thiophen-3-yl, and where substituted the substituents
10 are selected from the group consisting of acetamido, aminocarbonyl, benzyl, benzyloxy, halogen, hydroxyl-lower alkyl, lower alkyl, lower alkoxy-lower alkyl, phenoxy, phenyl, lower alkoxy and trifluoro-methoxy.

More preferred are those compounds of formula (I), wherein Ar₂ is pyridine-3-yl.

Within this group, those compounds of formula (I), wherein Ar₂ is pyridin-3-yl
15 substituted by halogen, are especially preferred.

Another group of preferred compounds of formula (I) are those, wherein Ar₂ is 1-naphthyl.

Further preferred compounds of formula (I) are those, wherein Ar₂ is benzo[1,3]dioxol-5-yl.

20 Also preferred are compounds of formula (I), wherein Ar₂ is thiophen-3-yl.

Furthermore, compounds of formula (I) of the present invention are preferred, wherein Ar₂ is phenyl substituted by at least one substituent selected from the group consisting of acetamido, aminocarbonyl, benzloxy, hydroxyl-lower alkyl, lower-alkoxy-lower alkyl, phenoxy, phenyl, pyrazol-1-yl and trifluoromethoxy.

25 Especially preferred are those compounds of formula (I), wherein Ar₂ is phenyl substituted in the meta position by acetamido, aminocarbonyl or hydroxymethyl.

Also especially preferred are compounds of formula (I), wherein Ar₂ is phenyl substituted in the ortho position by trifluoromethoxy.

Another group of especially preferred compounds of formula (I) are those, wherein
30 Ar₂ is phenyl substituted in the ortho position by methoxymethyl, benzyloxy or phenoxy.

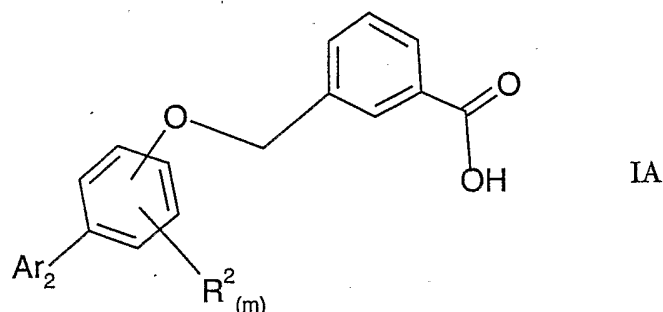
Furthermore, those compounds of formula (I) according to the invention are preferred, wherein Ar is selected from the group consisting of phenyl, thiazolyl and pyridyl.

Preferred are also compounds of formula (I), wherein p is 0.

- 5 Also preferred are compounds of formula (I) according to the present invention, wherein R⁴ is hydrogen.

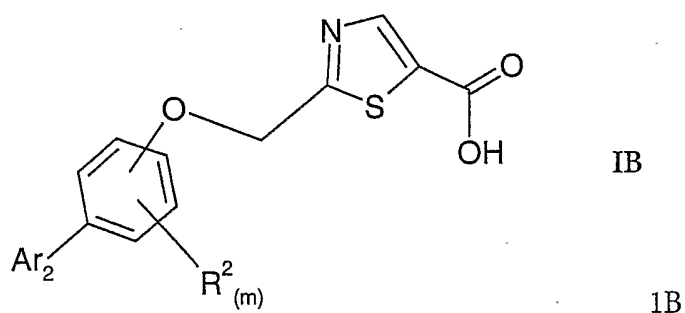
Further preferred compounds of formula (I) are those, wherein s is 0.

A preferred group of compounds of formula (I) are those having the formula



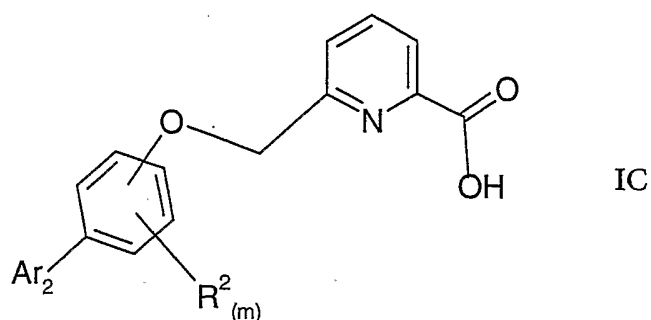
- 10 wherein Ar₂, R² and m are as defined herein before, and the pharmaceutically acceptable salts thereof.

Another group of preferred compounds of formula (I) are those having the formula



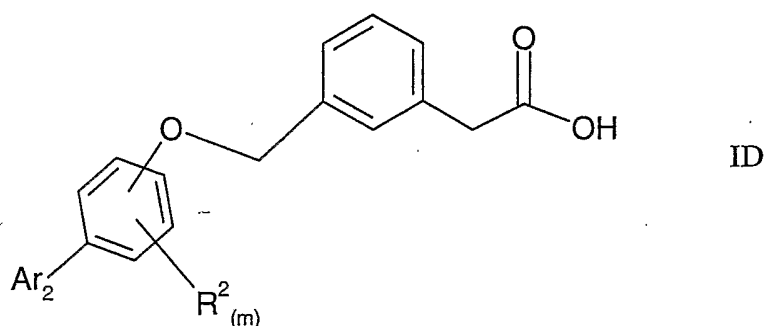
- 15 wherein Ar₂, R² and m are as defined herein before, and the pharmaceutically acceptable salts thereof.

Also preferred are compounds of formula (I) according to the invention having the formula



wherein Ar_2 , R^2 and m are as defined in claim 1, and the pharmaceutically acceptable salts thereof.

A further group of preferred compounds of formula (I) are those having the formula



wherein Ar_2 , R^2 and m are as defined in claim 1, and the pharmaceutically acceptable salts thereof.

Other preferred compounds of general formula (I) are those selected from the group consisting of

- 3-(3'-acetylamino-biphenyl-4-yloxymethyl)-benzoic acid;
- 3-(4-benzo[1,3]dioxol-5-yl-phenoxy-methyl)-benzoic acid;
- 15 3-(3'-carbamo-yl-biphenyl-4-yloxymethyl)-benzoic acid;
- 3-[4-(2-chloro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid;
- 3-[4-(6-chloro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid;
- 3-[4-(3,5-dimethyl-isoxazol-4-yl)-phenoxy-methyl]-benzoic acid;

- 3-[4-(2-fluoro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid;
3-[4-(6-fluoro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid;
3-(4-furan-2-yl)-phenoxy-methyl)-benzoic acid;
3-(3'-hydroxymethyl-biphenyl-4-yl)-oxy-methyl)-benzoic acid;
5 3-(4-isoquinolin-5-yl)-phenoxy-methyl)-benzoic acid;
3-(2'-methoxymethyl-biphenyl-4-yl)-oxy-methyl)-benzoic acid;
3-(3'-methoxymethyl-biphenyl-4-yl)-oxy-methyl)-benzoic acid;
3-(4-naphthalen-1-yl)-phenoxy-methyl)-benzoic acid;
3-(2'-phenoxy-biphenyl-4-yl)-oxy-methyl)-benzoic acid;
10 3-(3'-pyrazol-1-yl-biphenyl-4-yl)-oxy-methyl)-benzoic acid;
3-(4-pyridin-3-yl)-phenoxy-methyl)-benzoic acid;
3-(4-thiophen-3-yl)-phenoxy-methyl)-benzoic acid;
3-(2'-trifluoromethoxy-biphenyl-4-yl)-oxy-methyl)-benzoic acid;
3-(4'-trifluoromethoxy-biphenyl-4-yl)-oxy-methyl)-benzoic acid;
15 2-(3'-acetylamino-biphenyl-4-yl)-oxy-methyl)-thiazole-4-carboxylic acid;
2-(4-benzo[1,3]dioxol-5-yl)-phenoxy-methyl)-thiazole-4-carboxylic acid;
2-(2'-benzyloxy-biphenyl-4-yl)-oxy-methyl)-thiazole-4-carboxylic acid;
2-[4-(1-benzyl-1H-pyrazol-4-yl)-phenoxy-methyl]-thiazole-4-carboxylic acid;
2-([1,1';3',1'']terphenyl-4-yl)-oxy-methyl)-thiazole-4-carboxylic acid;
20 2-(3'-carbamoyl-biphenyl-4-yl)-oxy-methyl)-thiazole-4-carboxylic acid;
2-[4-(2-chloro-pyridin-3-yl)-phenoxy-methyl]-thiazole-4-carboxylic acid;
2-[4-(6-fluoro-pyridin-3-yl)-phenoxy-methyl]-thiazole-4-carboxylic acid;
2-(3'-hydroxymethyl-biphenyl-4-yl)-oxy-methyl)-thiazole-4-carboxylic acid;

- 2-(4-isoquinolin-5-yl-phenoxyethyl)-thiazole-4-carboxylic acid;
- 2-(2'-methoxyethyl-biphenyl-4-yloxyethyl)-thiazole-4-carboxylic acid;
- 2-(3'-methoxyethyl-biphenyl-4-yloxyethyl)-thiazole-4-carboxylic acid;
- 2-(4-naphthalen-1-yl-phenoxyethyl)-thiazole-4-carboxylic acid;
- 5 2-(2'-phenoxy-biphenyl-4-yloxyethyl)-thiazole-4-carboxylic acid;
- 2-(4-thiophen-3-yl-phenoxyethyl)-thiazole-4-carboxylic acid;
- 2-(2'-trifluoromethoxy-biphenyl-4-yloxyethyl)-thiazole-4-carboxylic acid;
- 6-(4-benzo[1,3]dioxol-5-yl-phenoxyethyl)-pyridine-2-carboxylic acid;
- 6-(2'-methoxyethyl-biphenyl-4-yloxyethyl)-pyridine-2-carboxylic acid;
- 10 6-(4-thiophen-2-yl-phenoxyethyl)-pyridine-2-carboxylic acid;
- [3-(3'-acetylamino-biphenyl-4-yloxyethyl)-phenyl]-acetic acid;
- [3-(3'-hydroxyethyl-biphenyl-4-yloxyethyl)-phenyl]-acetic acid;
- [3-(2'-methoxyethyl-biphenyl-4-yloxyethyl)-phenyl]-acetic acid;
- {3-[4-(2-methoxy-pyridin-3-yl)-phenoxyethyl]-phenyl}-acetic acid;
- 15 [3-(2'-trifluoromethoxy-biphenyl-4-yloxyethyl)-phenyl]-acetic acid;

and the pharmaceutically acceptable salts thereof.

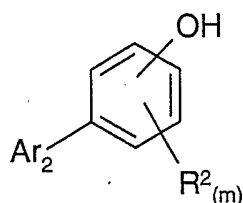
Compounds of formula (I) that have one or more asymmetric carbon atoms can exist in the form of optically pure enantiomers or as racemates. The invention embraces all of these forms.

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

The invention further relates to a process for the preparation of a compound of formula (I), which process comprises

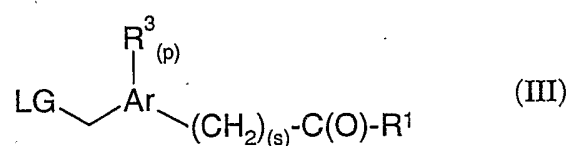
- 17 -

a) reacting a compound of formula (II)



(II)

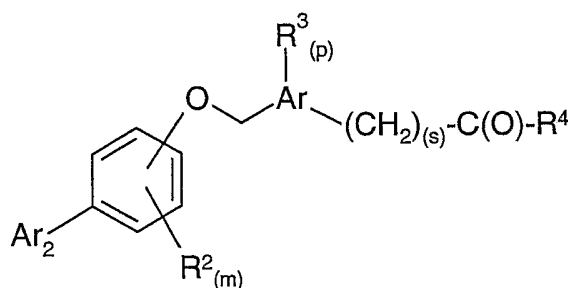
wherein Ar_2 , R^1 , R^2 , m and n are as defined herein before,
in the presence of a base with a compound of formula (III)



(III)

5

wherein Ar , R^3 , p and s are as defined herein before, LG represents a leaving group such as chloro, bromo or iodo, and R^1 represents a protecting group, and subsequently cleaving the protecting group to obtain a compound of formula (I)



(I)

10

wherein R^4 signifies hydroxy, and Ar , Ar_2 , R^2 , R^3 , m , n , p and s are as defined herein before, and

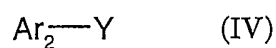
optionally reacting this compound with an ester of an amino acid in the presence of EDC and DMAP and subsequently cleaving the ester group, to obtain a compound of formula I, wherein R^4 is an amino acid attached through a nitrogen atom of the

15

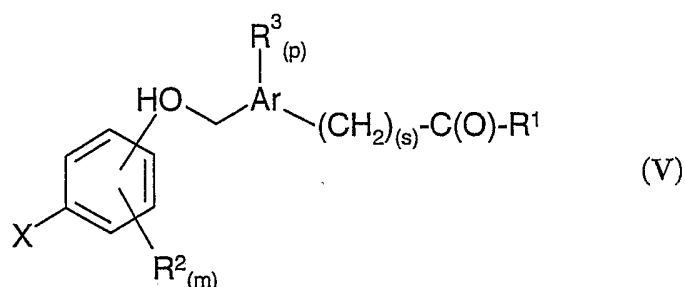
amino acid, or

alternatively,

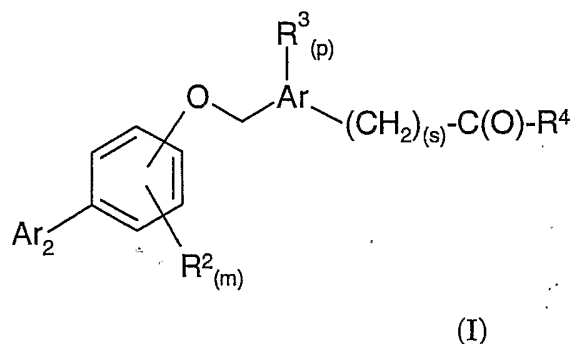
b) reacting a compound of formula (IV)



wherein Ar₂ is as defined herein before and Y represents B(OH)₂, in the presence of a catalytic amount of a palladium (0) complex, with a compound of formula (V)



5 wherein Ar, R², R³, m, p and s are as defined herein before, X represents a leaving group such as bromo, iodo or triflate, and R¹ represents a protecting group, and subsequently cleaving the protecting group to obtain a compound of formula (I)



10 wherein R⁴ signifies hydroxy, and Ar, R², R³, m, n, p and s are as defined herein before, and optionally reacting this compound with an ester of an amino acid in the presence of EDC and DMAP and subsequently cleaving the ester group, to obtain a compound of formula I, wherein R⁴ is an amino acid attached through a nitrogen atom of the amino acid.

15 As described above, the compounds of formula I of the present invention may be used as medicaments for the treatment and/or prophylaxis of diseases mediated by the activation of the glycogen synthase enzyme. Preferably, the compounds of the present invention may be used to treat type 2 diabetes or impaired glucose tolerance.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

20 The compounds of formula I and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally,

e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

5 The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula (I) and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible
10 solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for
15 example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and
20 vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

25 Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavor-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula I can vary within wide limits depending
30 on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 100 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or
35 several daily dosage units, e.g. in 1 to 4 dosage units.

The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula I.

The following examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

5 General Methods

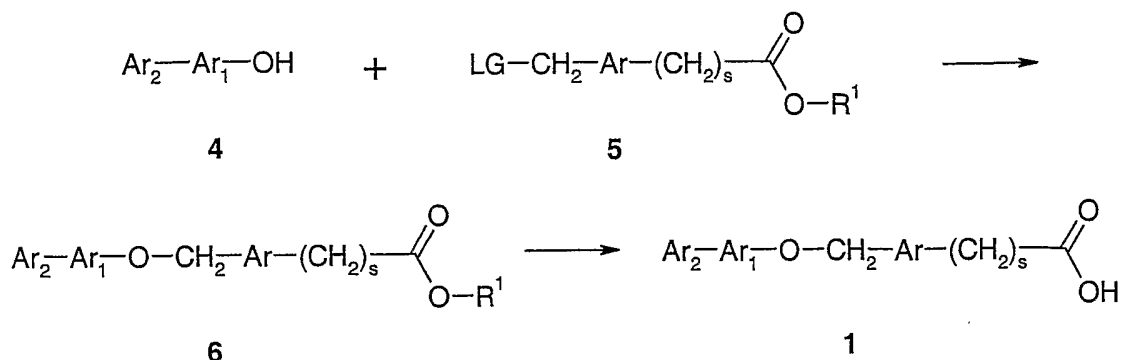
The compounds of formula I can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to the person skilled in the art. Starting materials are either commercially available or can be prepared by methods
10 analogous to the methods given below or in the examples or by methods known in the art.

The compounds used in the present invention can be prepared by any conventional means. Suitable processes for synthesizing these compounds are provided in the examples. Generally, compounds of formula I can be prepared according to one of the
15 synthetic routes described below: Nucleophilic Displacement or Suzuki Coupling. The sources of the starting materials for these reactions are described subsequently.

Nucleophilic Displacement

As shown in Scheme 1, compounds of the invention can be prepared by nucleophilic displacement of a leaving group LG from a compound of formula 5 by a
20 hydroxybiaryl of formula 4 to form a compound of formula 6 in which R¹ represents a protective group commonly used for the protection of a carboxylic acid. The protective group is then cleaved to give the compound of the invention of formula 1.

Many protective groups R¹ are known to those of skill in the art of organic synthesis. For example, several suitable protective groups are enumerated in "Protective
25 Groups in Organic Synthesis" [T. W. Greene and P. G. M. Wuts, 2nd Edition, John Wiley & Sons, N.Y. 1991]. Preferred protective groups are those compatible with the reaction conditions used to prepare compounds of the invention. Examples of such protective groups are lower alkyl straight-chain or branched esters (e.g., methyl (R¹ = CH₃), ethyl (R¹ = CH₂CH₃), or tert-butyl (R¹ = C(CH₃)₃) esters), or the benzyl ester (R¹ = CH₂C₆H₅).

Scheme 1

The nucleophilic displacement of the leaving group LG in compound 5 can be effected by any conventional means. For example, in the case where LG represents the leaving group chlorine, bromine, or iodine, the reaction can conveniently be carried out by treating compound 5 with compound 4 in the presence of a base such as an alkali metal hydride (for example, sodium hydride) in an inert solvent (e.g., N,N-dimethylformamide) or an alkali metal carbonate (for example, potassium carbonate) in an inert solvent (e.g., a polar aprotic solvent such as N,N-dimethylformamide or a ketone such as acetone or methyl ethyl ketone) at a temperature between about room temperature and about 100 °C degrees.

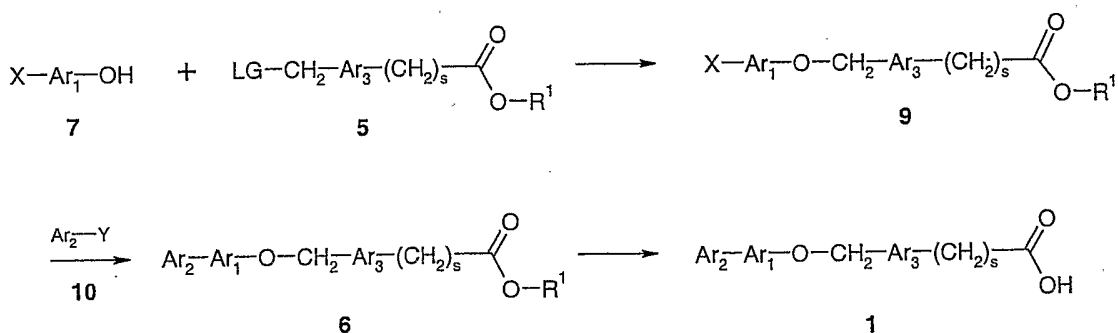
The conversion of compound 6, in which R¹ represents a protective group commonly used for the protection of a carboxylic acid, to compound 1 by deprotection of the carboxylic acid protective group is carried out using reaction conditions that are well known in the field of organic synthesis, and many of which are outlined in "Protective Groups in Organic Synthesis" [T. W. Greene and P. G. M. Wuts, 2nd Edition, John Wiley & Sons, N.Y. 1991]. For example, in the case where R¹ is methyl or ethyl, the reaction can be conveniently effected by treating the compound with one equivalent of an alkali metal hydroxide, such as potassium hydroxide, sodium hydroxide, or lithium hydroxide, preferably lithium hydroxide, in a suitable solvent, such as a mixture of tetrahydrofuran, methanol, and water. The reaction can be carried out at a temperature between about 0 °C degrees and about room temperature, preferably at about room temperature. As another example, in the case where R¹ is a group that can be cleaved under acidic conditions, such as a tert-butyl group, the ester may be treated with a strong inorganic acid, for example a hydrohalic acid such as hydrogen chloride or hydrogen bromide, or a strong organic acid, for example a halogenated alkane carboxylic acid such as trifluoroacetic acid and the like. The reaction is conveniently carried out in the presence of an inert organic solvent (such as dichloromethane) and at a temperature between about 0 °C degrees and about room temperature, preferably at about room temperature. As a final (but not limiting) example, in the case where R¹ is a group that

can be cleaved by catalytic hydrogenation, and with the further condition that the rest of the molecule is stable to such conditions, the reaction may be carried out by hydrogenation in the presence of a noble metal catalyst such as palladium-on-carbon in the presence of an inert solvent (for example, an alcohol such as ethanol) at about room temperature and under atmospheric pressure.

Suzuki Coupling

As shown in Scheme 2, compounds of the invention can be prepared by a reaction sequence starting with nucleophilic displacement of a leaving group LG from a compound of formula 5 by a compound of formula 7, in which X represents a group that can act as a leaving group in a noble metal-catalyzed coupling reaction such as a Suzuki reaction or a Stille reaction, to form a compound of formula 9 in which R¹ represents a protective group commonly used for the protection of a carboxylic acid. The compound of formula 9 can then be reacted with an organometallic reagent of formula 10 (for example, a boronic acid or an organotin reagent) under noble metal catalysis to give a biaryl compound of formula 11. The protective group is then cleaved to give the compound of the invention of formula 1.

Scheme 2



Many protective groups R¹ are known to those of skill in the art of organic synthesis. For example, several suitable protective groups are enumerated in "Protective Groups in Organic Synthesis" [T. W. Greene and P. G. M. Wuts, 2nd Edition, John Wiley & Sons, N.Y. 1991]. Preferred protective groups are those compatible with the reaction conditions used to prepare compounds of the invention. Examples of such protective groups are lower alkyl straight-chain or branched esters (e.g., methyl (R¹ = CH₃), ethyl (R¹ = CH₂CH₃), or tert-butyl (R¹ = C(CH₃)₃) esters), or the benzyl ester (R¹ = CH₂C₆H₅).

The nucleophilic displacement of the leaving group LG in compound 5 can be effected by any conventional means. For example, in the case where LG represents the leaving group chlorine, bromine, or iodine, the reaction can conveniently be carried out by treating compound 5 with compound 7 in the presence of a base such as an alkali

metal hydride (for example, sodium hydride) in an inert solvent (e.g., N,N-dimethylformamide) or an alkali metal carbonate (for example, potassium carbonate) in an inert solvent (e.g., a polar aprotic solvent such as N,N-dimethylformamide or a ketone such as acetone or methyl ethyl ketone) at a temperature between about room
5 temperature and about 100 °C degrees.

The reaction of a compound of formula 9, where X represents a leaving group such as iodine, bromine, or triflate, with a compound of formula 10, where Y represents boronic acid, boronate ester, trimethyltin or tri-n-butyl-tin, to give a compound of formula 11 can be effected using Suzuki or Stille coupling conditions which are well
10 known to one of average skill in the art. For example, the reaction can be conveniently carried out by reacting a compound of formula 9 where X represents iodine with a compound of formula 10 where Y represents B(OH)₂, in a convenient inert solvent such as a polar aprotic solvent (e.g., N,N-dimethylformamide) or an ether (e.g., dioxane) or water, in the presence of a catalytic amount of a palladium(0) complex (e.g.,
15 tetrakis(triphenylphosphine)palladium(0)) or a compound which can be reduced in situ to give palladium(0) (for example, palladium(II) acetate or bis(triphenylphosphine)palladium(II) chloride), in the optional additional presence of a catalytic amount of a phosphine ligand, for example tri-o-tolylphosphine or tri-tert-butylphosphine, or alternatively in the presence of a preformed complex of palladium(0)
20 with a phosphine ligand such as bis(tri-cyclohexylphosphine)palladium, and also in the presence of an inorganic base, for example, an alkali metal carbonate, bicarbonate or phosphate (e.g., potassium phosphate or sodium carbonate) at a temperature between about room temperature and about 100 °C degrees, and preferably at between about room temperature and about 50 °C degrees. It is also possible to use an alkali metal
25 hydroxide such as sodium hydroxide or potassium hydroxide as the base in this reaction, but as is clear to one of average skill in the art, this may lead to other side reactions such as hydrolysis of any hydrolytically labile moiety (for example, a carboxylate ester) in the molecule, and this effect may be desired or not desired by the experimenter. Consequently, the selection of the base depends on whether or not it is desired to avoid a
30 hydrolysis reaction. If so, then an alkali metal hydroxide should not be selected as the base and one of the other bases outlined above should be selected.

The conversion of compound 11, in which R¹ represents a protective group commonly used for the protection of a carboxylic acid, to compound 1 by deprotection of the carboxylic acid protective group is carried out using reaction conditions that are
35 well known in the field of organic synthesis, and many of which are outlined in "Protective Groups in Organic Synthesis" [T. W. Greene and P. G. M. Wuts, 2nd Edition, John Wiley & Sons, N.Y. 1991]. For example, in the case where R¹ is methyl or ethyl, the

reaction can be conveniently effected by treating the compound with one equivalent of an alkali metal hydroxide, such as potassium hydroxide, sodium hydroxide, or lithium hydroxide, preferably lithium hydroxide, in a suitable solvent, such as a mixture of tetrahydrofuran, methanol, and water. The reaction can be carried out at a temperature
5 between about 0 °C degrees and about room temperature, preferably at about room temperature. As another example, in the case where R¹ is a group that can be cleaved under acidic conditions, such as a tert-butyl group, the ester may be treated with a strong inorganic acid, for example a hydrohalic acid such as hydrogen chloride or hydrogen bromide, or a strong organic acid, for example a halogenated alkane carboxylic acid such
10 as trifluoroacetic acid and the like. The reaction is conveniently carried out in the presence of an inert organic solvent (such as dichloromethane) and at a temperature between about 0 °C degrees and about room temperature, preferably at about room temperature. As a final (but not limiting) example, in the case where R¹ is a group that can be cleaved by catalytic hydrogenation, and with the further condition that the rest of
15 the molecule is stable to such conditions, the reaction may be carried out by hydrogenation in the presence of a noble metal catalyst such as palladium-on-carbon in the presence of an inert solvent (for example, an alcohol such as ethanol) at about room temperature and under atmospheric pressure.

Depending on the reaction conditions and the substrate employed, it is sometimes
20 possible to prepare the carboxylic acid of formula 1 directly from the Suzuki reaction of a compound of formula 9, where X represents a leaving group such as iodine, bromine, or triflate, with a boronic acid of formula 10, where Y represents B(OH)₂ without a separate hydrolysis step. For example, a compound of formula 9 where X represents iodide can be treated with a boronic acid of formula 10, where Y represents B(OH)₂ in the presence of a
25 complex of palladium(0) with a trialkylphosphine (such as bis(tricyclohexylphosphine) palladium) in the presence of potassium carbonate in an aqueous solvent such as a mixture of water and dioxane, at elevated temperature, such as at about 170 °C degrees. The reaction is carried out in a sealed tube and the heating is conveniently carried out using microwave irradiation. Alternatively, reactions conditions known in the literature
30 can be employed. Examples of such conditions can be seen in the supplementary material for the article by W. Jiang et al. *J. Med. Chem.* 2003, 46, 441-444, and also in S. C. Tucker et al. *Tetrahedron* 2001, 57, 2545-2554.

Starting Materials: Compounds of Formula 4

Many compounds of formula 4 are known compounds and can be synthesized
35 according to literature procedures. Some examples are included in the table.

Name	Reference
2-(3-Amino-4-hydroxy-phenyl)-thiophene	M. A. Al'perovich et al., <i>Zhurnal Obshchei Khimii</i> 1964, 34, 645-50 CAN 60:83351
4-(2-Bromo-thiophen-3-yl)-phenol	A. Cravino et al., <i>J. Phys. Chem. B</i> 2002, 106, 70-76
2-Chloro-5-(4-chloro-3,5-diethyl-1H-pyrazol-1-yl)-4-fluoro-phenol	H. Ohyama et al., US 4752326
4-Chloro-2-(3-ethyl-5-methyl-1(2)H-pyrazol-4-yl)-phenol	K. Takagi et al., <i>Chem. Pharm. Bull.</i> 1975, 23, 2427-31
4-(5-Chloro-3-methyl-pyrazol-1-yl)-phenol	A. Michaelis et al., <i>Chem. Ber.</i> 1900, 33, 2595-2607
2-(4-Chloro-pyridin-3-yl)-phenol	W. S. Yue et al., <i>Org. Lett.</i> 2002, 4, 2201 - 2204.
4-(5-Chloro-thiophen-2-yl)-phenol	S. Gronowitz et al., <i>Acta Pharm. Suec.</i> 1974, 11, 211-224
4-(5-Chloro-thiophen-3-yl)-phenol	S. Gronowitz et al., <i>Acta Pharm. Suec.</i> 1974, 11, 211-224
2-(3,5-Diethyl-isoxazol-4-yl)-phenol	R. Royer et al., <i>Bull. Soc. Chim. France</i> 1963, 1746-1752
3,5-Dimethoxy-2-(2-methyl-naphthalen-1-yl)-phenol	G. Bringmann et al., <i>J. Org. Chem.</i> 2002, 67, 5595-5610.
3-(3,5-Dimethyl-pyrazol-1-yl)-phenol	D. J. Alsop, US 3929828
5-(3,5-Dimethyl-1H-pyrazol-4-yl)-2-methyl-phenol	F. Langer et al., <i>Monatsh. Chem.</i> 1957, 88, 298-306
2-(3,5-Dimethyl-isoxazol-4-yl)-3-methyl-phenol	E. Bonfand et al., <i>Synlett.</i> 2000, 475-478.
3,5-Dimethyl-2-(2-methyl-naphthalen-1-yl)-phenol	G. Bringmann et al., <i>Tetrahedron: Asymmetry</i> 1999, 10, 3025-3032

Name	Reference
4-(3,5-Dimethyl-pyrazol-1-yl)-phenol	L. Claisen et al., <i>Liebigs Ann. Chem.</i> 1894, 278, 295
2-(3,5-Dimethyl-pyrazol-1-yl)-phenol	G. Fukata et al., <i>Heterocycles</i> 1982, 19, 1487-1495
2-(3-Ethyl-isoxazol-4-yl)-phenol	R. Royer et al., <i>Bull. Soc. Chim. France</i> 1963, 1746-1752
2-(5-Ethyl-isoxazol-4-yl)-phenol	R. Royer et al., <i>Bull. Soc. Chim. France</i> 1963, 1746-1752
2-(5-Ethyl-1-methyl-1H-pyrazol-4-yl)-phenol	M. Hubert-Habart et al., <i>Bull. Soc. Chim. France</i> 1966, 1587-1598.
2-(5-Ethyl-3-methyl-isoxazol-4-yl)-phenol	M. Hubert-Habart et al., <i>Bull. Soc. Chim. France</i> 1966, 1587-1598.
2-(3-Ethyl-5-methyl-isoxazol-4-yl)-phenol	R. Royer et al., <i>Bull. Soc. Chim. France</i> 1963, 1746-1752
2-(3-Ethyl-5-phenyl-isoxazol-4-yl)-phenol	R. Royer et al., <i>Bull. Soc. Chim. France</i> 1963, 1746-1752
4-(5-Ethyl-thiophen-2-yl)-phenol	N. L. Campbell et al., <i>J. Mater. Chem.</i> 2002, 12, 2706-2721
4-(5-Fluoro-thiophen-2-yl)-phenol	S. Gronowitz et al., <i>Acta Pharm. Suec.</i> 1974, 11, 211-224
3-Fluoro-5-(thiophen-2-yl)-phenol	R. Friesen et al., Canadian Patent Application CA 2169231
2-Furan-2-yl-4-hydroxy-benzonitrile	Y. Yamamoto et al., <i>Synthesis</i> 1996, 949-953
4-Furan-2-yl-phenol	F. D. King et al., <i>Synthesis</i> 1976, 40-42
1-(2'-Hydroxy-4',6'-dimethylphenyl)-2-methylnaphthalene	G. Bringmann et al., <i>Chem. Europ. J.</i> 1999, 5, 3029-3038

Name	Reference
4-Hydroxy-2-(2-furanyl)-benzotrile	Y. Yamamoto et al., <i>Synthesis</i> 1996, 949-953
4'-Hydroxy-4,5-methylenedioxy-2-biphenylmethanol,	T. Ikeda et al., <i>J. Chem. Soc.</i> 1956, 4749-4761
3-(4-Hydroxy-2-nitrophenyl)pyridine	H. Shigyo et al., <i>Chem. Pharm. Bull.</i> 1993, 41, 1573-1582
2-(4'-Hydroxyphenyl)benzyl alcohol	C.-G.Huang et al., <i>J. Org. Chem.</i> 1991, 56, 4846-4853.
4-p-Hydroxyphenyl-3,5-dimethylpyrazole	C. Foces-Foces et al., <i>J. Chem. Crystallogr.</i> 1996, 26, 127-132
4-(4-Hydroxyphenyl)pyrazole	J. Elguero et al., <i>Synthesis</i> 1997, 563-566.
4-Hydroxy-2-(2-thienyl)-benzotrile	Y. Yamamoto et al., <i>Synthesis</i> 1996, 949-953
5-(3-Iodo-thiophen-2-yl)-2-methoxy-phenol	B. L. Flynn et al., <i>Bioorg. Med. Chem. Lett.</i> 2001, 11, 2341-2344
2'-Methoxymethyl-biphenyl-4-ol	Y. Shi et al., <i>J. Chem. Soc. Chem. Commun.</i> 1995, 1217-1218
4-(3',4'-Methylenedioxyphenyl)phenol	L. Balazs et al., <i>Tetrahedron Lett.</i> 2000, 41, 7583-7587
4-(3',4'-Methylenedioxyphenyl)3-trifluoromethyl-phenol	T. Hiyama et al., <i>Synlett</i> 1990, 53-4
3-(5-Methyl-furan-2-yl)-phenol	M. A. Tobias, <i>J. Org. Chem.</i> 1970, 35, 267-269
3-(5-Methyl-furan-2-yl)-phenol	M. A. Tobias, <i>J. Org. Chem.</i> 1970, 35, 267-269
2-Methyl-5-(p-hydroxyphenyl)furan	A. F. Oleinik et al., <i>Khim.-Farm. Zh.</i> 1984, 18, 697-699 CAN 101:230269
3-Methyl-2-(naphthalen-1-yl)-phenol	E. Bonfand et al., <i>Synlett.</i> 2000, 475-478.

Name	Reference
4-(4-Methyl-6-propyl-pyridin-3-yl)-phenol	J. M. Gourley et al., <i>J. Chem. Soc. D</i> 1969, 709-710
2-(3-Methyl-pyrazol-1-yl)-phenol	G. Fukata et al., <i>Heterocycles</i> 1982, 19, 1487-1495
3-(3-Methyl-pyrazol-1-yl)-phenol	Geigy French Patent Application FR 1320597, 1963; Chem.Abstr. CAN 60:17449
4-(3-Methyl-1H-pyrazol-1-yl)-phenol	J. C. Antilla et al., <i>J. Org. Chem.</i> 2004, 69, 5578-5587
2-(5-Methyl-pyridin-3-yl)-phenol	R. A. Abramovitch et al., <i>J. Am. Chem. Soc.</i> 1974, 96, 5265-5267
2-(6-Methyl-pyridin-3-yl)-phenol	R. A. Abramovitch et al., <i>J. Am. Chem. Soc.</i> 1974, 96, 5265-5267
2-(2-Methyl-pyridin-3-yl)-phenol	R. A. Abramovitch et al., <i>J. Am. Chem. Soc.</i> 1974, 96, 5265-5267
4-Methyl-2-(3-pyridyl)phenol	G. Petrillo et al., <i>Tetrahedron</i> 1990, 46, 7977-7990
4-(5-Methyl-thiophen-2-yl)-phenol	N. L. Campbell et al., <i>J. Mater. Chem.</i> 2002, 12, 2706-2721
4-(Naphthalen-1-yl)-phenol	J. Jacques et al. <i>Bull. Soc. Chim. France</i> 1966, 128-144.
3-(Naphthalen-1-yl)-phenol	D. Nasipuri et al., <i>J. Chem. Soc. Perkin Trans. 1</i> 1973, 1451-1456
2-(Naphthalen-1-yl)-phenol	M. Orchin, <i>J. Am. Chem. Soc.</i> 1948, 70, 495-497
2-(5-Phenyl-isoxazol-4-yl)-phenol	M. Martynoff, <i>Bull. Soc. Chim. France</i> 1952, 1056-1060
4-(5-Propyl-thiophen-2-yl)-phenol	N. L. Campbell et al., <i>J. Mater. Chem.</i> 2002, 12, 2706-2721

Name	Reference
2-Pyrazol-1-yl-phenol	G. Fukata et al., <i>Heterocycles</i> 1982, 19, 1487-1495
4-Pyrazol-1-yl-phenol	H. Jones et al. <i>J. Med. Chem.</i> 1978, 21, 1100-1104
2-Pyridin-3-yl-phenol	R. A. Abramovitch et al., <i>J. Am. Chem. Soc.</i> 1974, 96, 5265-5267
4-Pyridin-3-yl-phenol	R. A. Johnson et al., <i>J. Med. Chem.</i> 1986, 29, 1461-1468.
3-(Pyridin-3-yl)-phenol	V. Prelog et al., <i>Helv. Chim. Acta</i> 1947, 30, 675-89
4-Thiophen-2-yl-phenol	L. J. Baldwin et al., <i>J. Heterocycl. Chem.</i> 1985, 22, 1667-1669
4-Thiophen-3-yl-phenol	L. J. Baldwin et al., <i>J. Heterocycl. Chem.</i> 1985, 22, 1667-1669
3-Thiophen-3-yl-phenol	L. J. Baldwin et al., <i>J. Heterocycl. Chem.</i> 1985, 22, 1667-1669
3-(Thiophen-2-yl)-phenol	V. Prelog et al., <i>Helv. Chim. Acta</i> 1947, 30, 675-89

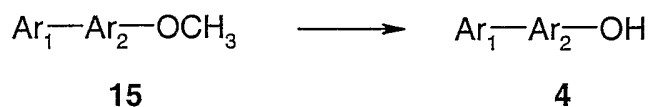
In addition, some compounds of formula 4 are commercially available, including the following:

Name	Supplier
4'-Hydroxy-biphenyl-3-carboxylic acid amide	Ambinter SARL, Paris, France
4-(5-Chloro-thiophen-2-yl)-phenol	Specs and Biospecs, Rijswijk, Netherlands
2-(3,5-Dimethyl-pyrazol-1-yl)-phenol	ChemDiv, Inc. San Diego, CA
4-(5-Methyl-furan-2-yl)-phenol	ChemDiv, Inc. San Diego, CA

Name	Supplier
1-Phenyl-1H-5-(5'-chloro-2'-hydroxy-4'-methylphenyl)pyrazole	Aldrich Chemical Company, Inc., Milwaukee, WI
2-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-phenol	ChemDiv, Inc. San Diego, CA

Compounds of formula 4 that are not known in the literature may be prepared using reactions that are known per se. For example, they may be conveniently prepared according to Scheme 3.

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Scheme 3

The reaction of a compound of formula 15 to give a compound of formula 4 can be carried out by several different methods that are well known in the field of organic synthesis. Several of these methods are outlined in "Protective Groups in Organic
 10 Synthesis" (T. W. Greene and P. G. M. Wuts, 2nd Edition, John Wiley & Sons, N.Y. 1991). It will be clear to one skilled in the art that this approach to the synthesis of compounds of formula 4 is most suitable in the case where any substituents in the compound of formula 4 are stable to the conditions used to convert the compound of formula 15 to the compound of formula 4, and especially in the case where the compound of formula 4
 15 does not bear any lower-alkoxy substituents.

For example, a compound of formula 15 can be treated with trimethylsilyl iodide in an inert solvent such as a halogenated hydrocarbon (for example, chloroform) at a temperature between about room temperature and the boiling point of the solvent, conveniently at about 60 °C degrees. The trimethylsilyl iodide can be added as a reagent,
 20 or it can be prepared in situ from trimethylsilyl chloride and an inorganic iodide, such as potassium iodide.

As another example, the compound of formula 15 can be treated with boron tribromide in an inert solvent such as a halogenated hydrocarbon (for example, methylene chloride) at low temperature (such as -78 °C degrees) to give the compound of
 25 formula 4. Examples of the conversion of a compound of formula 15 to a compound of formula 4 using this process can be seen in L. I. Kruse et al. *J. Med. Chem.* 1987, 30, 486-494, in D. J. Cram et al. *J. Am. Chem. Soc.* 1985, 107, 3645-3657, in A. Kende et al. *J. Am.*

Chem. Soc. 1988, 110, 2210-2218, and in A. G. Myers et al. *J. Am. Chem. Soc.* 1997, 119, 6072-6094.

As a further example, the compound of formula 15 can be treated with a lower-alkyl thiolate (for example, sodium ethanethiolate) in N,N-dimethylformamide at a temperature between around 100 °C degrees and around 153 °C degrees, to give the compound of formula 4. Conditions appropriate for this reaction can be seen in G. I. Feutrill et al. *Tetrahedron Lett.* 1970, 11, 1327 and also in J. A. Dodge et al. *J. Org. Chem.* 1995, 60, 739-741.

As yet another example, the compound of formula 15 can be treated with pyridine hydrochloride at elevated temperature (for example, at between about 160 °C degrees and about 220 °C degrees) to give the compound of formula 4. Examples of the conversion of a compound of formula 15 to a compound of formula 4 using this process can be seen in L. J. Baldwin et al. *J. Heterocycl. Chem.* 1985, 22, 1667-1669, in S. Gauthier et al. *Tetrahedron* 2000, 56, 703-709, in J. Gilbert et al. *J. Med. Chem.* 1983, 26, 693-699, in M. Konno et al. *Synlett* 1997, 1472-1474, and in P. C. Astles et al. *J. Med. Chem.* 1998, 41, 2732-2744.

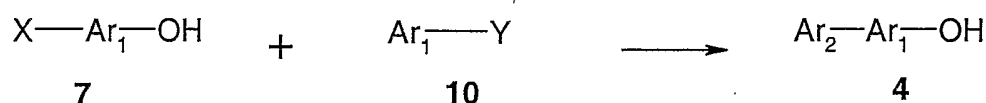
Several compounds of formula 15 are available commercially, and some of these are shown in the table below. Other compounds of formula 15 are known in the literature, or can be made by methods that are well known in the art. Specifically, compounds of formula 15 can be made using Stille or Suzuki reactions analogous to those described below for the synthesis of compounds of formula 4 (see Scheme 4), except that an anisole is used in place of the phenolic compound of formula 7.

Name	Supplier
3-(3-Bromo-4-methoxyphenyl)pyridine	Synchem Inc., Des Plaines, IL
3-(3,5-Dimethyl-4-methoxyphenyl)thiophene	Rieke Metals, Inc., Lincoln, NE
3-(3-Fluoro-4-methoxyphenyl)thiophene	Rieke Metals, Inc., Lincoln, NE
3-(5-Fluoro-2-methoxyphenyl)thiophene	Rieke Metals, Inc., Lincoln, NE
3-(2-Methoxy-5-methylphenyl)-4-methylthiophene	Rieke Metals, Inc., Lincoln, NE
3-(4-Methoxy-3-methylphenyl)-4-methylthiophene	Rieke Metals, Inc., Lincoln, NE
3-(2-Methoxy-5-methylphenyl)thiophene	Rieke Metals, Inc., Lincoln, NE

Name	Supplier
3-(4-Methoxy-2-methylphenyl)thiophene	Rieke Metals, Inc., Lincoln, NE
3-(4-Methoxy-3-methylphenyl)thiophene	Rieke Metals, Inc., Lincoln, NE
4-(2-Methoxyphenyl)-3-methyl-1H-pyrazole	Maybridge plc, Tintagel, UK
4-(4-Methoxyphenyl)-1-methyl-1H-pyrazole	Peakdale Molecular, High Peak, UK
3-(3-Methoxyphenyl)-4-methylthiophene	Rieke Metals, Inc., Lincoln, NE
4-(4-Methoxyphenyl)-1-phenyl-1H-pyrazole	Peakdale Molecular, High Peak, UK
4-(4-Methoxyphenyl)-1H-pyrazole	Peakdale Molecular, High Peak, UK
2-(4-Methoxyphenyl)thiophene	Fluorochem Ltd., Old Glossop, UK
3-(2-Methoxyphenyl)thiophene	Rieke Metals, Inc., Lincoln, NE
3-(3-Methoxyphenyl)thiophene	Rieke Metals, Inc., Lincoln, NE
3-(4-Methoxyphenyl)thiophene	Rieke Metals, Inc., Lincoln, NE

An alternative approach to the synthesis of compounds of formula 4 is shown in Scheme 4.

Scheme 4



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The reaction of a compound of formula 7, where X represents a leaving group such as iodine, bromine, chlorine, or triflate, with a compound of formula 10, where Y represents boronic acid, boronate ester, trimethyltin or tri-n-butyl-tin, to give a compound of formula 4 can be effected using Suzuki or Stille coupling conditions which are well known to one of average skill in the art. For example, the reaction can be conveniently carried out by reacting a compound of formula 7 where X represents iodine with a compound of formula 10 where Y represents B(OH)₂, in a convenient inert solvent such as a polar aprotic solvent (e.g., N,N-dimethylformamide) or an ether (e.g., dioxane) or water, in the presence of a catalytic amount of a palladium(0) complex (e.g., tetrakis(triphenylphosphine)palladium(0)) or a compound which can be reduced in situ

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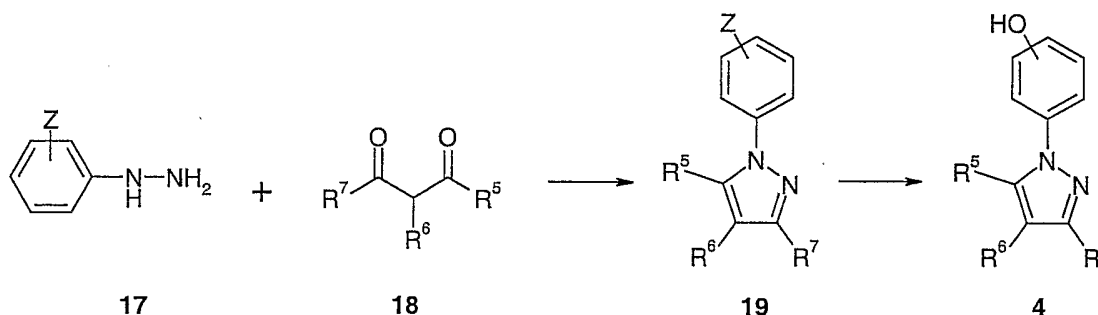
to give palladium(0) (for example, palladium(II) acetate or bis(triphenylphosphine)palladium(II) chloride), in the optional additional presence of a catalytic amount of a phosphine ligand, for example tri-*o*-tolylphosphine or tri-*tert*-butylphosphine, and also in the presence of an inorganic base, for example, an alkali metal carbonate, bicarbonate or phosphate (e.g., potassium phosphate or sodium carbonate) at a temperature between about room temperature and about 100 °C degrees, and preferably at between about room temperature and about 50 °C degrees. As further examples, the reaction can be run according to the conditions of H. Sakurai et al. *J. Org. Chem.* 2002, 67, 2721, or the reaction can be run on solid phase using the conditions of J. D. Revell and A. Ganesan

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In the case where Ar₂ is pyrazol-1-yl, compounds of formula 4 can be prepared according to Scheme 5, where Z is a group that can be converted to a hydroxy group. Examples of suitable Z groups will be evident to one of skill in the art, and include methoxy, nitro, and methanesulfonyloxy.

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Scheme 5



The compound of formula 17 is treated with a diketone of formula 18 in an inert solvent, such as an alcohol (e.g., ethanol) at the reflux temperature to give a pyrazole of formula 19, and then the Z group is converted to the hydroxy group to give the compound of formula 4. In the case where Z is methoxy, the reaction is conveniently carried out using reactions analogous to those described above in connection with Scheme 3. In the case where Z is nitro, the transformation takes place in two steps: hydrogenation to the aniline followed by a diazotization reaction to give the phenol. Conditions appropriate for this transformation can be seen in A. Michaelis et al. *Chem. Ber.* 1900, 33, 2595-2607. In the case where R is methanesulfonyloxy, the transformation of the Z group to a hydroxy group is effected by a hydrolysis reaction where the compound of formula 19 is treated with an aqueous base, such as an alkali metal hydroxide (e.g., sodium hydroxide) in the optional additional presence of a co-solvent to ensure that the reaction mixture is in solution. Examples of suitable co-solvents are ethanol and dioxane. The reaction is conveniently carried out at between

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about 50 °C degrees and about the reflux temperature of the solvent or mixture of solvents. Conditions appropriate for this reaction can be seen in H. Ohyama et al., US 4752326.

Starting Materials: Compounds of Formula 5

- 5 Many compounds of formula 5, in which R¹ represents a protective group commonly used for the protection of a carboxylic acid, are known compounds and can be synthesized according to literature procedures. Some examples are included in the table.

Name	Reference
2-Bromomethyl-benzoic acid tert-butyl ester	T. Ziegler et al., <i>Tetrahedron Lett.</i> 2001, 42, 569-572
3-Bromomethyl-benzoic acid tert-butyl ester	W. Danho et al., US 5,508,437
2-Bromomethyl-benzoic acid methyl ester	V. Dvornikovs et al., <i>J. Org. Chem.</i> 2002, 67, 2160-2167
3-Bromomethyl-benzoic acid methyl ester	V. Dvornikovs et al., <i>J. Org. Chem.</i> 2002, 67, 2160-2167
5-Bromomethyl-2-furancarboxylic acid ethyl ester	S. Tsuboi et al., <i>Bull. Chem. Soc. Japan</i> 1987, 60, 1807-1812
5-Bromomethyl-2-furancarboxylic acid methyl ester	J. Wityak et al., <i>Bioorg. Med. Chem. Lett.</i> 1995, 5, 2097-2100
6-Bromomethyl-pyridine-2-carboxylic acid methyl ester	D. I. C. Scopes et al., <i>J. Med. Chem.</i> 1992, 35, 490-501
2-Bromomethyl-thiazole-4-carboxylic acid ethyl ester	E. A. Hallinan et al., <i>Bioorg. Med. Chem.</i> 2001, 9, 1-6
5-Bromomethyl-thiophene-2-carboxylic acid methyl ester	M. L. Curtin et al., <i>J. Med. Chem.</i> 1998, 41, 74-95
3-Chloromethyl-benzoic acid benzyl ester	D.-W. Chen et al., <i>J. Chem. Soc. Perkin Trans. 1</i> 2001, 2796-2803
2-Chloromethyl-benzoic acid ethyl ester	F. Gadiant et al., <i>Helv. Chim. Acta</i> 1962, 45, 1860-1870

Name	Reference
3-Chloromethyl-benzoic acid methyl ester	T. Matsukawa et al., <i>Yakugaku Zasshi</i> 1950, 70, 535-537. <i>Chem. Abs.</i> 45:36092 (1951)
5-Chloromethyl-2-furancarboxylic acid n-butyl ester	J. G. M. Bremner et al., US 2,450,108
5-Chloromethyl-2-furancarboxylic acid ethyl ester	T. K. Chakraborty et al., <i>Tetrahedron Lett.</i> 2002, 43, 1317-1320
6-Chloromethyl-pyridine-2-carboxylic acid ethyl ester	R. Fornasier et al., <i>J. Chem. Soc. Perkin Trans. 2</i> 1986, 233-238
5-Chloromethyl-thiophene-2-carboxylic acid methyl ester	V. Kozmik et al., <i>Collect. Czech. Chem. Commun.</i> 1992, 57, 1483-1486
3-Iodomethyl-benzoic acid methyl ester	R. C. Fuson et al., <i>J. Am. Chem. Soc.</i> 1940, 62, 1180-1183
5-Iodomethyl-2-furancarboxylic acid allyl ester	P. D. Greenspan et al., <i>J. Med. Chem.</i> 2001, 44, 4524-4534
5-Methanesulfonyloxymethyl-furan-2-carboxylic acid ethyl ester	J. B. Summers, Jr. et al., US 5,486,525

In addition, some compounds of formula 5 are commercially available, including the following:

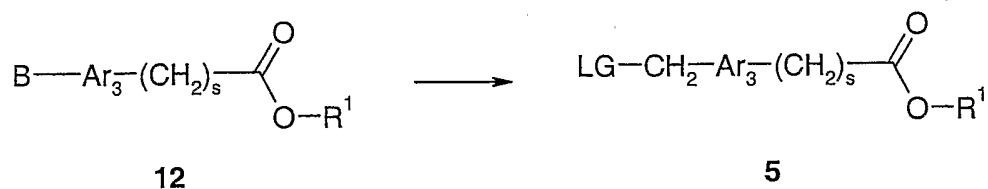
Name	Supplier
6-Bromomethyl-pyridine-2-carboxylic acid methyl ester	ChemPacific, Baltimore, MD
5-Chloromethyl-2-furancarboxylic acid ethyl ester	Aldrich Chemical Company, Inc., Milwaukee, WI
5-Chloromethyl-2-furancarboxylic acid methyl ester	Aldrich Chemical Company, Inc., Milwaukee, WI
2-Bromomethyl-benzoic acid ethyl ester	Pfaltz & Bauer, Inc., Waterbury, CT

Name	Supplier
2-Bromomethyl-benzoic acid methyl ester	ChemPacific, Baltimore, MD
3-Bromomethyl-benzoic acid methyl ester	Lancaster Synthesis Ltd., Lancashire, UK

Compounds of formula 5 that are neither known in the literature nor commercially available may be conveniently prepared by reactions that are well known in the field of organic synthesis, and these reactions can be represented generically as in Scheme 6.

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Scheme 6



Three examples of reactions represented by Scheme 6 are described below. As will be clear to one of average skill in the art, not all reactions can be used to prepare all compounds of formula 5, but reactions appropriate for the preparation of specific compounds of formula 5 will be apparent to a synthetic organic chemist.

For example, a compound of formula 5, where LG represents chlorine, can be prepared from a compound of formula 12 where B represents hydrogen by an electrophilic aromatic substitution reaction by treating the compound of formula 12 where B represents hydrogen with formaldehyde and hydrogen chloride, in the presence of a Lewis acid catalyst, preferably zinc chloride, in a suitable inert solvent, for example, a halogenated alkane (such as methylene chloride, chloroform, 1,2-dichloroethane, or the like) at a temperature between about room temperature and the boiling point of the solvent, preferably at about 35 °C degrees. Clearly this reaction is limited to cases where the compound of formula 12 is susceptible to electrophilic aromatic substitution at the desired point of attachment, and further, to cases where the compound of formula 5 is stable to mineral acids and to Lewis acids. Examples of compounds of formula 5 which fulfill these criteria will be known to one of average skill in the art. An example of such a reaction can be found in O. Moldenhauer et al. *Justus Liebigs Ann. Chem.* 1953, 580, 176.

Compounds of formula 5 where LG represents bromine can be prepared by treating a compound of formula 12 where B represents CH₃ with N-bromosuccinimide

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or 3,3-dimethyl-N,N'-dibromohydantoin in an inert solvent such as a halogenated alkane (for example, carbon tetrachloride) or acetonitrile, in the optional additional presence of a catalyst such as azobis(isobutyronitrile) or benzoyl peroxide at a suitable temperature, conveniently at the boiling point of the solvent, and in the optional additional presence
5 of a source of light; or by treating a compound of formula 12 where B represents CH₃ with with bromine in an inert solvent such as a mixture of water and an aromatic hydrocarbon (e.g., benzene) or a halogenated alkane (e.g., chloroform) under irradiation with an incandescent light.

Compounds of formula 5 where LG represents chlorine can be prepared by treating
10 a compound of formula 12 where B represents CH₃ with N-chlorosuccinimide or sulfuryl chloride in an inert solvent such as a halogenated alkane (for example, carbon tetrachloride) or acetonitrile in the optional additional presence of a catalyst such as azobis(isobutyronitrile) or benzoyl peroxide at a suitable temperature, conveniently at the boiling point of the solvent, and in the optional additional presence of a source of
15 light; or by treating a compound of formula 12 where B represents CH₃ with chlorine in an inert solvent such as a mixture of water and an aromatic hydrocarbon (e.g., benzene) or a halogenated alkane (e.g., chloroform or carbon tetrachloride) under irradiation with an incandescent light.

A compound of formula 5 where LG represents bromine can be prepared by
20 treating a compound of formula 12 where B represents CH₂OH with phosphorus tribromide or a mixture of N-bromosuccinimide and triphenylphosphine in an inert solvent such as a halogenated alkane (e.g., methylene chloride or carbon tetrachloride) at a temperature between about 0 °C degrees and the boiling point of the solvent, conveniently at about 0 °C degrees. A compound of formula 5 where LG represents
25 chlorine can be prepared by treating a compound of formula 12 where B represents CH₂OH with thionyl chloride or a mixture of N-chlorosuccinimide and triphenylphosphine in an inert solvent such as a halogenated alkane (e.g., methylene chloride or carbon tetrachloride) at a temperature between about 0 degrees and the boiling point of the solvent, conveniently at about 0 °C degrees. A compound of formula 5 where LG
30 represents OSO₂E where E represents lower alkyl or aryl can be prepared by treating a compound of formula 12 where B represents CH₂OH with a sulfonyl chloride ESO₂Cl (for example, methanesulfonyl chloride or p-toluenesulfonyl chloride) in the presence of a base such as a tertiary amine (e.g., triethylamine or diisopropylethylamine) in an inert solvent such as a halogenated hydrocarbon (e.g., methylene chloride) at a temperature
35 between about 0 °C degrees and about room temperature, preferably at about 0 °C degrees. A compound of formula 5 where LG represents iodine can be prepared by treating a compound of formula 5 where LG represents chlorine, bromine, or OSO₂E

where E represents lower alkyl or aryl, with an alkali metal iodide (e.g., sodium iodide) in an inert solvent such as a ketone (e.g., acetone or methyl ethyl ketone) at a temperature between about 50 °C degrees and about 80 °C degrees, conveniently at about the boiling point of the solvent.

5 Starting Materials: Compounds of Formula 7

Many compounds of formula 7, where X represents a leaving group such as chlorine, iodine, bromine, or triflate, are known compounds and can be synthesized according to literature procedures. Some examples are included in the table.

Name	Reference
3-Bromo-4-chloro-phenol	Liedholm, B., <i>Acta Chem. Scand Series B</i> 1984, B38, 877-894
4-Bromo-2-chloro-phenol	Jaeger, R. et al., US 4,223,166
6-Bromo-5-chloro-pyridin-3-ol	Koch, V. et al., <i>Synthesis</i> 1990, 499-501
4-Bromo-2,6-dichlorophenol	Malm, J. et al., WO 02/62780
5-Bromo-2-hydroxy-benzene-sulfonamide	Meyer, W. et al., US 4,479,821
4-Bromo-3-nitro-phenol	Lavoie, E. J. et al., US 6,486,167
3-Bromo-4-methyl-phenol	Jacquesy, J. C., <i>J. Chem. Soc. Chem. Commun.</i> 1980, 110-111
5-Bromo-2-nitro-phenol	Makosza, M. et al., <i>J. Org. Chem.</i> 1998, 63, 4199-4208
3-Bromo-phenol	Matarasso-Tchiroukhine, E., <i>Ann. Chim. (Paris)</i> 1958, 3, 405-459 <i>Chem. Abs.</i> 53:34694
2-tert-Butyl-4-iodophenol	Tashiro, M. et al., <i>J. Org. Chem.</i> 1977, 42, 835-838
3,5-Dimethyl-4-iodophenol	Lu, Y. et al., <i>Synthesis</i> 2001, 1639-1644
3-Iodo-phenol	Noelting and Stricker, <i>Chem. Ber.</i> 1887, 20, 3019
5-Bromo-2-hydroxy-thiazole-4-carboxylic acid ethyl ester	Serra, G. et al., <i>Heterocycles</i> 1995, 41, 2701-2712

Name	Reference
5-Bromo-3-hydroxy-thiophene-2-carbonitrile	Binder, D. et al., <i>Arch. Pharm. (Weinheim)</i> 1988, 321, 391-395
6-Bromo-pyridin-2-ol	Wibaut, J. P. et al., <i>Recl. Trav. Chim. Pays-Bas</i> 1940, 59, 202-206
6-Bromo-pyridin-3-ol	den Hertog, H. J. et al., <i>Recl. Trav. Chim. Pays-Bas</i> 1950, 69, 1281-1288
2-Chloro-4,6-dimethyl-pyrimidinol	Hurst, D. T., <i>Heterocycles</i> 1984, 22, 79-84
2-Chloro-4-methoxy-6-methyl-pyrimidin-5-ol	Dohmori, R. et al., <i>Chem. Pharm. Bull.</i> 1970, 18, 1908-1914
2-Chloro-pyrimidin-5-ol	Hurst, D. T. et al., <i>J. Chem. Soc.</i> 1965, 7116-7119
6-Iodo-pyridin-3-ol	Edgar, K. J. et al., <i>J. Org. Chem.</i> 1990, 55, 5287-5291

In addition, many compounds of formula 7 are commercially available, including the following:

Name	Supplier
4-Bromo-2-chloro-phenol	Aldrich Chemical Company, Inc., Milwaukee, WI
4-Bromo-2-chloro-6-methyl-phenol	Lancaster Synthesis Ltd., Lancashire, UK
5-Bromo-2,3-difluoro-phenol	Lancaster Synthesis Ltd., Lancashire, UK
4-Bromo-3,5-dimethyl-phenol	Aldrich Chemical Company, Inc., Milwaukee, WI
5-Bromo-2-hydroxy-benzamide	SALOR, Aldrich Chemical Company, Inc., Milwaukee, WI
5-Bromo-2-hydroxy-benzonitrile	Oakwood Products, West Columbia, SC
5-Bromo-2-hydroxy-3-nitro-pyridine	Oakwood Products, West Columbia, SC
3-Bromo-5-hydroxy-pyridine	Specs and Biospecs, Rijswijk, Netherlands

Name	Supplier
4-Bromo-phenol	Aldrich Chemical Company, Inc., Milwaukee, WI
2-Chloro-3-fluoro-5-hydroxy-pyridine	Asymchem International, Inc., Durham, NC
5-Chloro-2-hydroxy-4,6-dimethyl-nicotinonitrile	Maybridge plc, Tintagel, UK
2-Chloro-5-hydroxy-pyridine	Asymchem International, Inc., Durham, NC
2-Hydroxy-5-bromo-pyrimidine	Lancaster Synthesis Ltd., Lancashire, UK
4-Iodo-2-methyl-phenol	Aldrich Chemical Company, Inc., Milwaukee, WI
3-Iodo-phenol	Aldrich Chemical Company, Inc., Milwaukee, WI
4-Iodo-phenol	Aldrich Chemical Company, Inc., Milwaukee, WI

Compounds of formula 7 that are neither known in the literature nor commercially available may be conveniently prepared by reactions that are well known in the field of organic synthesis as shown in Scheme 7.

5

Scheme 7.



A compound of formula 7 can be prepared from a compound of formula 13 where G and X represent the same substituent selected from among chlorine, bromine, and iodine, and Y represents methyl, using reactions that are well known in the field of organic synthesis. Several of these methods are outlined in "Protective Groups in Organic Synthesis" (T. W. Greene and P. G. M. Wuts, 2nd Edition, John Wiley & Sons, N.Y. 1991). For example, a compound of formula 7 can be formed by treating with trimethylsilyliodide a compound of formula 13 where G and X represent the same substituent selected from among chlorine, bromine, and iodine, and Y represents methyl. The reaction is conveniently carried out in an inert solvent, such as a halogenated alkane (e.g., chloroform) or acetonitrile, at a temperature between about room temperature and

15

the boiling point of the solvent, preferably at about 50 °C degrees. Alternatively, a compound of formula 7 can be formed by heating a compound of formula 13 where G and X represent the same substituent selected from among chlorine, bromine, and iodine, and Y represents methyl with hydrogen bromide in acetic acid or water at reflux.

5 As a third alternative, a compound of formula 7 can be formed by treating a compound of formula 13 where G and X represent the same substituent selected from among chlorine, bromine, and iodine, and Y represents methyl with boron tribromide in an inert solvent such as such as a halogenated alkane (e.g., chloroform or methylene chloride) at a temperature between about 0 °C degrees and about 40 °C degrees,

10 conveniently at about room temperature.

A compound of formula 7 where X represents chlorine and the position of attachment of X is para to the hydroxy group can be prepared by treating a compound of formula 13 where G represents hydrogen and Y represents hydrogen with sulfuryl chloride in an inert solvent such as ether or a halogenated hydrocarbon (e.g.

15 chloroform), at a temperature between about 0 °C degrees and about 35 °C degrees, preferably at about room temperature. A compound of formula 7 where X represents bromine and the position of attachment of X is para to the hydroxy group can be prepared by treating a compound of formula 13 where G represents hydrogen and Y represents hydrogen with bromine in an inert solvent such as water, or carbon

20 tetrachloride, or acetic acid, at a temperature between about 0 °C degrees and about room temperature, preferably at about room temperature. Alternatively, the same compound 7 where X represents bromine and the position of attachment of X is para to the hydroxy group can be prepared by treating a compound of formula 13 where G represents hydrogen and Y represents hydrogen with a tribromide salt (e.g.,

25 tetrabutylammonium tribromide or benzyltrimethylammonium tribromide) in an inert solvent such as a halogenated hydrocarbon (e.g. methylene chloride or chloroform) at a temperature between about 0 °C degrees and about room temperature, preferably at about room temperature. A compound of formula 7 where X represents iodine and the position of attachment of X is para to the hydroxy group can be prepared by treating a

30 compound of formula 13 where G represents hydrogen and Y represents hydrogen with iodine, or iodine monochloride in an inert solvent such as water, in the presence of an inorganic base such as an alkali metal hydroxide (e.g., sodium hydroxide) or an alkali metal carbonate (e.g., sodium carbonate) at a temperature between about 0 °C degrees and about room temperature, preferably at about room temperature. The same

35 compound of formula 7 where X represents iodine and the position of attachment of X is para to the hydroxy group can be prepared by treating a compound of formula 13 where G represents hydrogen and Y represents hydrogen with sodium iodide and sodium hypochlorite in an inert solvent such as a mixture of water and an alcohol (e.g.,

methanol), at a temperature close to 0 °C degrees. This last reaction and several alternatives are described in K. J. Edgar and S. N. Falling *J. Org. Chem.* 1990, 55, 5287-5291.

A compound of formula 7 where X represents chlorine, bromine, or iodine can be prepared by treating a compound of formula 13 where G represents NH₂ and Y represents hydrogen using the Sandmeyer reaction which is well known in the art of organic synthesis. Details of this reaction can be found in H. H. Hodgson *Chem. Rev.* 1947, 40, 251-277 and also in D. C. Nonhebel, Copper-catalyzed Single-electron Oxidations and Reductions, Special Publication—Chemical Society (London) 1970, 24, 409-437 ISSN: 0577-618X. For example, a compound of formula 13 where G represents NH₂ and Y represents hydrogen can be converted to a diazonium intermediate of formula 13 where G represents N₂⁺ and Y represents hydrogen by treatment with sodium nitrite in the presence of a mineral acid (for example, hydrochloric acid or sulfuric acid) in water at a temperature between about -10 °C degrees and about 10 °C degrees, preferably about 0 °C degrees. Without isolation, this diazonium intermediate can then be converted to a compound of formula 7 where X represents chlorine by treatment with copper(I) chloride, to a compound of formula 7 where X represents bromine by treatment with copper(I) bromide, or to a compound of formula 7 where X represents iodine by treatment with potassium iodide.

20 Starting Materials: Compounds of Formula 10

Many compounds of formula 10, where Y represents boronic acid, boronate ester, trimethyltin or tri-n-butyl-tin, are known compounds and can be synthesized according to literature procedures. Some examples are included in the table.

Name	Reference
4-Bromo-3,5-dimethyl-thiophen-2-yl-boronic acid	M. Takeshita et al., <i>J. Org. Chem.</i> 1998, 63, 6643-6649
(4-Bromo-5-methyl-thiophen-2-yl)-boronic acid	S. L. Gilat et al., <i>Chem. Eur. J.</i> 1995, 1, 275-284
2-Chloro-6-methyl-pyridin-3-yl-boronic acid	M. Nishida et al., JP 2003160586
2,5-Dichloro-thiophen-3-yl-boronic acid	A. Kuno et al., PCT Int. Appl. WO 9604241

Name	Reference
2,6-Dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine	Cho, J.-Y. et al., <i>J. Am. Chem. Soc.</i> 2000, 122, 12868-12869
2-(1-Ethoxyethyl)-phenyl-boronic acid	Dale, W. J. et al., <i>J. Org. Chem.</i> 1962, 27, 2598-2603
5-(Ethoxymethyl-pyridin-3-yl)-boronic acid	D. S. Hays et al., PCT Int. Appl. WO 2004058759
7-Ethyl-benzo[1,3]dioxole-5-boronic acid	T. E. Jacks et al., <i>Org. Proc. Res. Dev.</i> 2004, 8, 201-212
(5-Ethyl-furan-2-yl)-boronic acid	L. Carles et al., <i>J. Org. Chem.</i> 2002, 67, 4304-4308
(5-Ethyl-furan-2-yl)-trimethylstannane	Sasabe, M. et al., <i>Perkin 1</i> 2000, 3786-3790
(5-Ethyl-thiophen-2-yl)-boronic acid	M. F. Chan et al., PCT Int. Appl. WO 9631492
4-Fluoro-naphthalen-1-yl-boronic acid	J. A. Lowe III et al., <i>J. Med. Chem.</i> 2004, 47, 1575-1586
(3-Hydroxymethyl-thiophen-2-yl)-boronic acid	Y. Han et al., PCT Int. Appl. WO 9918099
(4-Hydroxymethyl-thiophen-3-yl)-boronic acid	O. Axelsson et al., Eur. Pat. Appl. EP 604353
5-Methoxymethyl-pyridin-3-yl-boronic acid	S. Bourrain et al., PCT Int. Appl. WO 9745432
(5-Methyl-furan-2-yl)-boronic acid	D. Florentin et al., <i>J. Heterocycl. Chem.</i> 1976, 13, 1265-1272
4-Methyl-naphthalen-1-yl-boronic acid	J. A. Lowe III et al., PCT Int. Appl. WO 9910339
2-Methyl-naphthalen-1-yl-boronic acid	A. N. Cammidge et al., <i>Tetrahedron</i> 2004, 60, 4377-4386
(3-Methyl-thiophen-2-yl)-boronic acid	Y. Li et al., <i>Macromolecules</i> 2002, 35, 6900-6905

Name	Reference
2-Methyl-thiophen-3-yl-boronic acid	A. Kuno et al., PCT Int. Appl. WO 9604241
4-n-Propyl-pyridin-3-yl-boronic acid	A. D. Borthwick et al., PCT Int. Appl. WO 2003053925
(5-Propyl-thiophen-2-yl)-boronic acid	A. Seed et al., <i>Liquid Crystals</i> 2003, 30, 1089-1107
Pyridin-3-yl-boronic acid	Fischer, F. C. et al., <i>Recl. Trav. Chim. Pays-Bas</i> 1974, 93, 21-24

In addition, many compounds of formula 10, where Y represents boronic acid, boronate ester, trimethyltin or tri-n-butyl-tin, are commercially available, including the following:

Name	Supplier
3-Acetamidobenzeneboronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
4-Acetamidophenylboronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
4-Acetamidophenylboronic acid	Apollo Scientific Ltd., Stockport, UK
(2-Aminocarbonylphenyl)boronic acid	Combi-Blocks Inc., San Diego, CA
(3-Aminocarbonylphenyl)boronic acid	Apollo Scientific Ltd., Stockport, UK
(4-Aminocarbonylphenyl)boronic acid	Apollo Scientific Ltd., Stockport, UK
1-Benzyl-1H-pyrazole-4-boronic acid	Frontier Scientific, Inc., Logan, UT
4-Benzyloxy-3-fluorobenzeneboronic acid	Lancaster Synthesis Ltd., Morecambe, UK
(2-Benzyloxy-4-fluorophenyl)boronic acid	ABCR GmbH & CO. KG, Karlsruhe, Germany
(2-Benzyloxyphenyl)boronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
3-Benzyloxyphenylboronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI

Name	Supplier
Biphenyl-3-boronic acid	Lancaster Synthesis Ltd., Morecambe, UK
5-Bromopyridine-3-boronic acid	Lancaster Synthesis Ltd., Morecambe, UK
(3-Bromo-2-thienyl)-boronic acid	Rare Chemicals GmbH, Gettorf, Germany
4-Bromo-2-thienylboronic acid	Acros Organics USA, Morris Plains, NJ
5-Bromothiophene-2-boronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
2-Chloro-5-fluoropyridine-3-boronic acid	Asymchem Laboratories, Inc., Durham, NC
2-Chloropyridine-3-boronic acid	Lancaster Synthesis Ltd., Morecambe, UK
2-Chloropyridine-5-boronic acid	Asymchem Laboratories, Inc., Durham, NC
2-Chlorothiophene-3-boronic acid	Asymchem Laboratories, Inc., Durham, NC
4-Chlorothiophene-2-boronic acid	Digital Specialty Chemicals, Inc., Dublin, NH
5-Chlorothiophene-2-boronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
(2,6-Dichloro-3-pyridinyl)-boronic acid	Asymchem Laboratories, Inc., Durham, NC
3,5-Dimethylisoxazole-4-boronic acid	Acros Organics USA, Morris Plains, NJ
3,5-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	Boron Molecular Pty Ltd, Noble Park, Australia
2-Fluoro-6-methylpyridine-3-boronic acid	Asymchem Laboratories, Inc., Durham, NC
2-Fluoro-6-methylpyridine-5-boronic acid	Asymchem Laboratories, Inc., Durham, NC
4-Fluoronaphthylene-1-boronic acid	Apollo Scientific Ltd., Stockport, UK

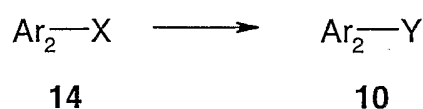
Name	Supplier
2-Fluoropyridine-3-boronic acid	Lancaster Synthesis Ltd., Morecambe, UK
2-Fluoropyridine-5-boronic acid	Frontier Scientific, Inc., Logan, UT
Furan-2-boronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
Furan-3-boronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
5-Hydroxymethylfuran-2-boronic acid	Asymchem Laboratories, Inc., Durham, NC
3-(Hydroxymethyl)phenylboronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
(2-Hydroxymethylphenyl)boronic acid dehydrate	Asymchem Laboratories, Inc., Durham, NC
5-Hydroxymethylthiophene-2-boronic acid	Asymchem Laboratories, Inc., Durham, NC
1-Isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	Boron Molecular Pty Ltd, Noble Park, Australia
5-Isoquinolineboronic acid	Frontier Scientific, Inc., Logan, UT
2-Methoxymethylphenylboronic acid	Apollo Scientific Ltd., Stockport, UK
3-Methoxymethylphenylboronic acid	Digital Specialty Chemicals, Inc., Dublin, NH
2-Methoxy-pyridine-3-boronic acid	Lancaster Synthesis Ltd., Lancashire, UK
3,4-Methylenedioxybenzeneboronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
4-Methyl-furan-2-boronic acid	Rare Chemicals GmbH, Gettorf, Germany
5-Methylfuran-2-boronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
(4-Methyl-1-naphthalene)boronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI

Name	Supplier
(4-Methyl-3-pyridinyl)-boronic acid	Synchem Laborgemeinschaft OHG, Kassel, Germany
(5-Methyl-3-pyridinyl)-boronic acid	Chontech, Inc., Waterford, CT
8-Methyl-5-quinolineboronic acid	ACB Blocks Ltd., Moscow, Russia
1-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan)-1H-pyrazole	Aldrich Chemical Company, Inc., Milwaukee, WI
4-Methylthiophene-2-boronic acid	Acros Organics USA, Morris Plains, NJ
4-Methylthiophene-3-boronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
5-Methylthiophene-2-boronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
1-Naphthaleneboronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
(2-Phenoxy)phenylboronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
5-Phenyl-2-thienylboronic acid	Acros Organics USA, Morris Plains, NJ
Pyridine-3-boronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
5-Quinolineboronic acid	Lancaster Synthesis Ltd., Morecambe, UK
4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	Aldrich Chemical Company, Inc., Milwaukee, WI
Thiophene-2-boronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
Thiophene-3-boronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
2-(Trifluoromethoxy)benzeneboronic acid	Apin Chemicals Ltd., Abingdon, UK
3-(Trifluoromethoxy)benzeneboronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI
4-(Trifluoromethoxy)benzeneboronic acid	Aldrich Chemical Company, Inc., Milwaukee, WI

Name	Supplier
Trimethyl(phenyl)tin	Aldrich Chemical Company, Inc., Milwaukee, WI
3-(Tri-n-butylstannyl)pyridine	Maybridge plc, Tintagel, UK
Tri-n-butyl(2-thienyl)tin	Aldrich Chemical Company, Inc., Milwaukee, WI

Compounds of formula 10, where Y represents boronic acid, boronate ester, trimethyltin or tri-n-butyl-tin, that are neither known in the literature nor commercially available can be synthesized by procedures that are well known to one skilled in the art of organic synthesis. For example, a compound of this type can conveniently be synthesized according to Scheme 8 from a compound of formula 14, in which X represents bromine or iodine, by treatment with an alkyllithium (e.g., n-butyllithium) or magnesium (to form the Grignard reagent) in a suitable inert solvent such as an ether (such as tetrahydrofuran or diethyl ether) at a temperature appropriate for the reaction (for example, at approximately -78 degrees for reaction with an alkyllithium, or at approximately room temperature for reaction with magnesium), followed by treatment with a trialkyl borate or trialkyltin chloride to form the compound of formula 10 where Y represents B(OH)₂ or trialkyltin, respectively.

Scheme 8



15

Additionally, the reaction can be carried out under noble metal catalysis. According to this route, the compound of formula 14 is conveniently reacted with a hexa-alkyl-distannane (such as hexamethyl-distannane or hexa-n-butyl-di-stannane) or 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane or 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl], in the presence of a noble metal catalyst (preferably a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) chloride or palladium (II) acetate), and in the optional additional presence of a catalytic amount of a phosphine ligand, for example tri-o-tolylphosphine or tri-tert-butylphosphine. In the case of reaction with a hexa-alkyl-distannane, the reaction is optionally carried out in the presence of an organic base, for example, a tertiary amine (e.g., triethylamine), while in the case of reaction with a dioxaborolane, the reaction is carried out in the presence of an inorganic base (e.g., cesium fluoride, or potassium acetate, preferably potassium acetate).

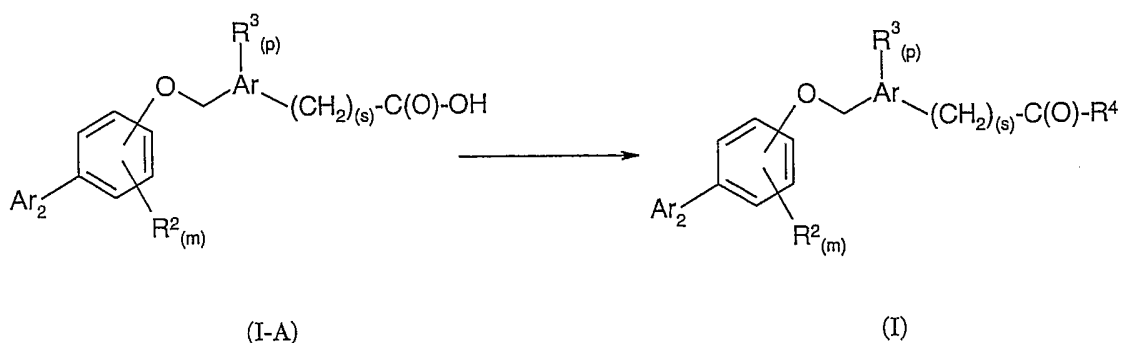
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The reaction is conveniently carried out in an appropriate inert solvent such as a polar aprotic solvent (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, or acetonitrile) or an aromatic hydrocarbon (e.g., toluene) at a temperature between about room temperature and about 100 °C degrees, and preferably at between about room temperature and about 50 °C degrees. As additional examples, the specific reaction conditions utilized in the following publications can be followed: O. Baudoin et al. *J. Org. Chem. Soc.* 2000, 65, 9268-9271; T. Ishiyama et al. *Tetrahedron Lett.* 1997, 38, 3447-3450; M. D. Hylarides *J. Organomet. Chem.* 1989, 367, 259-265; M. W. Read et al. *Org. Lett.* 2000, 2, 3201-3204; T. Ishiyama et al. *Tetrahedron* 1997, 57, 9813-9816; A. Fuerster et al. *Org. Lett.* 2002, 4, 541-544.

Acylated Amino Acids

As shown in Scheme 9, a compound of the invention of formula 1 where R⁴ represents a hydroxy group can be converted to a compound of formula 1 where R⁴ represents an amino acid attached through a nitrogen atom of the amino acid. This reaction can be carried out using a variety of procedures that are well known in the field of organic synthesis, and especially well known in the field of peptide synthesis. The reaction is typically carried out in two steps. First, the compound of formula 1 where R⁴ represents a hydroxy group is reacted with a suitably protected amino acid to give an intermediate of formula 1 where R⁴ represents a protected amino acid, and subsequently the protective group is removed to give the compound of formula 1 where R⁴ represents an amino acid attached through a nitrogen atom of the amino acid. Many examples of suitable protective groups for the amino acid are known to those of skill in the art of organic synthesis. For example, several suitable protective groups are enumerated in "Protective Groups in Organic Synthesis" [T. W. Greene and P. G. M. Wuts, 2nd Edition, John Wiley & Sons, N.Y. 1991]. Preferred protective groups are those compatible with the reaction conditions used to prepare compounds of the invention. Examples of such protective groups are lower alkyl straight-chain or branched esters (e.g., the methyl, the ethyl, or the tert-butyl ester), or the benzyl ester.

Scheme 9



For example, the first reaction can be carried out by treating the compound of formula 1 in which R⁴ represents a hydroxy group, with a protected amino acid in the presence of a coupling agent, many examples of which are well known per se in peptide chemistry, and in the optional presence of a substance that increases the rate of the reaction, such as 1-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole; or by reaction of the protected amino acid with a reactive derivative of the compound of formula 1 in which R⁴ represents a hydroxy group such as the corresponding acid halide (for example, the acid chloride), acid anhydride, mixed anhydride, activated ester etc. The reaction is conveniently carried out by treating the protected amino acid with the compound of formula 1 in which R⁴ represents a hydroxy group in the presence of a carbodiimide reagent such as diisopropyl carbodiimide and 1-hydroxy-7-azabenzotriazole in an inert solvent such as N,N-dimethylformamide or N-methylpyrrolidinone at a temperature between about 0 °C degrees and about room temperature, preferably at about room temperature.

The removal of the protective group from the compound of formula 1 in which R⁴ represents a protected amino acid attached through a nitrogen atom of the amino acid can be effected using one of several choices of reactions conditions, the selection of which will depend on the nature of the protective group, and the other functionality present in the compound of formula 1. Many suitable reaction conditions are outlined in "Protective Groups in Organic Synthesis" [T. W. Greene and P. G. M. Wuts, 2nd Edition, John Wiley & Sons, N.Y. 1991]. For example, in the case where the protective group is methyl or ethyl, the reaction can be conveniently effected by treating the compound with one equivalent of an alkali metal hydroxide, such as potassium hydroxide, sodium hydroxide, or lithium hydroxide, preferably lithium hydroxide, in a suitable solvent, such as a mixture of tetrahydrofuran, methanol, and water. The reaction can be carried out at a temperature between about 0 °C degrees and about room temperature, preferably at about room temperature. As another example, in the case where the protective group is a group that can be cleaved under acidic conditions, such as a tert-butyl group, the ester may be treated with a strong inorganic acid, for example a hydrohalic acid such as hydrogen chloride or hydrogen bromide, or a strong organic acid, for example a halogenated alkane carboxylic acid such as trifluoroacetic acid and the like. The reaction is conveniently carried out in the presence of an inert organic solvent (such as dichloromethane) and at a temperature between about 0 °C degrees and about room temperature, preferably at about room temperature. As a final (but not limiting) example, in the case where the protective group is a group that can be cleaved by catalytic hydrogenation, and with the further condition that the rest of the molecule is stable to such conditions, the reaction may be carried out by hydrogenation in the presence of a noble metal catalyst such as palladium-on-carbon in the presence of an inert solvent (for

example, an alcohol such as ethanol) at about room temperature and under atmospheric pressure.

Examples

The following examples illustrate preferred methods for synthesizing the
5 compounds and formulations of the present invention.

The purity of the exemplified compounds was determined by analytical HPLC. Where the purity of the compound did not exceed 85 percent as judged by UV absorption at 214 nm, the compound was purified by preparative HPLC. The conditions for analytical and preparative HPLC are given below.

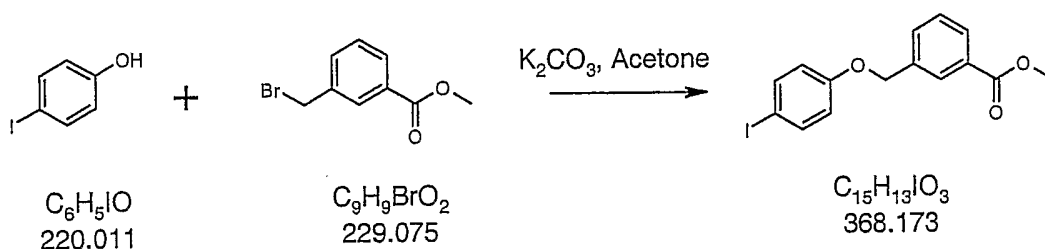
10 Analytical HPLC

Analytical HPLC was carried out with a Waters 600 LC pump and Supelco Discovery C18 column (5 μ m, 50 mm x 4.6 mm). Mobile phases A (0.1% formic acid in water) and B (0.1% formic acid in acetonitrile) were used in a gradient of 5% B rising to 98% B after 5 mins, held for 4 min at a flow rate of 2 mL/min. Photo-diode array (PDA)
15 detection was by a Waters 996 Photodiode Array Detector, range 210-400 nm UV and ELS detection with a Polymer Laboratories PL-ELS 1000 (Nitrogen flow rate 1.3 L/min. Nebulizer temp. 80 $^{\circ}$ C, Evap. temp. 110 $^{\circ}$ C). The Mass spectrometer was a Micromass ZQ operating in electrospray ionization mode.

Preparative HPLC

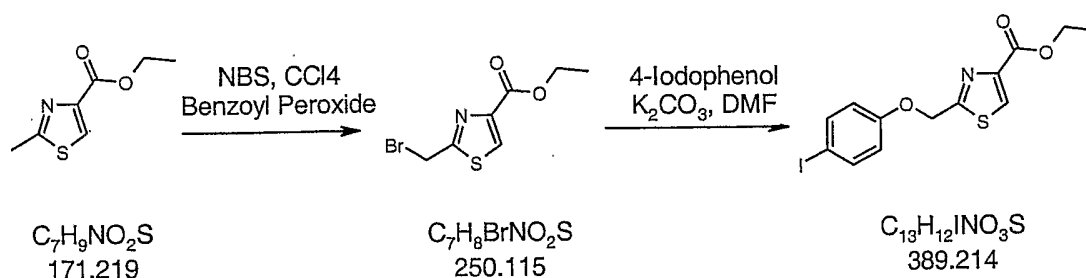
20 Samples that required purification were purified with a Waters mass-directed purification system utilizing a Waters 600 LC pump, Waters Xterra C18 column (5 μ m, 19 mm x 50 mm) and Micromass ZQ mass spectrometer, operating in positive ion electrospray ionization mode. Mobile phases A (0.1% formic acid in water) and B (0.1% formic acid in acetonitrile) were used in a gradient; 5% B to 30% B over 7 mins, held for
25 1 min, at a flow rate of 20 mL/min.

Intermediate 1: 3-(4-Iodo-phenoxy)methyl)-benzoic acid methyl ester



Freshly ground potassium carbonate (8.3 g, 60 mmol) was added to a solution of methyl 3-bromomethyl-benzoate (12.83 g, 56 mmol; available from Lancaster Synthesis Ltd., Lancashire, UK) and 4-iodophenol (13.2 g, 60 mmol; available from Aldrich Chemical Company, Inc., Milwaukee, WI) in acetone (600 mL). The reaction mixture was heated at reflux overnight and then it was filtered and water was added. The resulting white solid was filtered off and dried in a vacuum oven overnight to give 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (18.63 g, 90%) as a white solid.

Intermediate 2: 2-(4-Iodo-phenoxy-methyl)-thiazole-4-carboxylic acid ethyl ester



Step 1: 2-Bromomethyl-thiazole-4-carboxylic acid ethyl ester

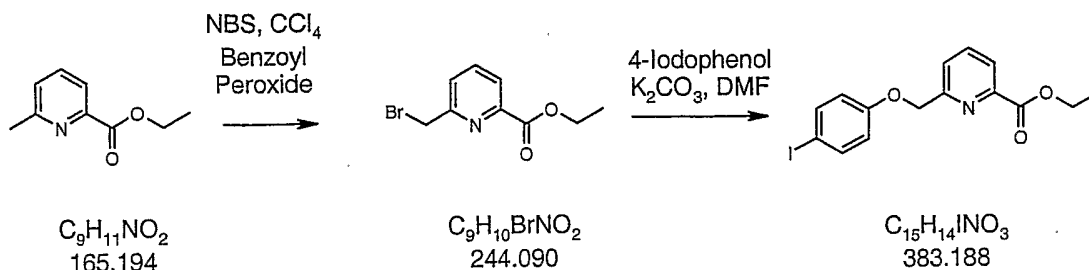
2-Bromomethyl-thiazole-4-carboxylic acid ethyl ester was prepared according to N. Kindon et al. (US 6,162,808): A mixture of 2-methyl-thiazole-4-carboxylic acid (available from Maybridge plc, Tintagel, UK; 9.8 g, 57.2 mmol), benzoyl peroxide (40 mg, 0.165 mmol) and NBS (10.6 g, 60.0 mmol) in carbon tetrachloride (250 mL) was heated at reflux over the weekend. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The crude material was partitioned between ethyl acetate and water. The organic layer was dried (magnesium sulfate), filtered, evaporated, and purified by chromatography on flash silica gel, eluting with 20% ethyl acetate/hexane to give 2-bromomethyl-thiazole-4-carboxylic acid ethyl ester (4.4 g, 31%) as an orange oil. ¹HNMR (CDCl₃): δ 9.23 (s, 1H), 4.77 (s, 2H), 4.44 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H). MS (APCI+): 252 (100), 250 (90).

Step 2: 2-(4-Iodo-phenoxy-methyl)-thiazole-4-carboxylic acid ethyl ester

Ground potassium carbonate (3.4 g, 24.6 mmol) was added to a solution of 2-bromomethyl-thiazole-4-carboxylic acid ethyl ester (12.83 g, 56 mmol; from Step 1 above) and 4-iodophenol (5.5 g, 25 mmol; available from Aldrich Chemical Company, Inc., Milwaukee, WI) in acetone (440 mL). The reaction mixture was heated at reflux for 15 h and then it was filtered and water was added to the filtrate until it turned cloudy. The filtrate was left on ice and then the resulting white solid was filtered off, washed with acetone/hexanes (2:1) and dried to give 2-(4-iodo-phenoxy-methyl)-thiazole-4-carboxylic acid ethyl ester (5.6 g, 65%) as a white solid. ¹HNMR (CDCl₃): δ 1.4 (t, 3H, J = 7 Hz),

4.46 (q, 2 H, J = 7 Hz), 5.4 (s, 2 H), 6.7 (d, 2 H, J = 9 Hz), 7.6 (d, 2 H, J = 9 Hz), 8.2 (s, 1 H).

Intermediate 3: 6-(4-Iodo-phenoxyethyl)-pyridine-2-carboxylic acid ethyl ester



5 Step 1: 6-Bromomethyl-pyridine-2-carboxylic acid ethyl ester

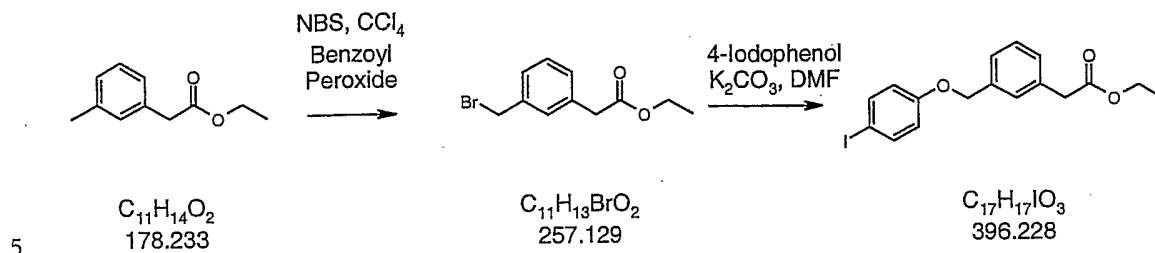
Finely ground N-bromo-succinimide (29.4 g, 165.2 mmol) was added in several portions to a solution of 6-methyl-pyridine-2-carboxylic acid ethyl ester (24.7 g, 150.0 mmol; available from Aldrich Chemical Company, Inc., Milwaukee, WI) in carbon tetrachloride (500 mL), and then benzoyl peroxide (100 mg, 0.4 mmol) was added. The mixture was heated at 84 °C degrees under nitrogen for approximately 40 h. Further portions of N-bromo-succinimide (14.8 g, 83.2 mmol) and then benzoyl peroxide (100 mg, 0.4 mmol) were added and heating was continued overnight. The reaction mixture was cooled to room temperature, filtered, evaporated, and purified by chromatography on silica gel using a Biotage system, eluting with 1:1 dichloromethane/hexane and dichloromethane to give 6-bromomethyl-pyridine-2-carboxylic acid ethyl ester (11.8 g, 32%) as a pale yellow oil. MS (MH⁺): 244/246. From HPLC, the purity was estimated at 85-90% and the material was used in the next step without further purification.

Step 2: 6-(4-Iodo-phenoxyethyl)-pyridine-2-carboxylic acid ethyl ester

6-Bromomethyl-pyridine-2-carboxylic acid ethyl ester (11.72 g, 48 mmol; from Step 1 above) was dissolved in acetone (250 mL) and 4-iodophenol (11.61 g, 52.8 mmol; available from Aldrich Chemical Company, Inc., Milwaukee, WI) was added, followed by potassium carbonate (7.55 g, 54.6 mmol). The mixture was heated overnight at 65 °C degrees, and it was then cooled and filtered. The solid was washed with small portions of acetone and the filtrate was concentrated to approximately 100 mL by evaporation. The solution was warmed and then diluted with water (approximately 70 mL). The resulting brown solution was cloudy and started to precipitate an oily solid. The mixture was scratched with a spatula and allowed to cool to room temperature. The off-white precipitate was filtered off, washed with several portions of acetone/water (1:1), and then dried in vacuo over phosphorus pentoxide to give 6-(4-iodo-phenoxyethyl)-pyridine-2-carboxylic acid ethyl ester (13.72 g, 75%) as an off-white crystalline solid. MS (MH⁺)

384. $^1\text{H NMR}$ (CDCl_3): δ 1.47 (t, 3H, $J = 7$ Hz), 4.52 (q, 2 H, $J = 7$ Hz), 5.33 (s, 2 H), 6.78 (d, 2 H, $J = 9$ Hz), 7.58 (d, 2 H, $J = 9$ Hz), 7.74 (d, 1 H, $J = 7.8$ Hz), 7.91 (dd, 1 H, $J = 7.8, 7.8$ Hz), 8.09 (d, 1 H, $J = 7.8$ Hz).

Intermediate 4: [3-(4-Iodo-phenoxy)methyl]-phenyl]-acetic acid ethyl ester

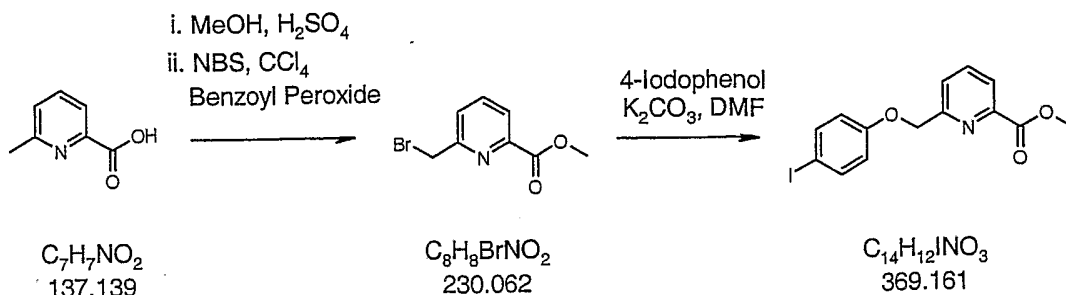


Step 1: (3-Bromomethyl-phenyl)-acetic acid ethyl ester

A mixture of N-bromo-succinimide (10.68 g, 60.0 mmol), m-tolyl-acetic acid ethyl ester (10.0 g, 56.1 mmol; available from Aldrich Chemical Company, Inc., Milwaukee, WI) and benzoyl peroxide (40 mg, 0.17 mmol) in carbon tetrachloride (250 mL) was heated at reflux under nitrogen for 36 h. The reaction mixture was filtered, evaporated, and purified by chromatography on silica gel, eluting with 0-100% dichloromethane in hexane to give (3-bromomethyl-phenyl)-acetic acid ethyl ester (4.79 g, 33%). MS m/z 257. $^1\text{H NMR}$ ($\text{DMSO}-d_6$): δ 7.2-7.35 (m, 4H), 4.50 (s, 2 H), 4.18 (q, 2 H), 3.62 (s, 2 H), 1.28 (t, 3 H).

15 Step 2: [3-(4-Iodo-phenoxy)methyl]-phenyl]-acetic acid ethyl ester

(3-Bromomethyl-phenyl)-acetic acid ethyl ester (4.37 g, 17.0 mmol; from Step 1 above) was dissolved in acetone (100 mL) and 4-iodophenol (4.11 g, 18.7 mmol; available from Aldrich Chemical Company, Inc., Milwaukee, WI) was added, followed by potassium carbonate (2.66 g, 19.3 mmol). The mixture was heated overnight at reflux, and it was then combined with material from an earlier run using the same conditions but on a 2 mmol scale. The combined materials were cooled and filtered. The solid was washed with acetone and the filtrate was evaporated to give an oil (8 g). The solution was purified by chromatography using a Biotage system with an S90 cartridge, eluting with 0-50% dichloromethane in hexane to give [3-(4-iodo-phenoxy)methyl]-phenyl]-acetic acid ethyl ester (4.3 g, 57%). $^1\text{H NMR}$ (CDCl_3): δ 1.26 (t, 3H, $J = 7$ Hz), 3.65 (s, 2 H), 4.16 (q, 2 H, $J = 7$ Hz), 5.04 (s, 2 H), 6.76 (d, 2 H, $J = 9$ Hz), 7.26-7.37 (m, 4 H + solvent), 7.57 (d, 2 H, $J = 9$ Hz).

Intermediate 5: 6-(4-Iodo-phenoxy)methyl-pyridine-2-carboxylic acid methyl ester

Step 1: 6-Methyl-pyridine-2-carboxylic acid methyl ester

Concentrated sulfuric acid (5 mL) was added cautiously with stirring to a
 5 suspension of 6-methyl-pyridine-2-carboxylic acid (available from Aldrich Chemical
 Company, Inc., Milwaukee, WI; 7.00 g, 51 mmol) in methanol (approximately 250 mL).
 The mixture was heated at reflux overnight (with a calcium chloride drying tube) and
 then the solution was concentrated almost to dryness. A little water was added and then
 aqueous sodium bicarbonate was added to bring the pH to 8. The solution was extracted
 10 with ethyl acetate (2 x 100 mL) and the extracts were washed with brine, then dried
 (magnesium sulfate), filtered, and evaporated to give 6-methyl-pyridine-2-carboxylic
 acid methyl ester (3.53 g, 46%) as a pale yellow oil. Mass spectrum *m/z* 152.

Step 2: 6-Bromomethyl-pyridine-2-carboxylic acid methyl ester

N-Bromosuccinimide (4.9 g, 27.3 mmol) was added in portions to a stirred
 15 solution of 6-methyl-pyridine-2-carboxylic acid methyl ester (3.90 g, 25.8 mmol) in
 carbon tetrachloride (100 mL). Dibenzoyl peroxide (20 mg) was added and the mixture
 was heated in an oil bath at 85 °C degrees for two days. TLC (eluting with
 dichloromethane) showed that there was unreacted starting material in addition to two
 new spots, so further quantities of N-bromosuccinimide (1.1g, 6.1 mmol) and dibenzoyl
 20 peroxide (20 mg) were added and the reaction mixture was heated at reflux for 24 hours,
 and then filtered to remove succinimide. The filtrate was evaporated to give an oil that
 was chromatographed on silica gel (Biotage 90) eluting with 0-100%
 dichloromethane/hexanes to give 6-bromomethyl-pyridine-2-carboxylic acid methyl
 ester (2.27 g, 38%) as a crystalline solid. Mass spectrum *m/z* 230/232.

25 Step 3: 6-(4-Iodo-phenoxy)methyl-pyridine-2-carboxylic acid methyl ester

6-Bromomethyl-pyridine-2-carboxylic acid methyl ester (2.27 g, 9.9 mmol; from
 Step 2 above) was dissolved in acetone (50 mL) and 4-iodophenol (2.37 g, 10.8 mmol;
 available from Aldrich Chemical Company, Inc., Milwaukee, WI) was added, followed by
 finely ground potassium carbonate (1.54 g, 11.2 mmol). The mixture was heated

overnight at 60 °C degrees, and it was then cooled and filtered. The solid was washed with acetone and the filtrate was concentrated to dryness. Ethyl acetate (100 mL) was added and the solution was washed twice with 2 M NaOH, with water, and with brine. The solution was dried (magnesium sulfate), filtered and evaporated to give the crude
5 product. This was dissolved in acetone (approximately 25 mL) with warming, and water (approximately 20 mL) was added. An oil came out of solution and it crystallized. The mixture was heated to redissolve the solid and the solution was seeded with a crystal of the product to give crystals of the product. The recrystallization was repeated to give 6-
(4-iodo-phenoxyethyl)-pyridine-2-carboxylic acid methyl ester (2.24 g, 62%) as a white
10 crystalline solid. Mass spectrum m/z 370.

General Procedure 1 for the Preparation of 3-Biaryloxyethyl-benzoic acids

A stock solution was prepared consisting of 3-(4-iodo-phenoxyethyl)-benzoic acid methyl ester (of intermediate 1; 962 mg, 2.6 mmol), potassium carbonate (1079 mg, 7.8 mmol), bis(tri-cyclohexylphosphine)palladium (available from Strem Chemicals,
15 Inc., Newburyport, MA; 91 mg, 0.14 mmol), water (approximately 5.8 mL), and dioxane (approximately 58 mL). The solution was sonicated and degassed by bubbling nitrogen gas through it. A portion of this solution (4.5 mL) was added to each of a number of tubes containing an aryl-boronic acid. The mixtures were each heated in a microwave oven at 170 °C degrees for 25 min. The mixtures were filtered in parallel with silica
20 cartridges and washed with dioxane (1 mL) and dimethylacetamide (1 mL). The filtrates were placed in vials and 2 M potassium hydroxide solution (0.4 mL) was added to each vial. The mixtures were stirred at room temperature overnight, then 1 M HCl (0.8 mL) was added to each vial and the solvents were evaporated using a Genevac system. Aqueous methanol (50%; approximately 2 mL) was added to each vial, then the vials
25 were centrifuged and the solvent was removed. This process was repeated and then the samples were dried overnight in the oven.

General Procedure 2 for the Preparation of 2-Biaryloxyethyl-thiazole-4-carboxylic acids

A first stock solution was prepared consisting of 2-(4-iodo-phenoxyethyl)-
30 thiazole-4-carboxylic acid ethyl ester (of intermediate 2; 1.87 g, 4.8 mmol), bis(tri-cyclohexyl-phosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 168 mg, 0.25 mmol), and dioxane (approximately 100 mL). A second stock solution was prepared consisting of potassium carbonate (1.99 g, 14.4 mmol) and water (approximately 10 mL). The solutions were sonicated and degassed by bubbling nitrogen
35 gas through them. 4 mL of the first stock solution and 0.4 mL of the second stock solution were added to each of a number of tubes containing an aryl-boronic acid. The

mixtures were each heated in a microwave oven at 170 °C degrees for 25 min. 1 M HCl (0.1 mL) was added to each vial, and the solution were passed through silica gel columns (1 g of silica), and washed with dimethylacetamide (2 x 1 mL). The solutions were evaporated to dryness and triturated with aqueous methanol (2 x 2 mL) to give the
5 product.

General Procedure 3 for the Preparation of 6-Biaryloxymethyl-pyridine-2-carboxylic acids

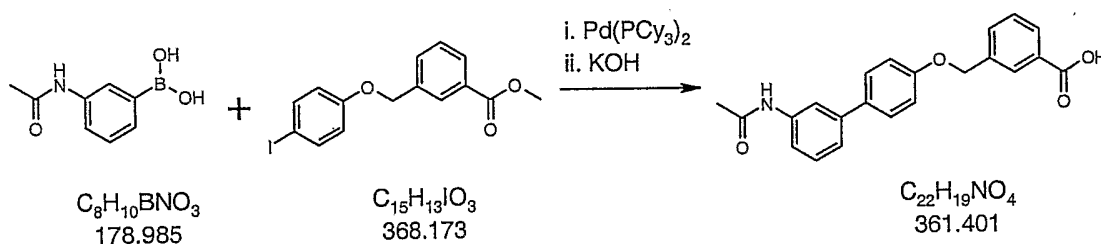
A first stock solution was prepared consisting of 6-(4-iodo-phenoxyethyl)-pyridine-2-carboxylic acid ethyl ester (of intermediate 3; 1.85 g, 4.8 mmol), bis(tri-
10 cyclohexyl-phosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 168 mg, 0.25 mmol), and dioxane (approximately 96 mL). A second stock solution was prepared consisting of potassium carbonate (1.99 g, 14.4 mmol) and water (approximately 9.6 mL). The solutions were sonicated and degassed by bubbling nitrogen gas through them. 4 mL of the first stock solution and 0.4 mL of the second stock
15 solution were added to each of a number of tubes containing an aryl-boronic acid. The mixtures were each heated in a microwave oven at 170 °C degrees for 25 min, then filtered through a 20 micron polyethylene filter and washed with dimethylacetamide (2 x 1 mL). The crude products were purified by preparative HPLC (see above for conditions). Fractions containing the purified product were evaporated to dryness using
20 a Genevac system.

General Procedure 4 for the Preparation of 3-Biaryloxymethyl-phenylacetic acids

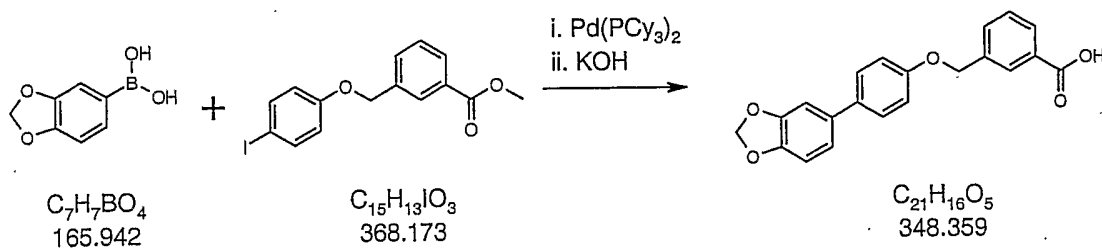
A first stock solution was prepared consisting of [3-(4-iodo-phenoxyethyl)-phenyl]-acetic acid ethyl ester (of intermediate 4; 1.89 g, 4.8 mmol), bis(tri-cyclohexyl-
25 phosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 168 mg, 0.25 mmol), and dioxane (approximately 96 mL). This solution was sonicated and degassed by bubbling nitrogen gas through it. A second stock solution was prepared consisting of potassium carbonate (1.99 g, 14.4 mmol) and water (approximately 9.6 mL). 4 mL of the first stock solution and 0.4 mL of the second stock solution were added to each of a number of tubes containing an aryl-boronic acid. The mixtures were each
30 heated in a microwave oven at 170 °C degrees for 25 min. To each reaction mixture was added 1 M KOH solution (0.8 mL, 0.8 mmol) and the solutions were heated at 60 °C degrees overnight. 1 M HCl (0.8 mL, 0.8 mmol) was added to each solution and the reactions were then filtered through silica (1 g) and washed with dimethylacetamide. The solutions were evaporated to dryness using a Genevac system and further dried in the
35 vacuum oven at 50 °C degrees.

General Procedure 5 for the Preparation of 3-Biaryloxymethyl-phenylacetic acids

A first stock solution was prepared consisting of [3-(4-iodo-phenoxy-methyl)-phenyl]-acetic acid ethyl ester (of intermediate 4; 1.89 g, 4.8 mmol), bis(tri-cyclohexyl-phosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 168 mg, 0.25 mmol), and dioxane (approximately 96 mL). This solution was sonicated and degassed by bubbling nitrogen gas through it. A second stock solution was prepared consisting of potassium carbonate (1.99 g, 14.4 mmol) and water (approximately 9.6 mL). 4 mL of the first stock solution and 0.4 mL of the second stock solution were added to each of a number of tubes containing an aryl-boronic acid. The mixtures were each heated in a microwave oven at 170 °C degrees for 25 min. To each reaction mixture was added 2 M KOH solution (0.4 mL, 0.8 mmol) and the solutions were heated at 65 °C degrees overnight. 2 M HCl (0.4 mL, 0.8 mmol) was added to each solution and the reactions were then filtered through silica (3 g). The solutions were evaporated to dryness using a Genevac system and the resulting solids were triturated with 50% aqueous methanol (2 x 2 mL) to give the products.

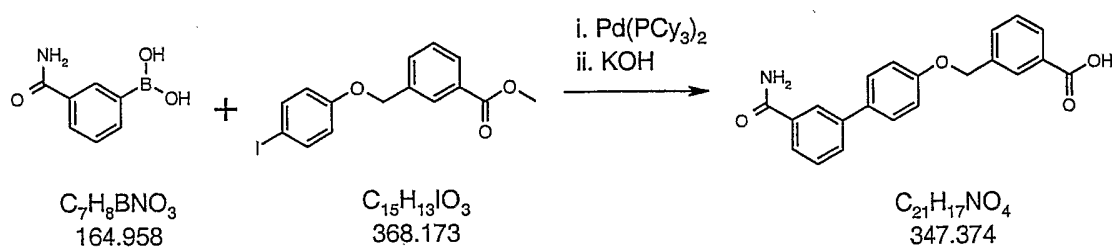
Example 1: 3-(3'-Acetylamino-biphenyl-4-yloxymethyl)-benzoic acid

3-(3'-Acetylamino-biphenyl-4-yloxymethyl)-benzoic acid was prepared using general procedure 1 from 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1) and 3-acetamidobenzeneboronic acid (ASDI Incorporated, Newark, DE). Mass spectrum $\text{MH}^+ = 362$.

Example 2: 3-(4-Benzo[1,3]dioxol-5-yl-phenoxy-methyl)-benzoic acid

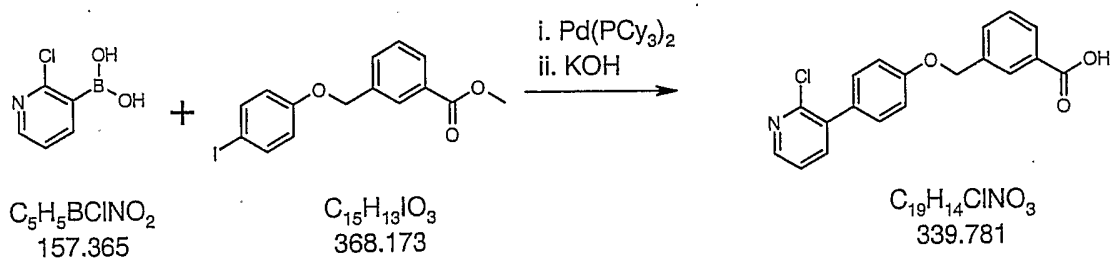
3-(4-Benzo[1,3]dioxol-5-yl-phenoxy-methyl)-benzoic acid was prepared using general procedure 1 from 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1) and 3,4-methylenedioxybenzeneboronic acid (ASDI Incorporated, Newark, DE). Mass spectrum $MH^+ = 349$.

5 Example 3: 3-(3'-Carbamoyl-biphenyl-4-yloxymethyl)-benzoic acid



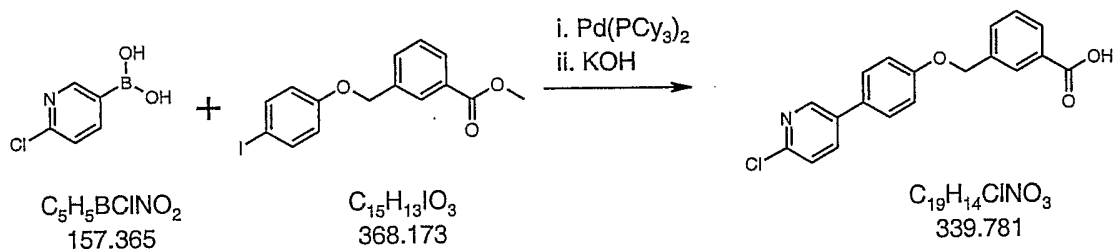
A first stock solution was prepared consisting of 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1; 1.11 g, 3 mmol), bis(tri-cyclohexyl-phosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 105 mg, 10
 0.16 mmol), and dioxane (approximately 62 mL). A second stock solution was prepared consisting of potassium carbonate (1.245 g, 9 mmol) and water (approximately 6.2 mL). The solutions were sonicated and degassed by bubbling nitrogen gas through them. 4 mL
 of the first stock solution and 0.4 mL of the second stock solution were added to a reaction vial containing (3-aminocarbonylphenyl)boronic acid (available from Apollo
 15 Scientific Ltd., Stockport, UK; 99 mg, 0.6 mmol). The mixture was heated in a microwave oven at 170 degrees for 25 min and then passed through a silica gel column (1 g of silica), and washed with dioxane (1 mL) and dimethylacetamide (1 mL). 2 M potassium
 hydroxide solution (0.4 mL) was added. The mixture was stirred at room temperature overnight, and then 1 M HCl (0.8 mL) was added and the solvents were removed in the
 20 Genevac. Aqueous methanol (50%; approximately 2 mL) was added, then the vial was centrifuged and the solvent was removed. This process was repeated to give 3-(3'-carbamoyl-biphenyl-4-yloxymethyl)-benzoic acid. Mass spectrum $MH^+ = 348$.

Example 4: 3-[4-(2-Chloro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid



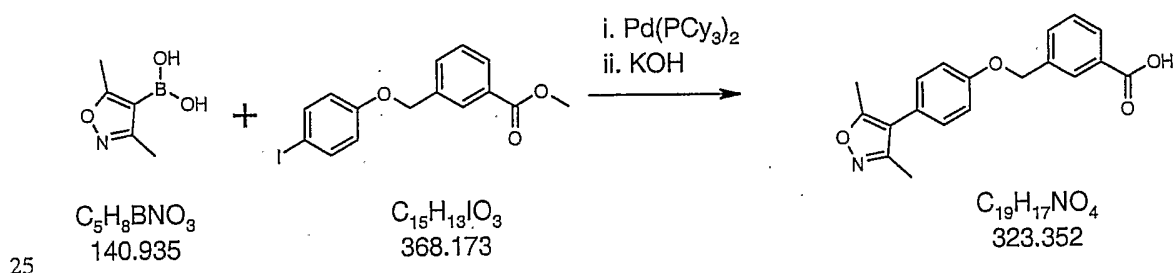
A first stock solution was prepared consisting of 3-(4-iodo-phenoxy)methyl-benzoic acid methyl ester (of Intermediate 1; 1.77 g, 4.8 mmol), bis(tri-cyclohexylphosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 168 mg, 0.25 mmol), and dioxane (approximately 100 mL). A second stock solution was prepared consisting of potassium carbonate (1.99 g, 14.4 mmol) and water (approximately 10 mL). The solutions were sonicated and degassed by bubbling nitrogen gas through them. 4 mL of the first stock solution and 0.4 mL of the second stock solution were added to a reaction vial containing 2-chloropyridine-3-boronic acid (ASDI Incorporated, Newark, DE; 94 mg, 0.6 mmol). The mixture was heated in a microwave oven at 170 °C degrees for 25 min and then passed through a silica gel column (1 g of silica), and washed with dioxane (1 mL) and dimethylacetamide (1 mL). 2 M potassium hydroxide solution (0.4 mL) was added. The mixture was stirred at room temperature overnight, and then 1 M HCl (0.8 mL) was added and the solvents were removed in the Genevac. Aqueous methanol (50%; approximately 2 mL) was added, then the vial was centrifuged and the solvent was removed. This process was repeated and then the sample was dried overnight in the oven to give 3-[4-(2-chloro-pyridin-3-yl)-phenoxy)methyl]-benzoic acid. Mass spectrum $MH^+ = 340$.

Example 5: 3-[4-(6-Chloro-pyridin-3-yl)-phenoxy)methyl]-benzoic acid



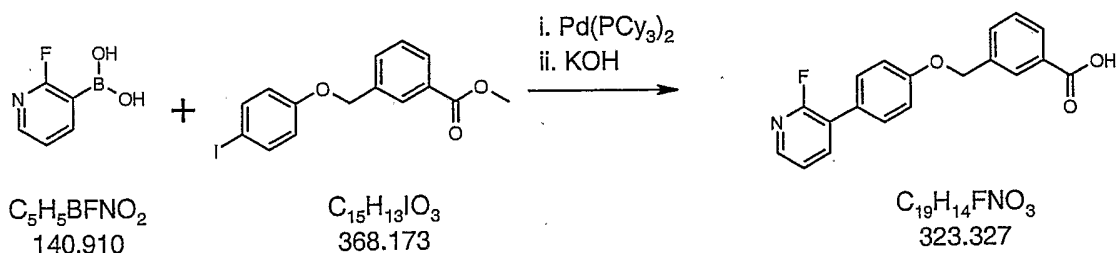
3-[4-(6-Chloro-pyridin-3-yl)-phenoxy)methyl]-benzoic acid was prepared using the procedure described above for the synthesis of Example 4 from 3-(4-iodo-phenoxy)methyl-benzoic acid methyl ester (of Intermediate 1) and 2-chloropyridine-5-boronic acid (ASDI Incorporated, Newark, DE). Mass spectrum $MH^+ = 340$.

Example 6: 3-[4-(3,5-Dimethyl-isoxazol-4-yl)-phenoxy)methyl]-benzoic acid



3-[4-(3,5-Dimethyl-isoxazol-4-yl)-phenoxy-methyl]-benzoic acid was prepared using general procedure 1 from 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1) and 3,5-dimethylisoxazole-4-boronic acid (ASDI Incorporated, Newark, DE). Mass spectrum $MH^+ = 324$.

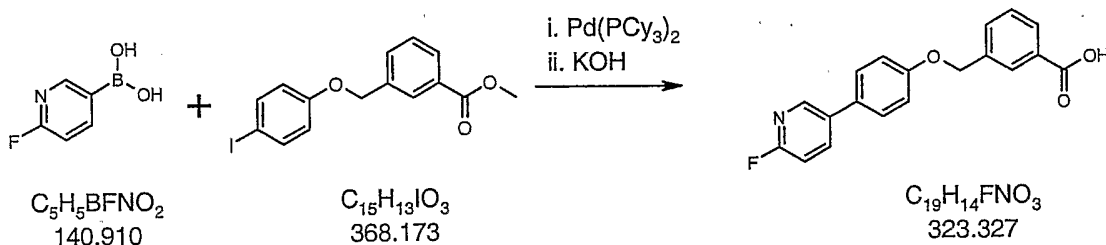
5 Example 7: 3-[4-(2-Fluoro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid



3-[4-(2-Fluoro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid was prepared using the procedure described above for the synthesis of Example 4 from 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1) and 2-fluoropyridine-3-boronic acid (ASDI Incorporated, Newark, DE). Mass spectrum $MH^+ = 324$.

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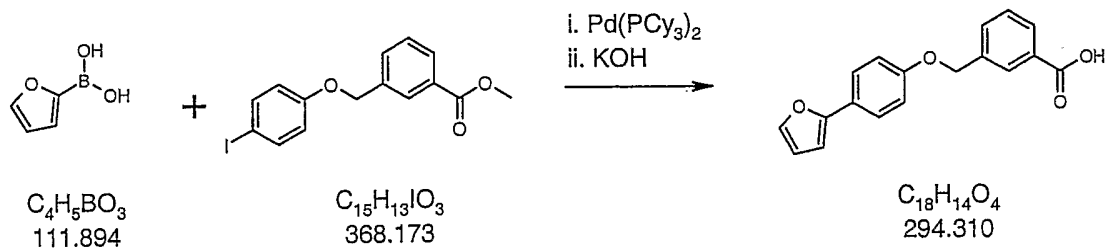
Example 8: 3-[4-(6-Fluoro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid



3-[4-(6-Fluoro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid was prepared using the procedure described above for the synthesis of Example 4 from 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1) and 2-fluoropyridine-5-boronic acid (ASDI Incorporated, Newark, DE). Mass spectrum $MH^+ = 324$.

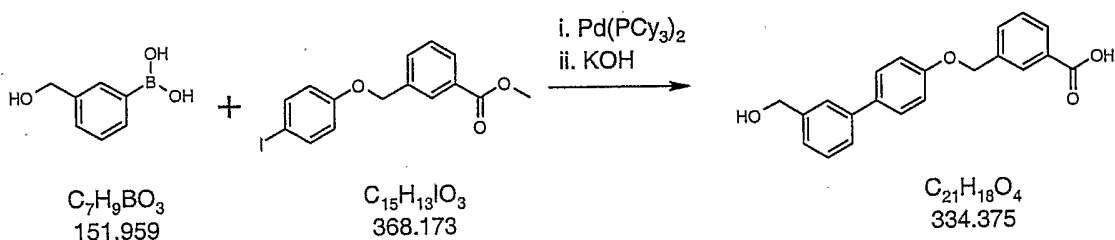
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Example 9: 3-(4-Furan-2-yl-phenoxy-methyl)-benzoic acid



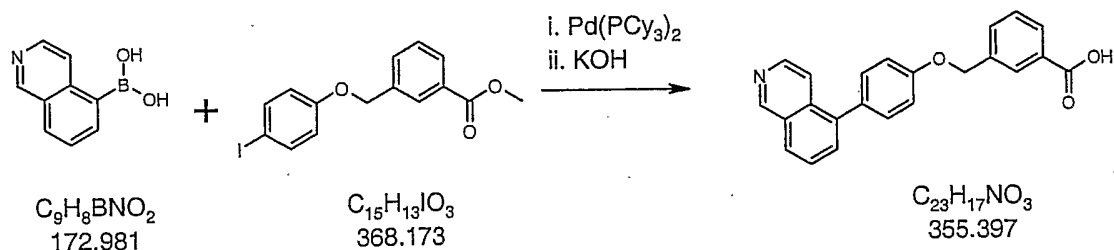
A solution of 3-(4-iodo-phenoxy)methyl)-benzoic acid methyl ester (of intermediate 1; 74 mg, 0.2 mmol) in dioxane/water (10:1, 4.4 mL) was degassed for 20 min and then added to a reaction vial containing potassium carbonate (82 mg, 0.6 mmol) and furan-2-boronic acid (0.6 mmol; available from Aldrich Chemical Company, Inc., Milwaukee, WI). The solution was degassed for a further 2 min and then bis(tri-cyclohexylphosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 14 mg, 0.02 mmol) was added. The mixture was degassed for 30 seconds and then heated in a microwave oven at 170 °C degrees for 25 min. The reaction mixture was filtered through silica and the silica washed with dioxane (1 mL), dimethylacetamide (1 mL), and 20% methanol in dichloromethane (1 mL). The filtrate was placed in a vial and 2 M potassium hydroxide solution (0.4 mL) was added. The mixture was stirred at room temperature overnight, and then 1 M HCl was added until a solid formed (approximately 2 mL). The vial was centrifuged and the solvent was removed. The product was dried overnight in the oven. Mass spectrum $MH^+ = 295$.

15 Example 10: 3-(3'-Hydroxymethyl-biphenyl-4-yloxymethyl)-benzoic acid



3-(3'-Hydroxymethyl-biphenyl-4-yloxymethyl)-benzoic acid was prepared using general procedure 1 from 3-(4-iodo-phenoxy)methyl)-benzoic acid methyl ester (of Intermediate 1) and 3-(hydroxymethyl)phenylboronic acid (available from Aldrich Chemical Company, Inc., Milwaukee, WI). Mass spectrum $MH^+ = 335$.

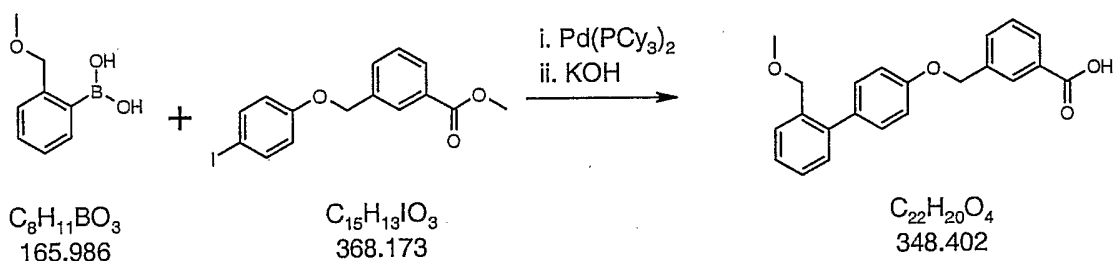
20 Example 11: 3-(4-Isoquinolin-5-yl-phenoxy)methyl)-benzoic acid



4.5 mL of a sonicated and degassed solution of 3-(4-iodo-phenoxy)methyl)-benzoic acid methyl ester (of Intermediate 1; 740 mg, 2 mmol), potassium carbonate (830 mg, 6 mmol), bis(tri-cyclohexylphosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 70 mg, 0.1 mmol), dioxane (41 mL) and water (4.1 mL) was added to a reaction vial containing 5-isoquinolineboronic acid (available from Frontier Scientific,

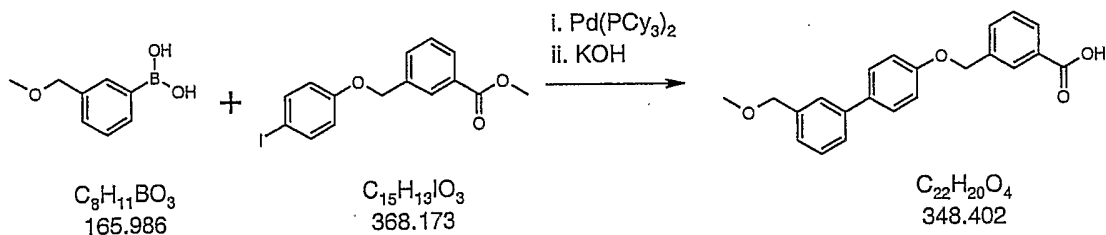
Inc., Logan, UT; 104 mg, 0.6 mmol). The solution was sonicated and degassed. The mixture was heated in a microwave oven at 170 °C degrees for 25 min. The reaction mixture was filtered through silica, and washed with dioxane (1 mL) and dimethylacetamide (1 mL). 2 M potassium hydroxide solution (0.4 mL) was added. The mixture was stirred at room temperature overnight, and then 1 M HCl (0.8 mL) was added. The solvents were removed in the Genevac and then 50% aqueous methanol (2 mL) was added. The vial was centrifuged and the solvent removed. This process was repeated and then the same was dried overnight in the oven to give 3-(4-isoquinolin-5-yl-phenoxy-methyl)-benzoic acid. Mass spectrum $MH^+ = 356$.

10 Example 12: 3-(2'-Methoxymethyl-biphenyl-4-yloxymethyl)-benzoic acid



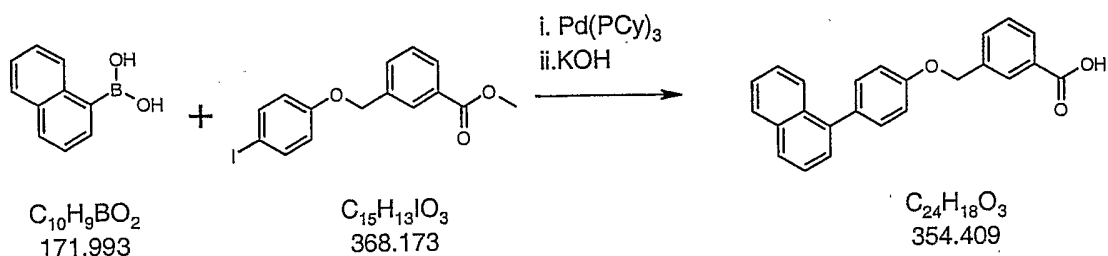
A solution of 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of intermediate 1; 37 mg, 0.1 mmol) in dioxane (2 mL) was degassed with nitrogen and then added to a reaction vial containing 2-methoxymethylphenylboronic acid (available from Apollo Scientific Ltd., Stockport, UK). The solution was sonicated and degassed and a solution of sodium hydroxide (4 M, 0.2 mL) was added, followed by bis(tri-cyclohexylphosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 0.005 mmol) was added. The mixture was degassed and then heated in a microwave oven at 170 °C degrees for 25 min. The reaction mixture was filtered through silica and the silica washed with dioxane (1 mL), and dimethylacetamide (1 mL). 1 M HCl was added until a solid formed. The vial was centrifuged and the solvent was removed. The crude product was washed with water and centrifuged again for 5 min. The water was decanted and the solid was dried in a vacuum oven at 50 °C degrees to give 3-(2'-methoxymethyl-biphenyl-4-yloxymethyl)-benzoic acid. Mass spectrum $MH^+ = 349$.

25 Example 13: 3-(3'-Methoxymethyl-biphenyl-4-yloxymethyl)-benzoic acid



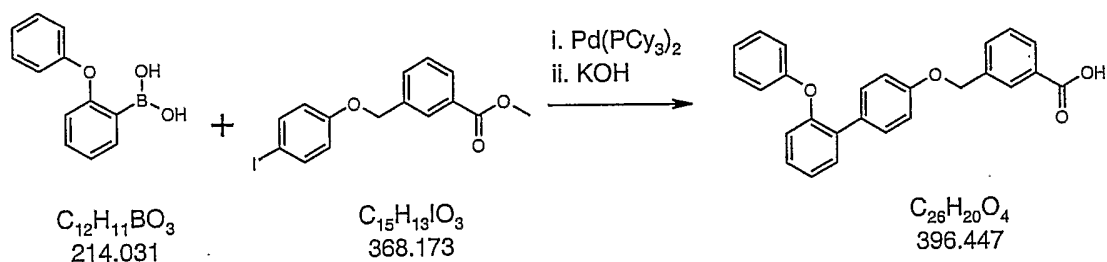
3-(3'-Methoxymethyl-biphenyl-4-yloxymethyl)-benzoic acid was prepared using the procedure described above for the preparation of Example 12 from 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1) and 3-methoxymethylphenylboronic acid (available from Digital Specialty Chemicals, Inc., Dublin, NH). Mass spectrum $MH^+ = 349$.

Example 14: 3-(4-Naphthalen-1-yl-phenoxy-methyl)-benzoic acid



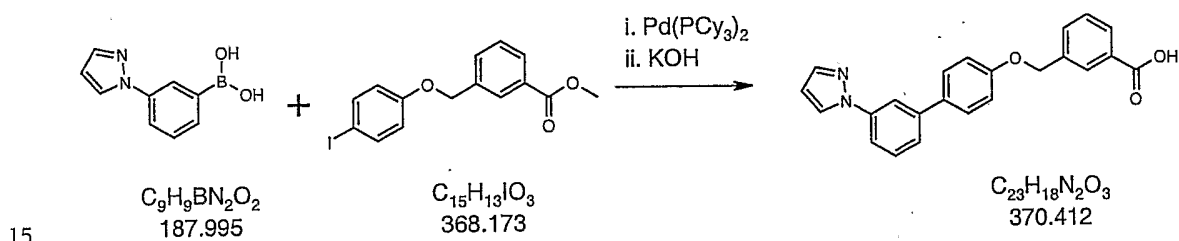
A solution of 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of intermediate 1; 74 mg, 0.2 mmol) in dioxane/water (10:1, 4.4 mL) was degassed for 20 min and then added to a reaction vial containing potassium carbonate (82 mg, 0.6 mmol) and 1-naphthaleneboronic acid (0.6 mmol; available from Aldrich Chemical Company, Inc., Milwaukee, WI). The solution was degassed for a further 2 min and then bis(tri-cyclohexylphosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 14 mg, 0.02 mmol) was added. The mixture was degassed for 30 seconds and then heated in a microwave oven at 170 °C degrees for 25 min. The reaction mixture was filtered through silica and the silica washed with dioxane (1 mL), dimethylacetamide (1 mL), and 20% methanol in dichloromethane (1 mL). The filtrate was placed in a vial and 2 M potassium hydroxide solution (0.4 mL) was added. The mixture was stirred at room temperature overnight, and then 1 M HCl was added until a solid formed (approximately 2 mL). The vial was centrifuged and the solvent was removed. The product was dried overnight in the oven to give 3-(4-naphthalen-1-yl-phenoxy-methyl)-benzoic acid. Mass spectrum $MH^+ = 355$.

Example 15: 3-(2'-Phenoxy-biphenyl-4-yloxymethyl)-benzoic acid



A degassed solution of 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1; 74 mg, 0.2 mmol) in dioxane (4 mL) and a degassed solution of potassium carbonate (83 mg) in water (0.4 mL) were added to a reaction vial containing (2-phenoxy)phenylboronic acid (available from Aldrich Chemical Company, Inc., Milwaukee, WI; 128 mg, 0.6 mmol). The solution was degassed and bis(tri-cyclohexylphosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 7 mg, 0.01 mmol) was added. The mixture was heated in a microwave oven at 170 °C degrees for 25 min. The reaction mixture was filtered through silica, and washed with dioxane (1 mL) and dimethylacetamide (1 mL). 2 M potassium hydroxide solution (0.4 mL) was added. The mixture was stirred at room temperature overnight, and then 1 M HCl (0.8 mL) was added. The solvent was evaporated and the residue was triturated with 50% aqueous methanol to give 3-(2'-phenoxy-biphenyl-4-yloxymethyl)-benzoic acid. Mass spectrum $MH^+ = 397$.

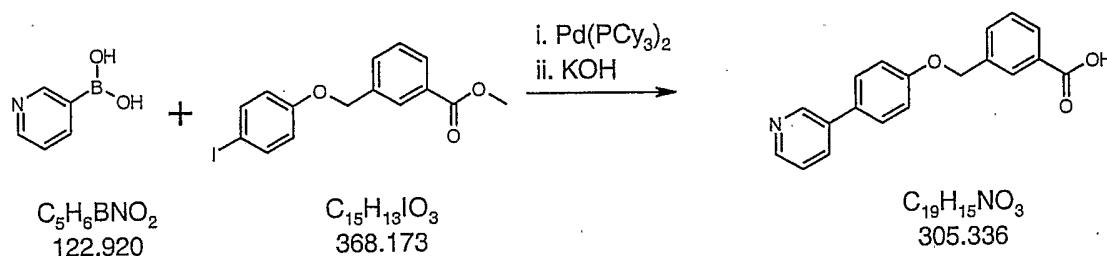
Example 16: 3-(3'-Pyrazol-1-yl-biphenyl-4-yloxymethyl)-benzoic acid



3-(3'-Pyrazol-1-yl-biphenyl-4-yloxymethyl)-benzoic acid was prepared using the procedure described above for the synthesis of Example 4 from 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1) and 3-(1H-pyrazol-1-yl)phenylboronic acid (available from ASDI Inc., Newark, DE). Mass spectrum $MH^+ = 371$.

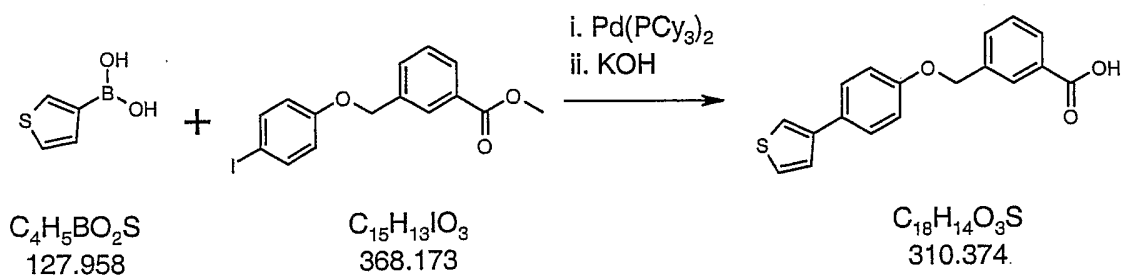
20

Example 17: 3-(4-Pyridin-3-yl-phenoxy-methyl)-benzoic acid

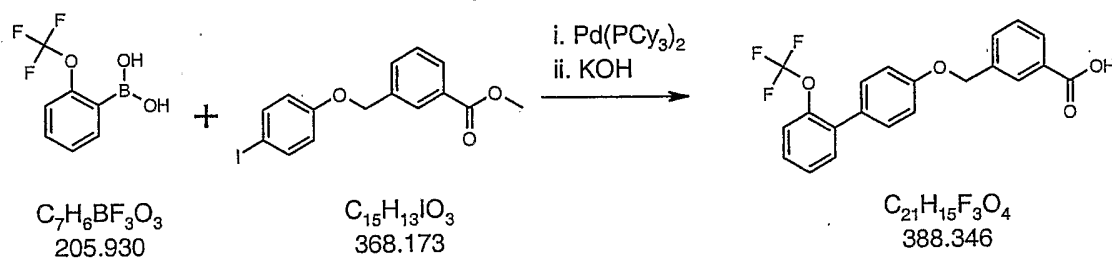


3-(4-Pyridin-3-yl-phenoxy-methyl)-benzoic acid was prepared using the procedure described above for the synthesis of Example 3 from 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1) and pyridine-3-boronic acid (available from Aldrich Chemical Company, Inc., Milwaukee, WI). Mass spectrum $MH^+ = 306$.

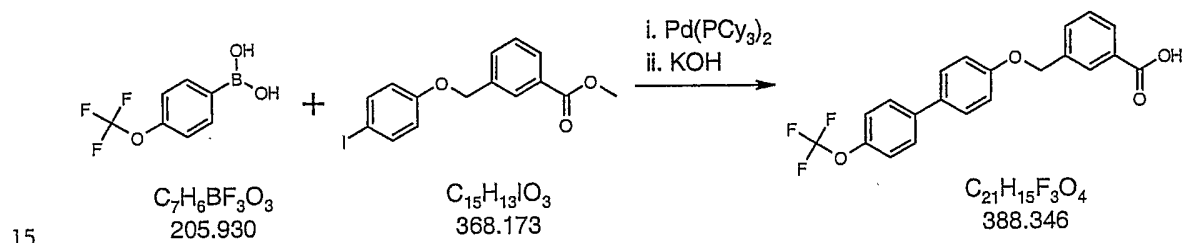
25

Example 18: 3-(4-Thiophen-3-yl-phenoxy-methyl)-benzoic acid

- 3-(4-Thiophen-3-yl-phenoxy-methyl)-benzoic acid was prepared using the procedure described above for the preparation of Example 15 from 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1) and thiophene-3-boronic acid (available from Aldrich Chemical Company, Inc., Milwaukee, WI). Mass spectrum $\text{MH}^+ = 311$.

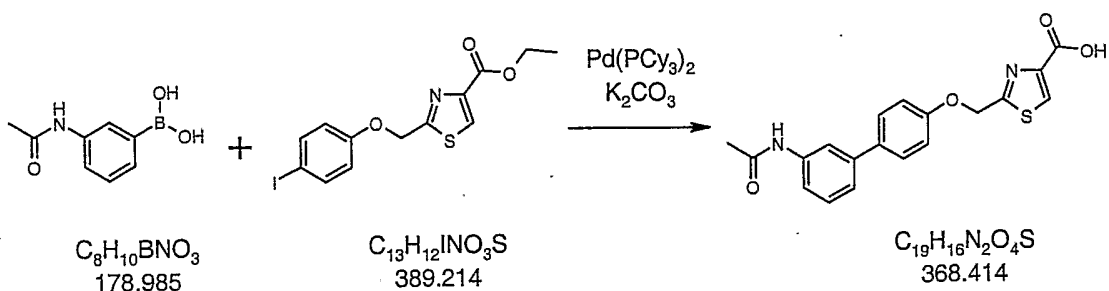
Example 19: 3-(2'-Trifluoromethoxy-biphenyl-4-yloxy-methyl)-benzoic acid

- 3-(2'-Trifluoromethoxy-biphenyl-4-yloxy-methyl)-benzoic acid was prepared using general procedure 1 from 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1) and 2-(trifluoromethoxy)benzeneboronic acid (ASDI Incorporated, Newark, DE). Mass spectrum $\text{MH}^+ = 389$.

Example 20: 3-(4'-Trifluoromethoxy-biphenyl-4-yloxy-methyl)-benzoic acid

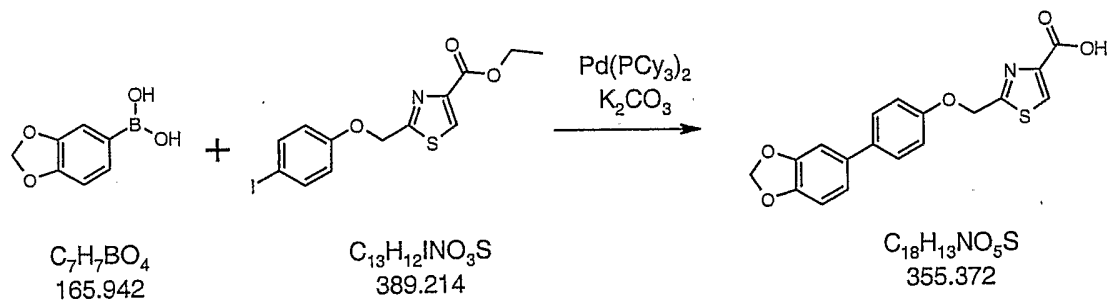
- 3-(4'-Trifluoromethoxy-biphenyl-4-yloxy-methyl)-benzoic acid was prepared using general procedure 1 from 3-(4-iodo-phenoxy-methyl)-benzoic acid methyl ester (of Intermediate 1) and 4-(trifluoromethoxy)benzeneboronic acid (ASDI Incorporated, Newark, DE). Mass spectrum $\text{MH}^+ = 389$.

Example 21: 2-(3'-Acetylamino-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid



A first stock solution was prepared consisting of 2-(4-iodo-phenoxy)methyl)-thiazole-4-carboxylic acid ethyl ester (of intermediate 2; 1.56 g, 4 mmol), bis(tri-cyclohexyl-phosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 140 mg, 0.21 mmol), and dioxane (approximately 82 mL). A second stock solution was prepared consisting of potassium carbonate (1.66 g, 12 mmol) and water (approximately 8.2 mL). The solutions were sonicated and degassed by bubbling nitrogen gas through them. 4 mL of the first stock solution and 0.4 mL of the second stock solution were added to a reaction vial containing 3-acetamidobenzenboronic acid (ASDI Incorporated, Newark, DE; 107 mg, 0.6 mmol). The mixture was heated in a microwave oven at 170 °C degrees for 25 min. 1 M HCl (0.1 mL) was added to each vial, and the solution were passed through silica gel columns (1 g of silica), and washed with dimethylacetamide (2 x 1 mL). The solution was evaporated to dryness to give 2-(3'-acetylamino-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid. Mass spectrum $\text{MH}^+ = 369$.

Example 22: 2-(4-Benzo[1,3]dioxol-5-yl-phenoxy)methyl)-thiazole-4-carboxylic acid

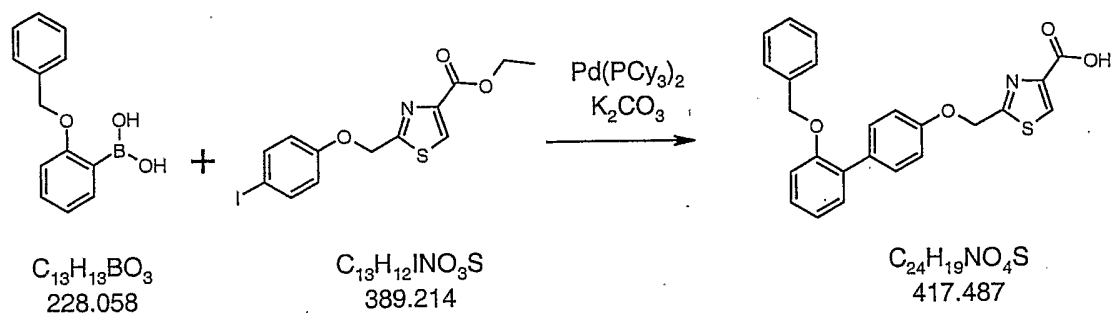


A solution of 2-(4-iodo-phenoxy)methyl)-thiazole-4-carboxylic acid ethyl ester (of intermediate 2; 75 mg, 0.2 mmol) in dioxane (4 mL) was added to a reaction tube containing 3,4-methylenedioxybenzenboronic acid (ASDI Incorporated, Newark, DE; 100 mg, 0.6 mmol). A solution of potassium carbonate (80 mg, 0.6 mmol) in water (0.4 mL) was added and the mixture was degassed. A solution of bis(tricyclohexylphosphine)-

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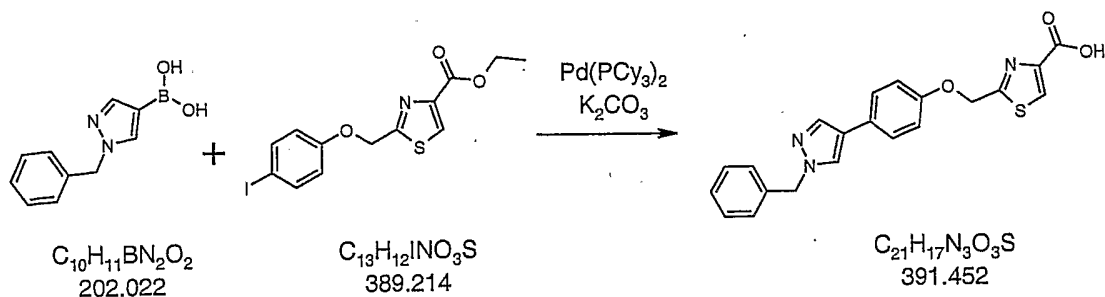
palladium (available from Strem Chemicals, Inc., Newburyport, MA; 7 mg, 0.01 mmol) in dioxane (0.5 mL) was added and the tube was heated in a microwave oven at 170 °C degrees for 25 min. The solution was acidified, filtered through silica gel, evaporated, and triturated with aqueous methanol to give 2-(4-benzo[1,3]dioxol-5-yl-phenoxyethyl)-thiazole-4-carboxylic acid. Mass spectrum $MH^+ = 356$.

Example 23: 2-(2'-Benzyloxy-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid



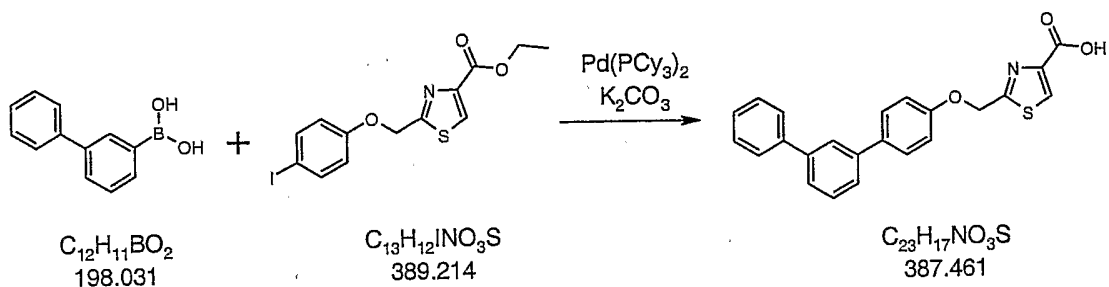
A first stock solution was prepared consisting of 2-(4-iodo-phenoxyethyl)-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2; 1.72 g, 4.4 mmol), bis(tri-cyclohexyl-phosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 154 mg, 0.23 mmol), and dioxane (approximately 90 mL). A second stock solution was prepared consisting of potassium carbonate (1.826 g, 13.2 mmol) and water (approximately 9 mL). The solutions were sonicated and degassed by bubbling nitrogen gas through them. 4 mL of the first stock solution and 0.4 mL of the second stock solution were added to a reaction vial containing (2-benzyloxyphenyl)boronic acid (available from Aldrich Chemical Company, Inc., Milwaukee, WI; 260 mg, 0.4 mmol). The mixture was heated in a microwave oven at 170 °C degrees for 25 min and then passed through a silica gel column (1 g of silica), and washed with dimethylacetamide (2 x 1 mL). The solvents were removed in the Genevac to give 2-(2'-benzyloxy-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid. Mass spectrum $MH^+ = 418$.

Example 24: 2-[4-(1-Benzyl-1H-pyrazol-4-yl)-phenoxyethyl]-thiazole-4-carboxylic acid



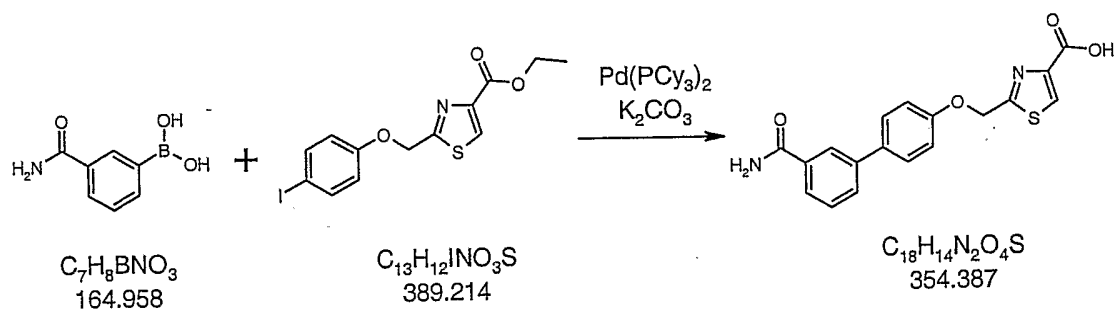
2-[4-(1-Benzyl-1H-pyrazol-4-yl)-phenoxy-methyl]-thiazole-4-carboxylic acid was prepared using general procedure 2 from 2-(4-iodo-phenoxy-methyl)-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2) and 1-benzyl-1h-pyrazole-4-boronic acid (available from Frontier Scientific, Inc., Logan, UT). Mass spectrum $MH^+ = 392$.

5 Example 25: 2-([1,1';3',1'']Terphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid



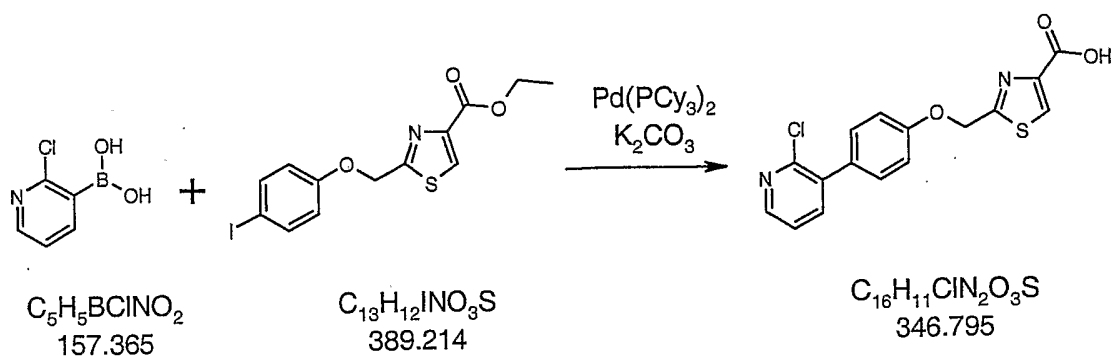
A solution of 2-(4-iodo-phenoxy-methyl)-thiazole-4-carboxylic acid ethyl ester (of intermediate 2; 71 mg, 0.2 mmol) in dioxane (3.5 mL) was added to a reaction tube containing biphenyl-3-boronic acid (available from Lancaster Synthesis Ltd.,
 10 Morecambe, UK; 119 mg, 0.6 mmol). A solution of potassium carbonate (74 mg, 0.5 mmol) in water (0.4 mL) was added and the mixture was degassed. A solution of bis(tricyclohexylphosphine)-palladium (available from Strem Chemicals, Inc., Newburyport, MA; 7 mg, 0.01 mmol) in dioxane (0.5 mL) was added and the tube was heated in a microwave oven at 170 °C degrees for 25 min. Concentrated hydrochloric
 15 acid (0.1 mL) was added and the mixture was passed through a silica gel column (1 g of silica), and washed with dimethylacetamide (2 x 1 mL). The filtrate was evaporated to dryness and the resulting gum was triturated twice with 50% aqueous methanol to give 2-([1,1';3',1'']terphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid. Mass spectrum $MH^+ = 388$

20 Example 26: 2-(3'-Carbamoyl-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid



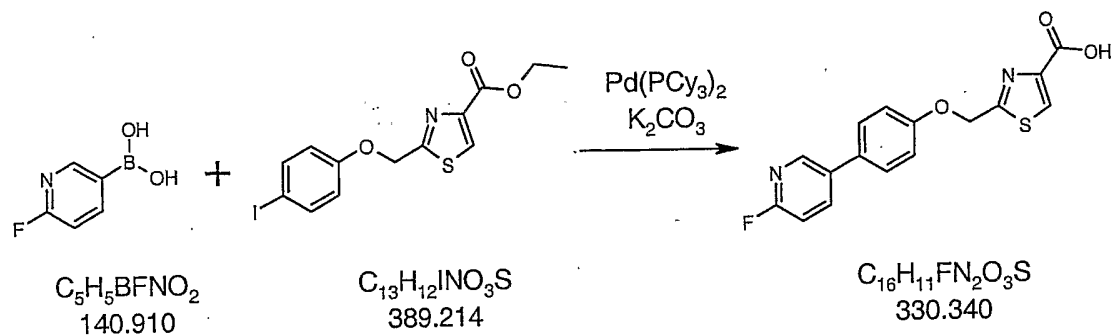
2-(3'-Carbamoyl-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid was prepared using general procedure 2 from 2-(4-iodo-phenoxy-methyl)-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2) and (3-aminocarbonylphenyl)boronic acid (available from
 25 Apollo Scientific Ltd., Stockport, UK). Mass spectrum $MH^+ = 355$.

Example 27: 2-[4-(2-Chloro-pyridin-3-yl)-phenoxy-methyl]-thiazole-4-carboxylic acid



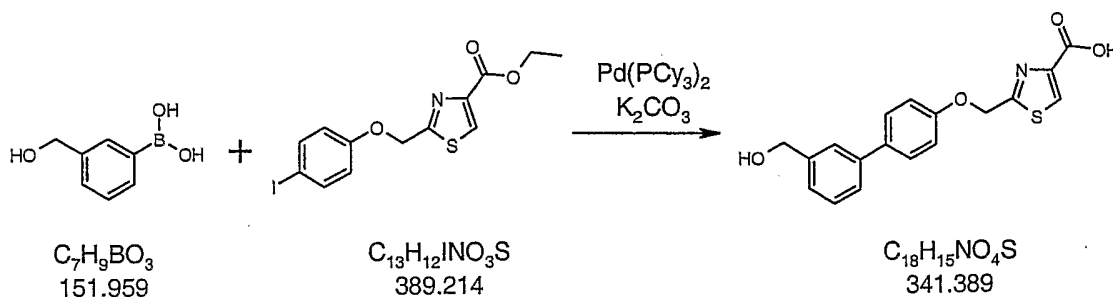
2-[4-(2-Chloro-pyridin-3-yl)-phenoxy-methyl]-thiazole-4-carboxylic acid was prepared using the procedure described above for the preparation of Example 23 from 2-(4-iodo-phenoxy-methyl)-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2) and 2-chloropyridine-3-boronic acid (available from Lancaster Synthesis Ltd., Morecambe, UK). Mass spectrum $MH^+ = 347$.

Example 28: 2-[4-(6-Fluoro-pyridin-3-yl)-phenoxy-methyl]-thiazole-4-carboxylic acid



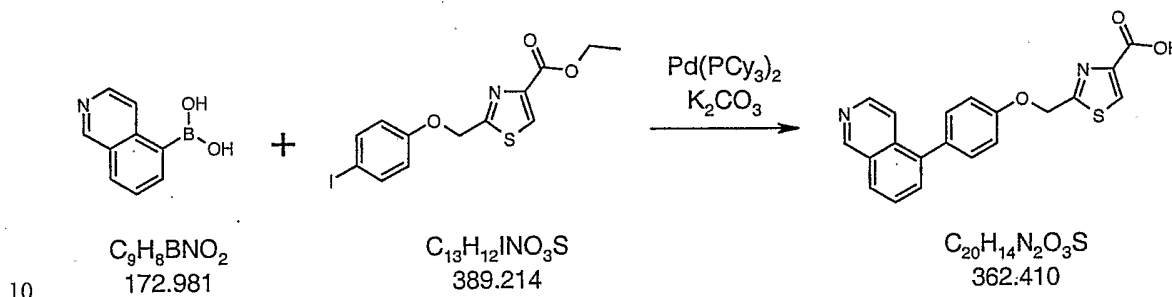
2-[4-(6-Fluoro-pyridin-3-yl)-phenoxy-methyl]-thiazole-4-carboxylic acid was prepared using the procedure described above for the preparation of Example 23 from 2-(4-iodo-phenoxy-methyl)-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2) and 6-fluoropyridine-5-boronic acid (available from Frontier Scientific, Inc., Logan, UT). Mass spectrum $MH^+ = 331$.

Example 29: 2-(3'-Hydroxymethyl-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid



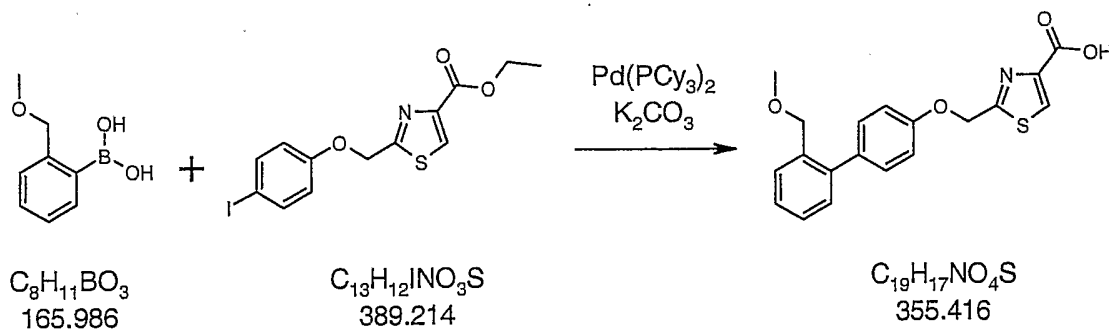
2-(3'-Hydroxymethyl-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid was prepared using the procedure described above for the preparation of Example 22 from 2-(4-iodo-phenoxy)methyl)-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2) and 3-(hydroxymethyl)phenylboronic acid (available from Aldrich Chemical Company, Inc., Milwaukee, WI). Mass spectrum $MH^+ = 342$.

Example 30: 2-(4-Isoquinolin-5-yl-phenoxy)methyl)-thiazole-4-carboxylic acid



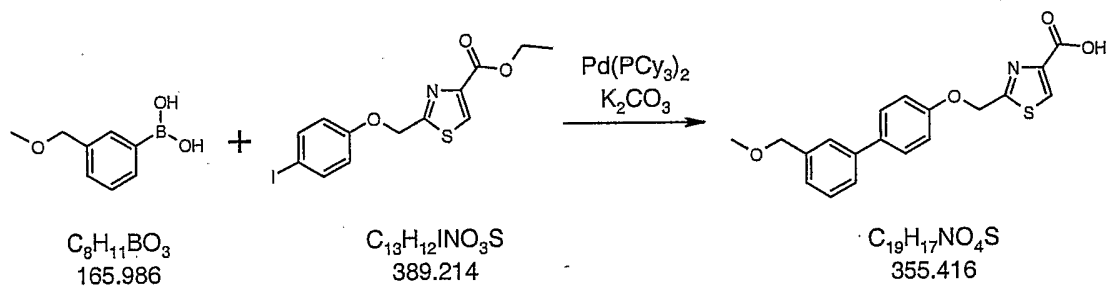
2-(4-Isoquinolin-5-yl-phenoxy)methyl)-thiazole-4-carboxylic acid was prepared using general procedure 2 from 2-(4-iodo-phenoxy)methyl)-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2) and 5-isoquinolineboronic acid (available from Frontier Scientific, Inc., Logan, UT). Mass spectrum $MH^+ = 363$.

Example 31: 2-(2'-Methoxymethyl-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid



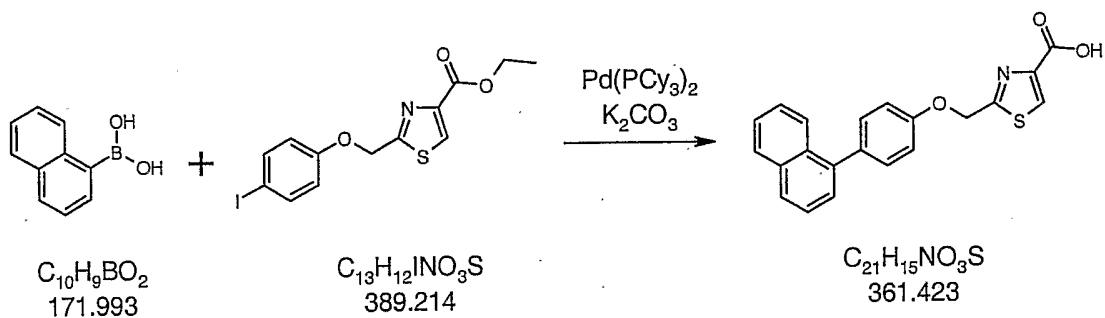
2-(2'-Methoxymethyl-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid was prepared using general procedure 2 from 2-(4-iodo-phenoxy-methyl)-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2) and 2-methoxymethylphenylboronic acid (available from Apollo Scientific Ltd., Stockport, UK). Mass spectrum $MH^+ = 356$.

5 Example 32: 2-(3'-Methoxymethyl-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid

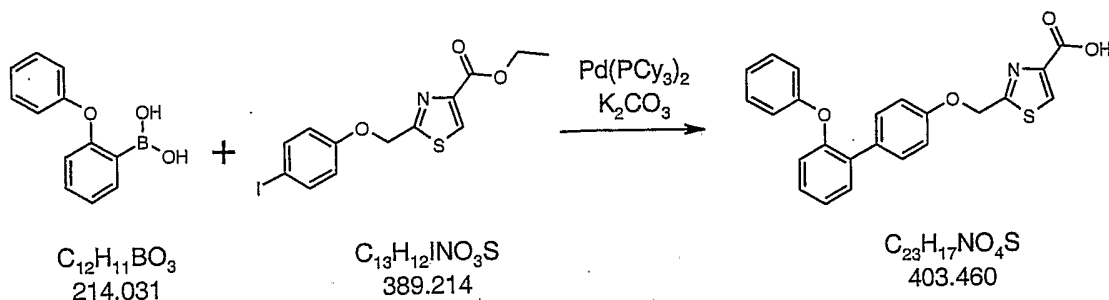


2-(3'-Methoxymethyl-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid was prepared using general procedure 2 from 2-(4-iodo-phenoxy-methyl)-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2) and 3-methoxymethylphenylboronic acid (available from Digital Specialty Chemicals, Inc., Dublin, NH). Mass spectrum $MH^+ = 356$.

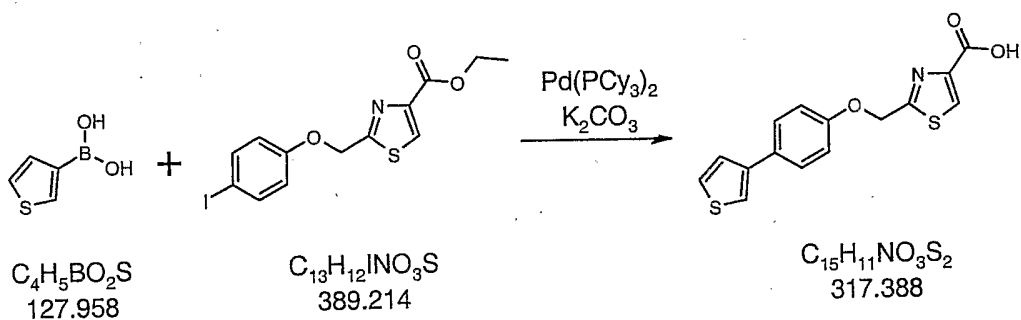
10 Example 33: 2-(4-Naphthalen-1-yl-phenoxy-methyl)-thiazole-4-carboxylic acid



15 2-(4-Naphthalen-1-yl-phenoxy-methyl)-thiazole-4-carboxylic acid was prepared using the procedure described above for the preparation of Example 22 from 2-(4-iodo-phenoxy-methyl)-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2) and 1-naphthaleneboronic acid (available from Aldrich Chemical Company, Inc., Milwaukee, WI). Mass spectrum $MH^+ = 362$.

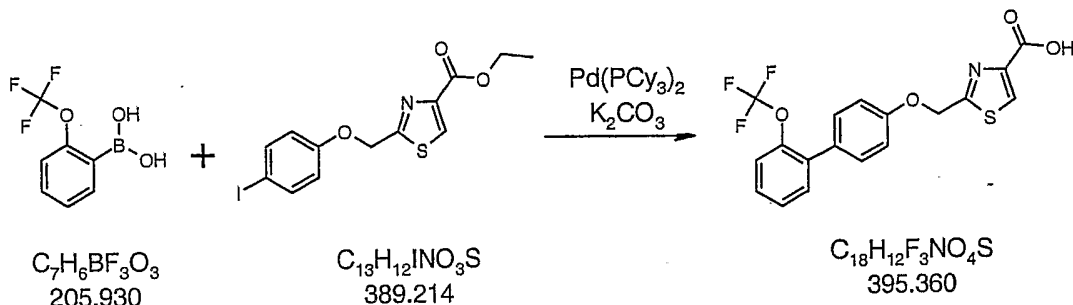
Example 34: 2-(2'-Phenoxy-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid

2-(2'-Phenoxy-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid was prepared using the procedure described above for the preparation of Example 25 from 2-(4-iodo-
 5 phenoxy)methyl)-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2) and (2-phenoxy)phenylboronic acid (available from Aldrich Chemical Company, Inc., Milwaukee, WI). Mass spectrum $MH^+ = 404$.

Example 35: 2-(4-Thiophen-3-yl-phenoxy)methyl)-thiazole-4-carboxylic acid

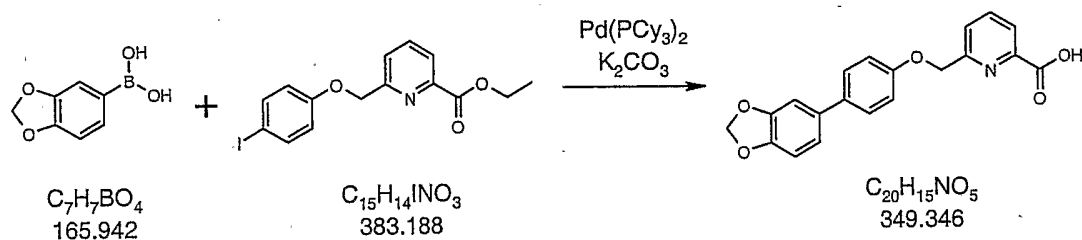
10 A solution of 2-(4-iodo-phenoxy)methyl)-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2; 78 mg, 0.2 mmol) in dioxane (2 mL) was degassed with nitrogen and then added to a reaction vial containing thiophene-3-boronic acid (available from
 Aldrich Chemical Company, Inc., Milwaukee, WI). The solution was sonicated and degassed and a solution of potassium carbonate (1.5 M, 0.4 mL) was added, followed by
 15 bis(tri-cyclo-hexylphosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 7 mg, 0.01 mmol) was added. The mixture was degassed and then heated in a microwave oven at 170 °C degrees for 25 min. The reaction mixture was evaporated in the Genevac to give 2-(4-thiophen-3-yl-phenoxy)methyl)-thiazole-4-carboxylic acid. Mass spectrum $MH^+ = 318$.

Example 36: 2-(2'-Trifluoromethoxy-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid



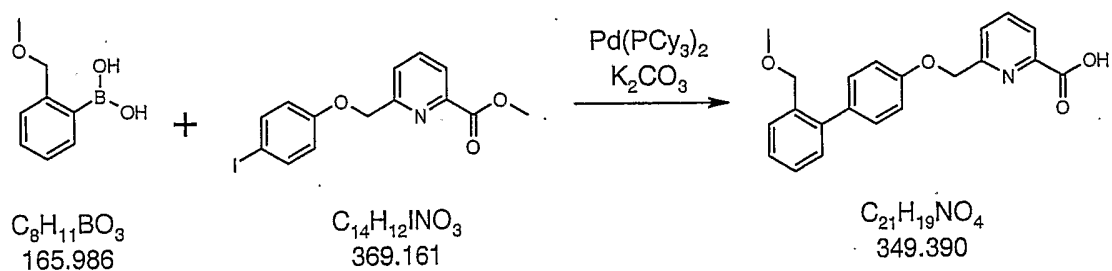
2-(2'-Trifluoromethoxy-biphenyl-4-yloxymethyl)-thiazole-4-carboxylic acid was prepared using the procedure described above for the preparation of Example 21 from 2-(4-iodo-phenoxy)methyl-thiazole-4-carboxylic acid ethyl ester (of Intermediate 2) and 2-(trifluoromethoxy)benzeneboronic acid (available from Apin Chemicals Ltd., Abingdon, UK). Mass spectrum $MH^+ = 396$.

Example 37: 6-(4-Benzo[1,3]dioxol-5-yl-phenoxy)methyl-pyridine-2-carboxylic acid



6-(4-Benzo[1,3]dioxol-5-yl-phenoxy)methyl-pyridine-2-carboxylic acid was prepared using general procedure 3 from 6-(4-iodo-phenoxy)methyl-pyridine-2-carboxylic acid ethyl ester (of Intermediate 3) and 3,4-methylenedioxybenzeneboronic acid (ASDI Incorporated, Newark, DE). Mass spectrum $MH^+ = 350$.

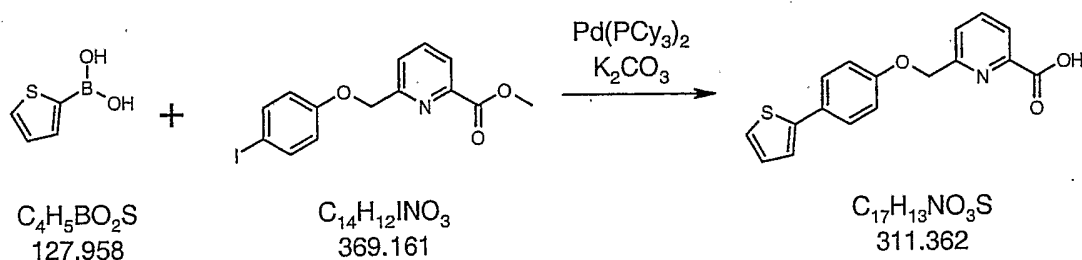
Example 38: 6-(2'-Methoxymethyl-biphenyl-4-yloxymethyl)-pyridine-2-carboxylic acid



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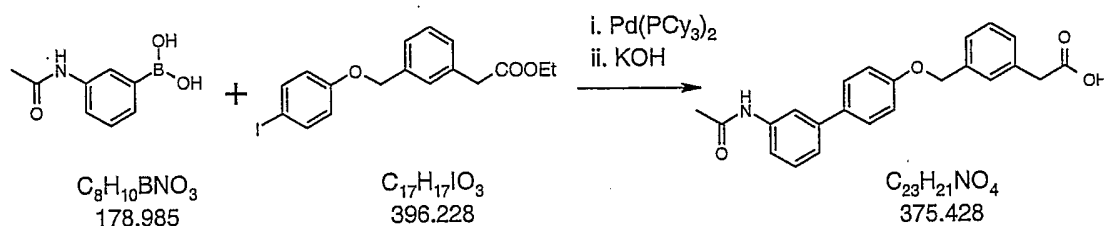
A first stock solution was prepared consisting of 6-(4-iodo-phenoxy)methyl-pyridine-2-carboxylic acid methyl ester (of intermediate 5; 1.77 g, 4.8 mmol), bis(tri-cyclohexyl-phosphine)palladium (available from Strem Chemicals, Inc., Newburyport, MA; 168 mg, 0.25 mmol), and dioxane (approximately 100 mL). A second stock solution
 5 was prepared consisting of potassium carbonate (1.99 g, 14.4 mmol) and water (approximately 10 mL). The solutions were sonicated and degassed by bubbling nitrogen gas through them. 4 mL of the first stock solution and 0.4 mL of the second stock solution were added to a reaction tube containing 2-methoxymethyl-phenylboronic acid (available from Apollo Scientific Ltd., Stockport, UK; 100 mg, 0.6 mmol). The mixture
 10 was heated in a microwave oven at 170 °C degrees for 25 min, and then 1 M KOH solution (1 equivalent) was added and the reaction mixture was heated in the microwave for 10 minutes at 120 °C degrees, for 10 minutes at 130 °C degrees, and at 170 °C degrees for one hour. The reaction mixture was then filtered through a silica column (1 g) and washed with dimethylacetamide (2 x 1 mL). The solvent was evaporated to give 6-(2'-
 15 methoxymethyl-biphenyl-4-yloxymethyl)-pyridine-2-carboxylic acid. Mass spectrum $MH^+ = 350$.

Example 39: 6-(4-Thiophen-2-yl-phenoxy)methyl)-pyridine-2-carboxylic acid



6-(4-Thiophen-2-yl-phenoxy)methyl)-pyridine-2-carboxylic acid was prepared
 20 using the procedure described above for the preparation of Example 38 from 6-(4-iodo-phenoxy)methyl)-pyridine-2-carboxylic acid methyl ester (of Intermediate 5) and 2-methoxymethylphenylboronic acid (available from Aldrich Chemical Company, Inc., Milwaukee, WI). Mass spectrum $MH^+ = 312$.

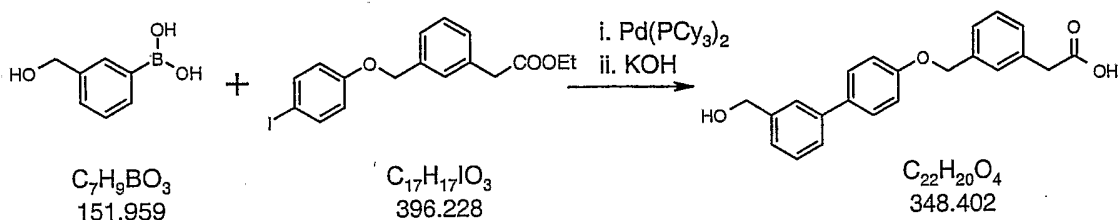
Example 40: [3-(3'-Acetylamino-biphenyl-4-yloxymethyl)-phenyl]-acetic acid



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[3-(3'-Acetylamino-biphenyl-4-yloxymethyl)-phenyl]-acetic acid was prepared using general procedure 5 from [3-(4-iodo-phenoxy-methyl)-phenyl]-acetic acid ethyl ester (of intermediate 4) and 3-acetamidobenzeneboronic acid (ASDI Incorporated, Newark, DE). Mass spectrum $MH^+ = 376$.

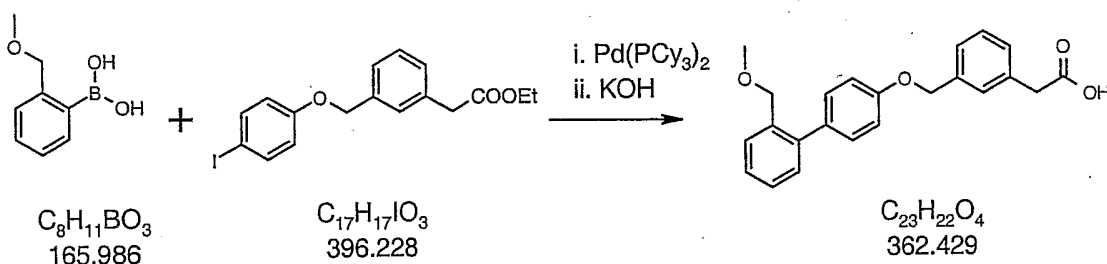
5 Example 41: [3-(3'-Hydroxymethyl-biphenyl-4-yloxymethyl)-phenyl]-acetic acid



[3-(3'-Hydroxymethyl-biphenyl-4-yloxymethyl)-phenyl]-acetic acid was prepared using general procedure 5 from [3-(4-iodo-phenoxy-methyl)-phenyl]-acetic acid ethyl ester (of intermediate 4) and 3-(hydroxymethyl)phenylboronic acid (available from Aldrich Chemical Company, Inc., Milwaukee, WI). Mass spectrum $MH^+ = 349$.

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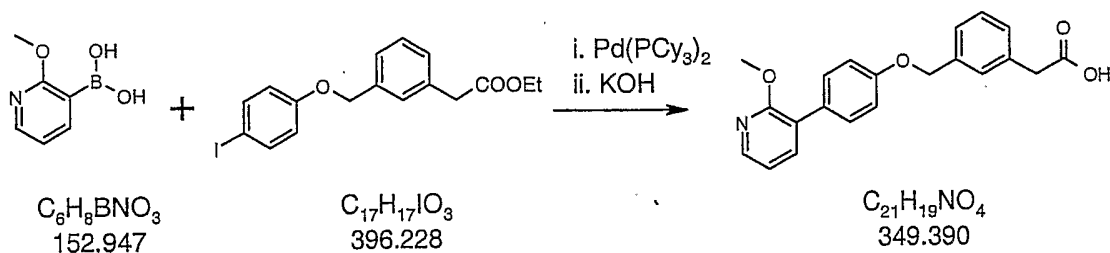
Example 42: [3-(2'-Methoxymethyl-biphenyl-4-yloxymethyl)-phenyl]-acetic acid



[3-(2'-Methoxymethyl-biphenyl-4-yloxymethyl)-phenyl]-acetic acid was prepared using general procedure 4 from [3-(4-iodo-phenoxy-methyl)-phenyl]-acetic acid ethyl ester (of intermediate 4) and 2-methoxymethylphenylboronic acid (available from Apollo Scientific Ltd., Stockport, UK). Mass spectrum $MH^+ = 363$.

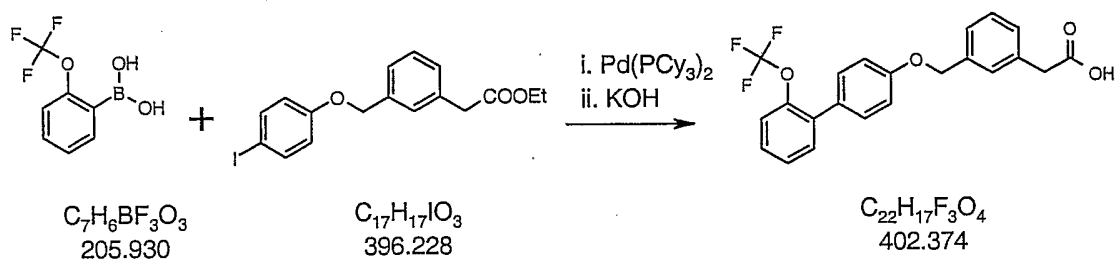
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Example 43: [3-[4-(2-Methoxy-pyridin-3-yl)-phenoxy-methyl]-phenyl]-acetic acid



{3-[4-(2-Methoxy-pyridin-3-yl)-phenoxy-methyl]-phenyl}-acetic acid was prepared using general procedure 4 from [3-(4-iodo-phenoxy-methyl)-phenyl]-acetic acid ethyl ester (of intermediate 4) and 2-methoxy-pyridine-3-boronic acid (available from Lancaster Synthesis Ltd., Lancashire, UK). Mass spectrum $MH^+ = 350$.

5 Example 44: [3-(2'-Trifluoromethoxy-biphenyl-4-yloxymethyl)-phenyl]-acetic acid



[3-(2'-Trifluoromethoxy-biphenyl-4-yloxymethyl)-phenyl]-acetic acid was prepared using general procedure 5 from [3-(4-iodo-phenoxy-methyl)-phenyl]-acetic acid ethyl ester (of intermediate 4) and 2-(trifluoromethoxy)benzeneboronic acid (ASDI Incorporated, Newark, DE). Mass spectrum $MH^+ = 403$.

10

Glycogen synthase (GS) assay

The following tests were carried out in order to determine the activity of the compounds of formula (I).

Twelve μ L per well of substrate solution containing glycogen (4.32 mg/mL), 21.6 mM UDP-glucose, 21.6 mM phospho(enol)pyruvate and 2.7 mM NADH in 30 mM glycyglycine, pH 7.3 buffer was added into a polystyrene 384-well assay plate (BD Biosciences). Compound solution (8 μ L/well) at various concentrations (0-57 μ M) in 30 mM glycyglycine, pH 7.3, 40 mM KCl, 20 mM MgCl₂ plus 9.2 % DMSO were added to the assay plate (columns 5-24). Enzyme solution (12 μ L/well) containing glycogen synthase (16.88 μ g/mL), pyruvate kinase (0.27 mg/mL), lactate dehydrogenase (0.27 mg/mL) in 50 mM Tris-HCl, pH 8.0, 27 mM DTT and bovine serum albumin (BSA, 0.2 mg/mL) was added to the assay plate (columns 3-24). As a blank control, enzyme solution without glycogen synthase was added into the top half wells of columns 1-2. To the bottom half wells of columns 1-2 were added a known activator, glucose 6-phosphate (18.9 mM) in addition to the enzyme solution. The reaction mixture was incubated at 37 °C. The assay plate was then read for absorbance at 340 nm on a Tecan Ultra reader every 3 minutes up to a total of 30 minutes.

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The enzyme activity (with or without compound) was calculated by the reaction rate and represented by the optical density change (ΔOD) per minute. Percent stimulation of glycogen synthase activity by a compound at various concentrations was calculated by the following formula:

5 $\% \text{ stimulation} = 100 * R_s/R_t,$

where R_s is the reaction rate of the enzyme in the presence of compound and R_t is the reaction rate of the enzyme in the absence of compound.

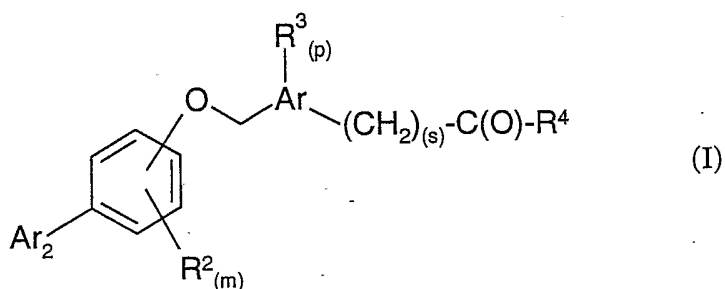
SC2.0 is defined as the compound concentration that is needed to stimulate 200% of the enzyme activity.

10 The compounds of the examples exhibit SC2.0 activities of less than $30\mu\text{M}$. Some specific SC2.0 activities are shown in the following table:

Example	Activity (SC2.0) [μM]
8	4.7
10	9.3
36	6.2

Claims

1. A compound of formula (I)



wherein

5 Ar is an aromatic carbocyclic or heterocyclic ring;

Ar₂ is a substituted or unsubstituted cyclic ring selected from the group consisting of benzo[1,3]dioxol-5-yl, furan-2-yl, isoquinolin-5-yl, isoxazol-4-yl, 1-naphthyl, pyrazol-1-yl, pyrazol-4-yl, pyridin-3-yl, thiophen-2-yl, thiophen-3-yl and phenyl, and where substituted the substituents are selected from the group consisting of acetamido, aminocarbonyl, benzyl, benzyloxy, halogen, hydroxyl-lower alkyl, lower alkyl, lower alkoxy-lower alkyl, phenoxy, phenyl, lower alkoxy and trifluoro-methoxy;

10

R² and R³ are independently selected from the group consisting of lower alkyl, lower alkoxy, trifluoromethyl, halogen, hydroxy, amino, alkylamino, dialkylamino, cyano and nitro;

15 R⁴ is hydroxy or an amino acid attached through a nitrogen atom of the amino acid;

m is 0, 1, 2, 3 or 4;

p is 0, 1 or 2, and

s is 0, 1 or 2,

20 or a pharmaceutically acceptable salt thereof,

provided that when Ar₂ is phenyl, the phenyl ring is substituted by at least one substituent selected from the group consisting of acetamido, aminocarbonyl, benzyloxy, hydroxyl-lower alkyl, lower-alkoxy-lower alkyl, phenoxy, phenyl, pyrazol-1-yl and trifluoromethoxy, and

when Ar₂ is phenyl, there are not two lower alkyl substituents ortho to the point of attachment of the Ar₂ ring.

2. The compound of formula (I) according to claim 1, wherein Ar₂ is a substituted or unsubstituted cyclic ring selected from the group consisting of benzo[1,3]dioxol-5-yl, furan-2-yl, isoquinolin-5-yl, isoxazol-4-yl, 1-naphthyl, pyrazol-1-yl, pyrazol-4-yl, pyridin-3-yl, thiophen-2-yl, and thiophen-3-yl, and where substituted the substituents are selected from the group consisting of acetamido, aminocarbonyl, benzyl, benzyloxy, halogen, hydroxyl-lower alkyl, lower alkyl, lower alkoxy-lower alkyl, phenoxy, phenyl, lower alkoxy and trifluoro-methoxy.

3. The compound of formula (I) according to claims 1 or 2, wherein Ar₂ is pyridin-3-yl.

4. The compound of formula (I) according to any of claims 1 to 3, wherein Ar₂ is pyridin-3-yl substituted by halogen.

5. The compound of formula (I) according to claims 1 or 2, wherein Ar₂ is 1-naphthyl.

6. The compound of formula (I) according to claims 1 or 2, wherein Ar₂ is benzo[1,3]dioxol-5-yl.

7. The compound of formula (I) according to claims 1 or 2, wherein Ar₂ is thiophen-3-yl.

8. The compound of formula (I) according to claim 1, wherein Ar₂ is phenyl substituted by at least one substituent selected from the group consisting of acetamido, aminocarbonyl, benzloxy, hydroxyl-lower alkyl, lower-alkoxy-lower alkyl, phenoxy, phenyl, pyrazol-1-yl and trifluoromethoxy.

9. The compound of formula (I) according to claim 1 or claim 8, wherein Ar₂ is phenyl substituted in the meta position by acetamido, aminocarbonyl or hydroxymethyl.

10. The compound of formula (I) according to claim 1 or claim 8, wherein Ar₂ is phenyl substituted in the ortho position by trifluoromethoxy.

11. The compound of formula (I) according to claim 1 or claim 8, wherein Ar₂ is phenyl substituted in the ortho position by methoxymethyl, benzyloxy or phenoxy.

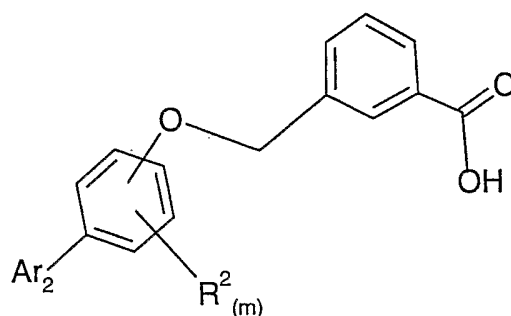
12. The compound of formula (I) according to any of claims 1 to 11, wherein Ar is selected from the group consisting of phenyl, thiazolyl and pyridyl.

5 13. The compound of formula (I) according to any of claims 1 to 12, wherein p is 0.

14. The compound of formula (I) according to any of claims 1 to 13, wherein R⁴ is hydrogen.

15. The compound of formula (I) according to any of claims 1 to 14, wherein s is 0.

16. The compound of formula (I) according to claim 1 having the formula



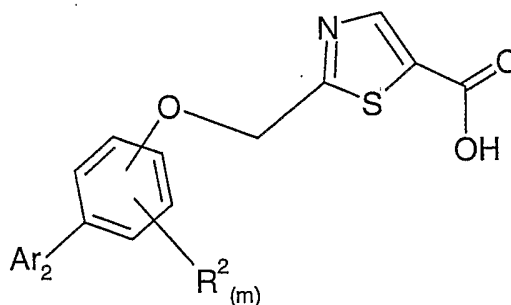
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wherein Ar₂, R² and m are as defined in claim 1,

and the pharmaceutically acceptable salts thereof.

17. A compound of formula (I) according to claim 1 having the formula



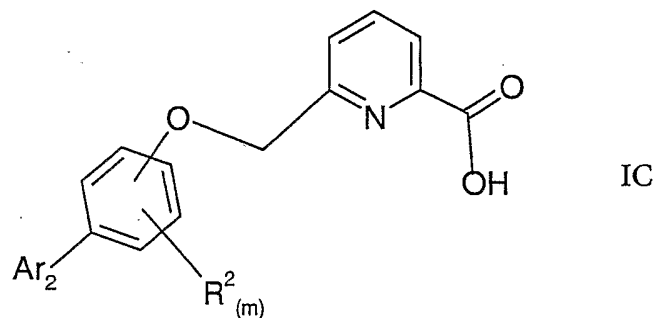
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1B

15 wherein Ar₂, R² and m are as defined in claim 1,

and the pharmaceutically acceptable salts thereof.

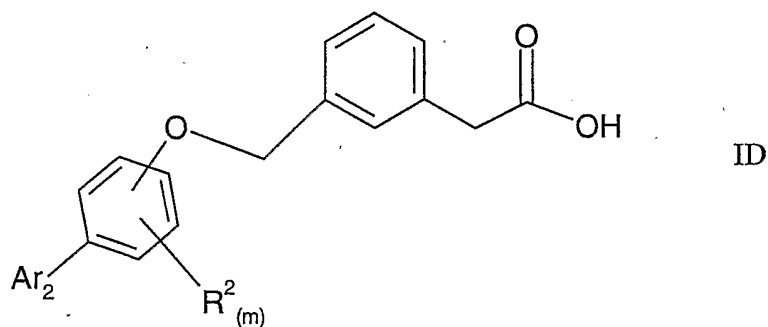
18. A compound of formula (I) according to claim 1 having the formula



wherein Ar_2 , R^2 and m are as defined in claim 1,

5 and the pharmaceutically acceptable salts thereof.

19. A compound of formula (I) according to claim 1 having the formula



wherein Ar_2 , R^2 and m are as defined in claim 1,

and the pharmaceutically acceptable salts thereof.

10 20. A compound of formula (I) according to claim 1 selected from the group consisting of

3-(3'-acetylamino-biphenyl-4-yloxymethyl)-benzoic acid;

3-(4-benzo[1,3]dioxol-5-yl-phenoxy-methyl)-benzoic acid;

3-(3'-carbamoyl-biphenyl-4-yloxymethyl)-benzoic acid;

15 3-[4-(2-chloro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid;

- 3-[4-(6-chloro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid;
3-[4-(3,5-dimethyl-isoxazol-4-yl)-phenoxy-methyl]-benzoic acid;
3-[4-(2-fluoro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid;
3-[4-(6-fluoro-pyridin-3-yl)-phenoxy-methyl]-benzoic acid;
5 3-(4-furan-2-yl-phenoxy-methyl)-benzoic acid;
3-(3'-hydroxymethyl-biphenyl-4-yloxy-methyl)-benzoic acid;
3-(4-isoquinolin-5-yl-phenoxy-methyl)-benzoic acid;
3-(2'-methoxymethyl-biphenyl-4-yloxy-methyl)-benzoic acid;
3-(3'-methoxymethyl-biphenyl-4-yloxy-methyl)-benzoic acid;
10 3-(4-naphthalen-1-yl-phenoxy-methyl)-benzoic acid;
3-(2'-phenoxy-biphenyl-4-yloxy-methyl)-benzoic acid;
3-(3'-pyrazol-1-yl-biphenyl-4-yloxy-methyl)-benzoic acid;
3-(4-pyridin-3-yl-phenoxy-methyl)-benzoic acid;
3-(4-thiophen-3-yl-phenoxy-methyl)-benzoic acid;
15 3-(2'-trifluoromethoxy-biphenyl-4-yloxy-methyl)-benzoic acid;
3-(4'-trifluoromethoxy-biphenyl-4-yloxy-methyl)-benzoic acid;
2-(3'-acetylamino-biphenyl-4-yloxy-methyl)-thiazole-4-carboxylic acid;
2-(4-benzo[1,3]dioxol-5-yl-phenoxy-methyl)-thiazole-4-carboxylic acid;
2-(2'-benzyloxy-biphenyl-4-yloxy-methyl)-thiazole-4-carboxylic acid;
20 2-[4-(1-benzyl-1H-pyrazol-4-yl)-phenoxy-methyl]-thiazole-4-carboxylic acid;
2-([1,1';3',1'']terphenyl-4-yloxy-methyl)-thiazole-4-carboxylic acid;
2-(3'-carbonyl-biphenyl-4-yloxy-methyl)-thiazole-4-carboxylic acid;
2-[4-(2-chloro-pyridin-3-yl)-phenoxy-methyl]-thiazole-4-carboxylic acid;

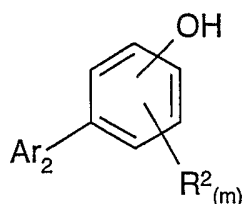
- 84 -

- 2-[4-(6-fluoro-pyridin-3-yl)-phenoxy-methyl]-thiazole-4-carboxylic acid;
2-(3'-hydroxymethyl-biphenyl-4-yloxy-methyl)-thiazole-4-carboxylic acid;
2-(4-isoquinolin-5-yl-phenoxy-methyl)-thiazole-4-carboxylic acid;
2-(2'-methoxymethyl-biphenyl-4-yloxy-methyl)-thiazole-4-carboxylic acid;
5 2-(3'-methoxymethyl-biphenyl-4-yloxy-methyl)-thiazole-4-carboxylic acid;
2-(4-naphthalen-1-yl-phenoxy-methyl)-thiazole-4-carboxylic acid;
2-(2'-phenoxy-biphenyl-4-yloxy-methyl)-thiazole-4-carboxylic acid;
2-(4-thiophen-3-yl-phenoxy-methyl)-thiazole-4-carboxylic acid;
2-(2'-trifluoromethoxy-biphenyl-4-yloxy-methyl)-thiazole-4-carboxylic acid;
10 6-(4-benzo[1,3]dioxol-5-yl-phenoxy-methyl)-pyridine-2-carboxylic acid;
6-(2'-methoxymethyl-biphenyl-4-yloxy-methyl)-pyridine-2-carboxylic acid;
6-(4-thiophen-2-yl-phenoxy-methyl)-pyridine-2-carboxylic acid;
[3-(3'-acetylamino-biphenyl-4-yloxy-methyl)-phenyl]-acetic acid;
[3-(3'-hydroxymethyl-biphenyl-4-yloxy-methyl)-phenyl]-acetic acid;
15 [3-(2'-methoxymethyl-biphenyl-4-yloxy-methyl)-phenyl]-acetic acid;
{3-[4-(2-methoxy-pyridin-3-yl)-phenoxy-methyl]-phenyl}-acetic acid;
[3-(2'-trifluoromethoxy-biphenyl-4-yloxy-methyl)-phenyl]-acetic acid;

and the pharmaceutically acceptable salts thereof.

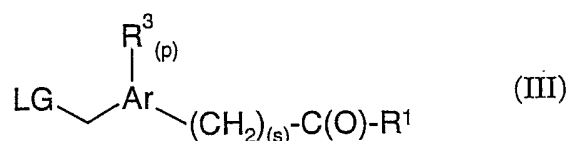
21. A process for the preparation of a compound of formula I according to claim 1,
20 which process comprises

a) reacting a compound of formula (II)



(II)

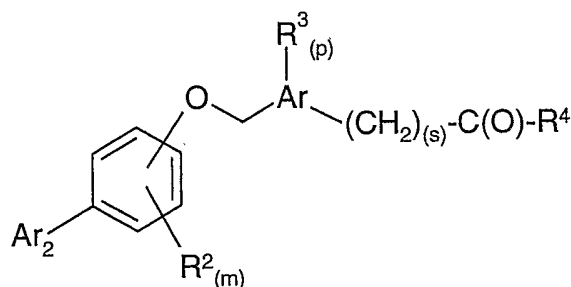
wherein Ar_2 , R^1 , R^2 , m and n are as defined in claim 1,
in the presence of a base with a compound of formula (III)



(III)

5

wherein Ar , R^3 , p and s are as defined in claim 1, LG represents a leaving group such as chloro, bromo or iodo, and R^1 represents a protecting group, and subsequently cleaving the protecting group to obtain a compound of formula (I)



(I)

10

wherein R^4 signifies hydroxy, and Ar , Ar_2 , R^2 , R^3 , m , n , p and s are as defined in claim 1, and

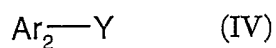
optionally reacting this compound with an ester of an amino acid in the presence of EDC and DMAP and subsequently cleaving the ester group, to obtain a compound of formula I, wherein R^4 is an amino acid attached through a nitrogen atom of the

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amino acid, or

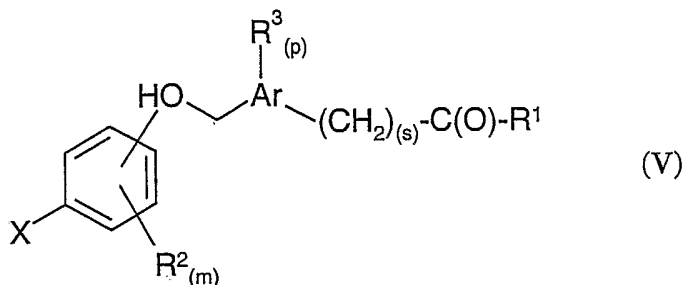
alternatively,

b) reacting a compound of formula (IV)

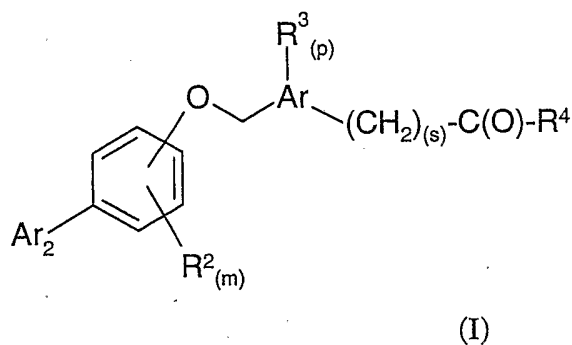


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wherein Ar_2 is as defined in claim 1 and Y represents $B(OH)_2$, in the presence of a catalytic amount of a palladium (0) complex, with a compound of formula (V)



5 wherein Ar, R^2 , R^3 , m, p and s are as defined in claim 1, X represents a leaving group such as bromo, iodo or triflate, and R^1 represents a protecting group, and subsequently cleaving the protecting group to obtain a compound of formula (I)



10 wherein R^4 signifies hydroxy, and Ar, R^2 , R^3 , m, n, p and s are as defined in claim 1, and optionally reacting this compound with an ester of an amino acid in the presence of EDC and DMAP and subsequently cleaving the ester group, to obtain a compound of formula I, wherein R^4 is an amino acid attached through a nitrogen atom of the amino acid.

15 22. A compound of formula (I) according to any one of claims 1 to 20, when manufactured by a process according to claim 21.

23. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 20 together with a pharmaceutically acceptable carrier and/or adjuvant.

20 24. The pharmaceutical composition according to claim 23 for the treatment of type 2 diabetes or impaired glucose tolerance.

25. A method for treating a disease mediated by activation of the glycogen synthase enzyme which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) according to any one of claims 1 to 20.

26. A compound of formula (I) according to any one of claims 1 to 20 for use as a
5 therapeutic active substance.

27. The use of a compound of formula (I) according to any one of claims 1 to 20 for the preparation of a medicament for the treatment and/or prophylaxis of diseases mediated by the activation of the glycogen synthase enzyme.

28. The use according to claim 27 for the preparation of a medicament for the
10 treatment of type 2 diabetes or impaired glucose tolerance.

29. The novel compounds, processes and methods as well as the use of such compounds substantially as described herein before.
