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SUBSTITUTED PYRIDINES AND BIPHENYLS AS ANTI-HYPERCHOLESTERINEMIC, ANTI-HYPERLIPOPROTEINEMIC AND ANTI-HYPERGLYCEMIC AGENTS**Field**

5 This application relates to substituted biaryl compounds which inhibit cholesterol ester transfer proteins (CETPs), stimulate reverse cholesterol transport, and inhibit the action of glucagon.

Background

10 The present invention concerns certain substituted pyridines, processes for the production thereof, and the use thereof in pharmaceutical products. It also concerns certain substituted biphenyls, processes for their production, pharmaceutical compositions containing them, and methods for their use.

15 7-(polysubstituted pyridyl) hept-6-enoates for the treatment of arteriosclerosis, lipoproteinemia, and hyperlipoproteinemia are known from US 5 169 857. In addition, the production of 7-(4-aryl-3-pyridyl)-3,5-dihydroxy-hept-6-enoate is described in EP 325 130.

20 Glucagon is a peptide hormone whose main function is to increase hepatic glucose production. Insulin, on the other hand, functions to decrease glucose production. Together, these two hormones are necessary for maintaining a correct level of glucose in the blood.

25 Diabetes is a complex disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetes is also associated with elevated glucagon levels. The heterogeneous nature of the disease requires different strategies to address the different abnormalities in metabolism found in affected individuals.

30 In the diabetic state (all forms of Type I and Type II), hyperglycemia often is associated with elevated glucagon levels. Accordingly, a means of treating all forms of diabetes is to block the glucagon receptor with a suitable antagonist, thereby inhibiting glucose production by the liver and reducing glucose levels in the patient.

Glucagon receptor antagonists, materials which block the action of endogenous glucagon, are known to have many and varied applications. Among these applications are the following:



- 0 1. Treatment of hyperglycemia associated with diabetes of any cause and associated with any other diseases or conditions. A glucagon receptor antagonist can be used either alone or in combination with any other therapies to treat hyperglycemia.
2. Treatment of impaired glucose tolerance (IGT).
- 5 3. Treatment of insulin resistance syndromes including those due to obesity, polycystic ovarian syndrome, "Syndrome X", drugs and hormones, endocrinopathies and genetic syndromes.
4. To decrease free fatty acid levels and treat conditions associated with elevated free fatty acids levels such as insulin resistance, obesity, all or part of
- 10 Syndrome X, Type I and II diabetes, hyperlipidemias and elevated hepatic glucose output associated with insulin resistance, Type I and Type II diabetes, obesity, and Syndrome X.
5. To treat conditions associated with genetic defects in insulin action due to alterations in insulin receptor structure and function or alterations in post
- 15 receptor signal transduction. To treat diabetes associated with anti-insulin antibodies, drug induced diabetes, diabetes associated with endocrinopathies and diabetes associated with genetic syndromes.
6. To treat gestational diabetes mellitus.
7. To treat autoimmune and non autoimmune causes of Type I diabetes
- 20 including those due to known genetic defects of the beta cell, pancreatic diseases, drug or toxin induced beta cell dysfunction, endocrinopathies, infectious causes, malnutrition associated and idiopathic Type I diabetes.
8. To prevent and treat diabetic ketoacidosis and decrease hepatic ketone body production
- 25 9. To treat hyperglycemia of exercise in diabetes.
10. To reduce fasting and postprandial glucose.
11. Treatment of insulin resistance in liver, muscle, and fat.
12. Treatment of conditions of hyperlipidemia.
13. To treat glucagonomas and all other conditions associated with elevated
- 30 glucagon levels.
14. To treat conditions of increased futile cycling of glucose in the liver.
15. To increase insulin secretion.
16. To decrease glucose toxicity.

- 0 17. To decrease the renal prostaglandin response to protein and amino acids.
18. To decrease elevated GFR and albumin clearance due to diabetes or proteins or amino acids.
19. To decrease renal albumin clearance and excretion.
- 5 20. To treat acute pancreatitis.
21. To treat cardiovascular disease including causes of increased cardiac contractility.
22. To treat cardiac hypertrophy and its consequences.
23. As a diagnostic agent and as a diagnostic agent to identify patients
- 10 having a defect in the glucagon receptor.
24. Treatment of gastrointestinal disorders, treatment of decreased gut motility.
25. As a therapy to increase gastric acid secretions.
26. To reverse intestinal hypomotility due to glucagon administration.
- 15 27. To reverse catabolism and nitrogen loss in states of negative nitrogen balance and protein wasting including all causes of Type I and Type II diabetes, fasting, AIDS, cancer, anorexia, aging and other conditions.
28. To treat any of the above conditions or diseases in post-operative or operative period.
- 20 29. To decrease satiety and increase energy intake.

 Glucagon receptor antagonists of the prior art, such as those described in WO9518153-A and references cited therein, are predominantly peptide analogues of glucagon. They are susceptible to the actions of endogenous proteases, may precipitate antibody production and immune reactions and can be difficult and

25 expensive to manufacture. Such peptides are usually unsuitable for oral delivery.

 One non-peptide glucagon receptor antagonist has been reported (Collins, et al; *BioMed. Chem Lett.* 1992, 2, 915-918). This quinoxaline derivative, CP-99,711, was shown to inhibit glucagon binding and glucagon action in rat liver membrane at micromolar concentrations.

30 It would be desirable to have inhibitors of CETP which possess valuable pharmacological properties that are superior to those of the state of the art. Certain of the substituted pyridine compounds of the invention are highly effective

0 inhibitors of cholesterol ester transfer proteins (CETP) and stimulate reverse
cholesterol transport. They cause a reduction in LDL cholesterol levels in the blood,
while at the same time increasing HDL cholesterol levels. They can therefore be
used for the treatment of hyperlipoproteinemia or arteriosclerosis.

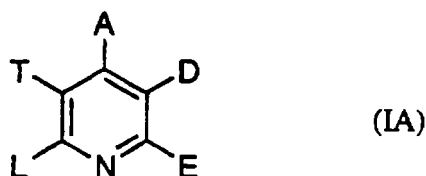
It would also be desirable to have readily prepared non-peptidic glucagon
5 receptor antagonists which are metabolically more stable than peptidic antagonists
of the prior art, and which afford good activity and bioavailability. Certain of the
substituted pyridine compounds as well as the substituted biphenyls of the
invention are highly effective inhibitors of the glucagon receptor. Accordingly,
these compounds may be used to treat glucagon-mediated conditions such as those
10 listed above.

Summary

The present invention concerns substituted biaryl compounds which fall
15 within the three general formulae (IA), (IB), and (IC) shown below. The definitions
of these general formulae are given broadly in the following text. In the
subsequent detailed description sections, each of these broad general formulae is
discussed in more detail in terms of its preferred and most preferred molecular
constituents, procedures for making, examples of particular materials made, testing
20 procedures, and results obtained.

It should be noted that in the text below, and in the subsequent detailed
description sections, the definitions of the various constituent and substituent
groups apply only to the particular subset of the compounds of the invention then
under consideration. The same symbols may have different definitions in
25 connection with the other subsets of compounds.

The present invention concerns substituted pyridines of the general formula
(IA),



30 in which

A stands for aryl with 6 to 10 carbon atoms, which is optionally substituted up
to 3 times in an identical manner or differently by halogen, hydroxy,
trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl,

0 acyl, or alkoxy with up to 7 carbon atoms each, or by a group of the formula
-NR¹R²,

wherein

5 R¹ and R² are identical or different and denote hydrogen, phenyl, or
straight-chain or branched alkyl with up to 6 carbon atoms,

D stands for straight-chain or branched alkyl with up to 8 carbon atoms, which
is substituted by hydroxy,

10 E and L are either identical or different and stand for straight-chain or branched
alkyl with up to 8 carbon atoms, which is optionally substituted by cycloalkyl
with 3 to 8 carbon atoms,

or

15 stand for cycloalkyl with 3 to 8 carbon atoms,

or

E has the above-mentioned meaning

20 and

L in this case stands for aryl with 6 to 10 carbon atoms, which is optionally
substituted up to 3 times in an identical manner or differently by halogen,
25 hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or
branched alkyl, acyl, or alkoxy with up to 7 carbon atoms each, or by a
group of the formula -NR³R⁴,

wherein

30 R³ and R⁴ are identical or different and have the meaning given above for
R¹ and R²,

or

35 E stands for straight-chain or branched alkyl with up to 8 carbon atoms,
or

stands for aryl with 6 to 10 carbon atoms, which is optionally substituted up to 3 times in an identical manner or differently by halogen, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or alkoxy with up to 7 carbon atoms each, or by a group of the formula $-NR^5R^6$,

wherein

R^5 and R^6 are identical or different and have the meaning given above for R^1 and R^2 ,

and

in this case stands for straight-chain or branched alkoxy with up to 8 carbon atoms or for cycloalkyloxy with 3 to 8 carbon atoms,

stands for a radical of the formula



wherein

R^7 and R^8 are identical or different and

denote cycloalkyl with 3 to 8 carbon atoms, or aryl with 6 to 10 carbon atoms,

or denote a 5- to 7-member aromatic, optionally benzo-condensed, heterocyclic compound with up to 3 heterocyclic atoms from the series S, N and/or O, which are optionally substituted up to 3 times in an identical manner or differently by trifluoromethyl, trifluoromethoxy, halogen, hydroxy, carboxyl, by straight-chain or branched alkyl, acyl, alkoxy, or alkoxycarbonyl with up to 6 carbon atoms each, or by phenyl, phenoxy, or thiophenyl, which can in turn be substituted by halogen, trifluoromethyl, or trifluoromethoxy,

and/or the rings are substituted by a group of the formula $-NR^{11}R^{12}$,

wherein

0 R^{11} and R^{12} are identical or different and have the meaning given
above for R^1 and R^2 ,

5 X denotes a straight or branched alkyl chain or alkenyl chain with 2 to
10 carbon atoms each, which are optionally substituted up to 2 times
by hydroxy,

R^9 denotes hydrogen,

and

10

R^{10} denotes hydrogen, halogen, azido, trifluoromethyl, hydroxy,
mercapto, trifluoromethoxy, straight-chain or branched alkoxy with
up to 5 carbon atoms, or a radical of the formula $-NR^{13}R^{14}$,

15

wherein

R^{13} and R^{14} are identical or different and have the meaning given
above for R^1 and R^2 ,

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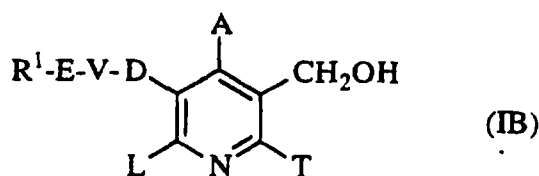
or

R^9 and R^{10} form a carbonyl group together with the carbon atom,

and the salts thereof.

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The present invention also concerns substituted pyridines of general formula
(IB)



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in which

A stands for aryl with 6 to 10 carbon atoms, which is optionally substituted up
to 3 times in an identical manner or differently by halogen, hydroxy,

- 0 trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl,
acyl, or alkoxy with up to 7 carbon atoms each, or by a group of the formula
-NR²R³ and/or -WR⁴,
- wherein
- 5 R² and R³ are the same or different and
 denote hydrogen, phenyl, or straight-chain or branched alkyl with up
 to 6 carbon atoms,
- 10 W denotes an oxygen or sulfur atom,
- R⁴ denotes aryl with 6 to 10 carbon atoms, which is optionally
 substituted up to 3 times in an identical manner or differently by
 halogen, trifluoromethyl, trifluoromethoxy, hydroxy, or by
15 straight-chain or branched alkyl or alkoxy with up to 6 carbon atoms
 each,
- D and E are identical or different and
 stand for a straight-chain or branched alkyl chain with up to 8 carbon atoms,
- 20 or
- E stands for a bond,
- 25 V stands for an oxygen or sulfur atom or for a group of the formula -NR⁵-,
 wherein
- R⁵ denotes hydrogen or straight-chain or branched alkyl with up to 6
30 - carbon atoms or phenyl,
- R¹ stands for cycloalkyl with 3 to 6 carbon atoms, or
 stands for aryl with 6 to 10 carbon atoms or for a 5- to 7-member, optionally
 benzocondensed, saturated or unsaturated, mono-, bi-, or tricyclic
35 heterocyclic compound with up to 4 carbon atoms from the series S, N,
 and/or O,

0 in which the heterocycles, also via the N function in the case of
nitrogen-containing rings, are optionally substituted up to 3 times in an
identical manner or differently by halogen, trifluoromethyl, hydroxy, cyano,
carboxyl, trifluoromethoxy, straight-chain or branched acyl, alkyl, alkylthio,
alkylalkoxy, alkoxy, or alkoxycarbonyl with up to 6 carbon atoms each, by
5 aryl with 6 to 10 carbon atoms, or by an optionally benzo-condensed,
aromatic 5- to 7-member heterocyclic compound with up to 3 heterocyclic
atoms from the series S, N, and/or O,
and/or are substituted by a group of the formula -OR⁶, -SR⁷, -SO₂R⁸, or
-NR⁹R¹⁰,

10

wherein

R⁶, R⁷, and R⁸ are identical or different and

15

denote aryl with 6 to 10 carbon atoms, which in turn is substituted up
to 2 times in an identical manner or differently by phenyl or halogen
or by straight-chain or branched alkyl with up to 4 carbon atoms,

R⁹ and R¹⁰ are identical or different and have the above-indicated meaning
of R² and R³,

20

L and T are identical or different and -

25

stand for trifluoromethyl or straight-chain or branched alkyl with up to 8
carbon atoms, which are optionally substituted by cycloalkyl with 3 to 7
carbon atoms, or by aryl with 6 to 10 carbon atoms, which in turn can be
substituted up to 2 times in an identical manner or differently by halogen,
trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl,
acyl, or alkoxy with up to 7 carbon atoms each,

or

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L and/or T stand for cycloalkyl with 3 to 7 carbon atoms or

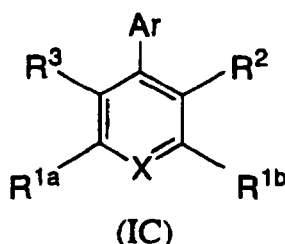
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stand for aryl with 6 to 10 carbon atoms or for a 5- to 7-member, saturated,
partially unsaturated, or unsaturated heterocyclic compound with up to 3
heterocyclic atoms from the series S, N and/or O, with binding in the case of
a nitrogen atom also being possible via this atom, with the heterocycles
optionally being substituted up to 3 times in an identical manner or
differently by halogen, nitro, trifluoromethyl, trifluoromethoxy, or by

0 straight-chain or branched alkyl, acyl, or alkoxy with up to 7 carbon atoms each,

and the salts thereof.

5 This invention also relates to compounds having glucagon receptor antagonistic activity and the general formula (IC) shown below.



10 In general formula IC, the groups X, R^{1a}, R^{1b}, R², R³, and Ar have the following meanings:

X represents N or CR⁸.

R⁸ represents hydrogen, halogen, trifluoromethyl, phenyl, substituted phenyl, (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₁-C₆)-alkoxy, (C₃-C₇)-cycloalkyl, phenyl-(C₁-C₃)-alkoxy, (C₁-C₆)-alkanoyloxy, (C₁-C₆)-alkoxycarbonyl, carboxy, formyl, or -NR⁴R⁵. The substituents on the substituted phenyl or substituted alkyl R⁸ groups are from 1 to 3 of, for example, hydroxy, fluoro, (C₁-C₆)-alkoxy, (C₃-C₇)-cycloalkyl, phenyl, phenyl-(C₁-C₃)-alkoxy, (C₁-C₆)-alkanoyloxy, (C₁-C₆)-alkoxycarbonyl, carboxy, formyl, or -NR⁴R⁵.

20 The groups R⁴ and R⁵ are independently hydrogen, (C₁-C₆)-alkyl, (C₃-C₆)-alkenyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₆)-alkyl, phenyl, substituted phenyl, phenyl-(C₁-C₆)-alkyl, substituted phenyl-(C₁-C₆)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C₁-C₆)-alkyl, or substituted naphthyl-(C₁-C₆)-alkyl. The substituents on the substituted phenyl or substituted naphthyl R⁴ and R⁵ groups are 1 to 3 of, for example, halogen, cyano, trifluoromethyl, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy groups.

25 R⁴ and R⁵ may be joined together to form -(CH₂)_rA(CH₂)_s- wherein the subscripts r and s are independently 1 to 3 and A is CHR⁶, NR⁶, O, or S(O)_n in which n is 0, 1, or 2; and R⁶ is hydrogen, (C₁-C₆)-alkyl, piperidin-1-yl, phenyl, or phenyl-(C₁-C₆)-alkyl.

30 R^{1a} and R^{1b} are independently trifluoromethyl, (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₂-C₁₀)-alkenyl, substituted (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl,

0 substituted (C₂-C₁₀)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkenyl, or (C₁-C₆)-
 alkanoyl. The substituents on the substituted alkyl, substituted alkenyl, and
 substituted alkynyl R^{1a} and R^{1b} groups are independently from 1 to 3 of, for
 example, -OR⁴, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁴R⁵, -NR⁴R⁵, or phenyl which is
 optionally substituted with from 1 to 3 of, for example, halogen, (C₁-C₄)-alkyl, or
 5 (C₁-C₄)-alkoxy groups.

R² is (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₂-C₁₀)-alkenyl,
 substituted (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, substituted (C₂-C₁₀)-alkynyl, (C₃-
 C₆)-cycloalkyl-(C₁-C₆)-alkyl, or substituted (C₃-C₆)-cycloalkyl-(C₁-C₆)-alkyl. The
 substituents on the substituted alkyl, substituted alkenyl, substituted alkynyl, and
 10 substituted cycloalkyl R² groups are independently from 1 to 3 of halogen, phenyl,
 substituted phenyl, 1,3-dioxolan-2-yl, -C(O)NR⁴R⁵, or -S(O)_mR⁷ wherein m is 0, 1,
 or 2. The substituents on the substituted phenyl R² substituent group are from 1 to
 3 of, for example, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy.

R⁷ is (C₁-C₆)-alkyl, phenyl, substituted phenyl, phenyl-(C₁-C₆)-alkyl,
 15 substituted phenyl-(C₁-C₆)-alkyl, pyridyl, substituted pyridyl, pyridyl-(C₁-C₆)-
 alkyl, substituted pyridyl-(C₁-C₆)-alkyl, naphthyl, substituted naphthyl, naphthyl-
 (C₁-C₆)-alkyl, or substituted naphthyl-(C₁-C₆)-alkyl. The substituents on the
 substituted phenyl, substituted pyridyl or substituted naphthyl R⁷ groups are from
 1 to 5 of, for example, halogen, trifluoromethyl, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy,
 20 nitro, cyano, or hydroxy.

R² and R^{1b} may be joined to form an alkylene bridge containing from 3 to 5
 carbon atoms, between the ring carbon atoms to which R² and R^{1b} are attached.

R³ is hydroxy, trifluoroacetyl, (C₁-C₆)-alkanoyl, substituted (C₁-C₆)-alkyl,
 or substituted (C₃-C₆)-alkenyl. The substituents on the substituted alkyl and
 25 substituted alkenyl R³ groups are from 1 to 3 hydroxy or trifluoromethyl groups.

Ar is an optionally substituted aromatic or heteroaromatic ring. Examples of
 possible Ar groups are: phenyls, naphthyls, pyridyls, furanyls, thiophenyls,
 pyrrolyls, imidazolyls, pyrazolyls, triazolyls, tetrazolyls, oxazolyls, isoxazolyls,
 thiazolyls and isothiazolyls. The optional substituents on the group Ar are
 30 independently 1 to 3 of, for example, halogen, (C₁-C₆)-alkyl, substituted (C₁-C₆)-
 alkyl, (C₂-C₆)-alkenyl, substituted (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, substituted
 (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, cyano, nitro, trifluoromethyl, -OR⁴, -C(O)R⁴, -
 OC(O)R⁴, -CO₂R⁴, -NR⁴R⁵, -C(O)NR⁴R⁵, or -S(O)_mR⁷. The substituents on the
 substituted alkyl, substituted alkenyl, and substituted alkynyl substituent groups on
 35 Ar are from 1 to 3 of, for example, halogen, hydroxy, -NR⁴R⁵, phenyl, or

- 0 substituted phenyl in which the phenyl group may bear, for example, one or more halogen, (C₁-C₄) alkyl, or (C₁-C₄) alkoxy groups.

Pharmaceutically acceptable salts of these materials are within the scope of the invention.

- 5 The invention also relates to a pharmaceutical product containing the substituted pyridines according to general formula (IA) and, if appropriate, a pharmacologically tolerable formulation adjuvant. It further relates to such pharmaceutical product for the inhibition of cholesterol ester transfer proteins, and to the use of the claimed substituted pyridines for the production of pharmaceutical
10 products, and to use of the claimed substituted pyridines for the production of cholesterol ester transfer protein inhibitors.

- The invention further relates to a pharmaceutical product containing the substituted pyridines 3-heteroalkyl-aryl-substituted pyridines according to general formula (IB) and, if appropriate, a pharmacologically tolerable formulation
15 adjuvant. It further relates to such pharmaceutical product for the treatment of hyperlipoproteinemia, and to the use of the claimed substituted pyridines for the production of pharmaceutical products, and to use of the claimed substituted pyridines for the production of pharmaceutical products for the treatment of hyperlipoproteinemia.

- 20 The invention also relates to a pharmaceutical composition for use in treating a glucagon-mediated condition, which comprises: a compound having glucagon receptor antagonistic activity and a structure within general structural formula IC, plus a pharmaceutically acceptable carrier.

- The invention further relates to a method for treating a glucagon-mediated
25 condition which comprises administering to a subject an effective amount of a compound having glucagon receptor antagonistic activity and a structure within general structural formula IC.

0 **Detailed description with reference to compounds of general formula (IA)**

The substituted pyridines according to the invention can also occur in the form of the salts thereof. In general, salts with organic or inorganic bases or acids are mentioned here.

5

Within the context of the present invention, physiologically safe salts are preferred. Physiologically safe salts of the compounds according to the invention can be salts of substances according to the invention with mineral acids, carboxylic acids, or sulfonic acids. Salts with, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalene disulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid, or benzoic acid are particularly preferred.

15 Physiologically safe salts can also be metallic or ammonium salts of the compounds according to the invention that possess a free carboxyl group. For example, sodium salts, potassium salts, magnesium salts, or calcium salts, as well as ammonium salts, that are derived from ammonia, or organic amines such as ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine, ethylenediamine, or 2-phenyl-ethylamine are particularly preferred.

25 The compounds according to the invention can exist in stereoisomeric forms, which either behave like an image and mirror image (enantiomers) or do not behave like an image and mirror image (diastereomers). The invention concerns both enantiomers or diastereomers or the mixtures thereof. These mixtures of enantiomers and diastereomers can be separated in the known manner into stereoisomerically homogeneous components.

30 Within the context of the invention, the heterocyclic compound, which is optionally benzo-condensed, stands in general for a saturated or unsaturated, 5-to 7-member, preferably 5- to 6-member, heterocyclic compound that can contain up to 3 heteroatoms from the series S, N, and/or O. Indolyl, isoquinolyl, quinolyl, benzothiazolyl, benzo[b]thiophene, benzo[b]furanyl, benzoxazolyl, pyridyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, morpholinyl, or piperidyl are cited as examples. Quinolyl, pyridyl, indolyl, benzothiazolyl, or benzoxazolyl are preferred.

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0

Compounds of the general formula (IA) are preferred,

in which

5 A stands for naphthyl or phenyl, which are optionally substituted up to 3 times in an identical manner or differently by fluorine, chlorine, bromine, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or alkoxy with up to 6 carbon atoms each, or by a group of the formula -NR¹R²,

10

wherein

R¹ and R² are identical or different and denote hydrogen, phenyl, or straight-chain or branched alkyl with up to 4 carbon atoms,

15

D stands for straight-chain or branched alkyl with up to 6 carbon atoms, which is substituted by hydroxy,

20

E and L are either identical or different and stand for straight-chain or branched alkyl with up to 6 carbon atoms, which is optionally substituted by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, or stand for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl,

or

25

E has the above-mentioned meaning

and

30

L in this case stands for naphthyl or phenyl, which are optionally substituted up to 3 times in an identical manner or differently by fluorine, chlorine, bromine, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl or alkoxy with up to 6 carbon atoms each, or by a group of the formula -NR³R⁴,

35

0 wherein

R^3 and R^4 are identical or different and have the meaning given above for R^1 and R^2 ,

5 or

E stands for straight-chain or branched alkyl with up to 5 carbon atoms, or stands for naphthyl or phenyl, which are optionally substituted up to 3 times in an identical manner or differently by fluorine, chlorine, bromine, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or alkoxy with up to 6 carbon atoms each, or by a group of the formula $-NR^5R^6$,

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wherein

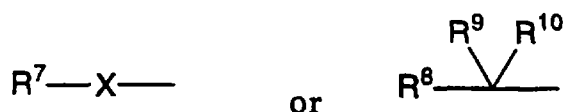
R^5 and R^6 are identical or different and have the meaning given above for R^1 and R^2 ,

and

20

L in this case stands for straight-chain or branched alkoxy with up to 6 carbon atoms, or for cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, or cycloheptyloxy,

25 T stands for a radical of the formula



wherein

30

R^7 and R^8 are identical or different and

denote cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or adamantyl, or

denote naphthyl, phenyl, pyridyl, quinolyl, indolyl, benzothiazolyl, or benzoxazolyl, which are optionally substituted up to 3 times in an identical manner or differently by trifluoromethyl, trifluoromethoxy,

35

fluorine, chlorine, bromine, hydroxy, carboxyl, by straight-chain or

0 branched alkyl, alkoxy, or alkoxycarbonyl with up to 5 carbon atoms each, or by phenyl, phenoxy, or thiophenyl, which can in turn be substituted by fluorine, chlorine, bromine, trifluoromethyl, or trifluoromethoxy,

5 and/or the rings are optionally substituted by a group of the formula $-NR^{11}R^{12}$,

wherein

10 R^{11} and R^{12} are identical or different and have the meaning given above for R^1 and R^2 ,

X denotes a straight or branched alkyl chain or alkenyl chain with 2 to 8 carbon atoms each, which are optionally substituted up to 2 times by hydroxy,

15

R^9 denotes hydrogen,

and

20 R^{10} denotes hydrogen, fluorine, chlorine, bromine, azido, trifluoromethyl, hydroxy, mercapto, trifluoromethoxy, straight-chain or branched alkoxy with up to 4 carbon atoms, or a radical of the formula $-NR^{13}R^{14}$,

25 wherein

R^{13} and R^{14} are identical or different and have the meaning given above for R^1 and R^2 ,

30 or

R^9 and R^{10} form a carbonyl group together with the carbon atom,

35 and the salts thereof.

0 Compounds of the general formula (IA) are particularly preferred,
in which

5 A stands for phenyl, which is optionally substituted up to 2 times in an identical
manner or differently by fluorine, chlorine, bromine, hydroxy,
trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl or
alkoxy with up to 5 carbon atoms each,

10 D stands for straight-chain or branched alkyl with up to 5 carbon atoms, which
is substituted by hydroxy,

E and L are either identical or different and stand for straight-chain or branched
alkyl with up to 5 carbon atoms, which is optionally substituted by
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, or
15 stand for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl,

or

20 E has the above-mentioned meaning
and

25 L in this case stands for phenyl, which is optionally substituted up to 2 times in
an identical manner or differently by fluorine, chlorine, bromine, hydroxy,
trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl or
alkoxy with up to 5 carbon atoms each,

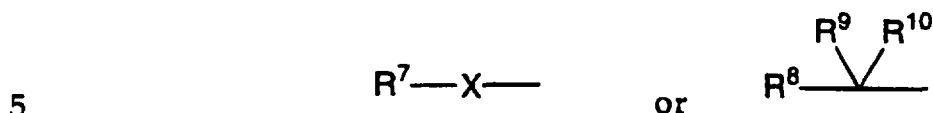
or

30 E stands for straight-chain or branched alkyl with up to 4 carbon atoms, or
stands for phenyl, which is optionally substituted up to 2 times in an identical
manner or differently by fluorine, chlorine, bromine, hydroxy,
trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl or
alkoxy with up to 5 carbon atoms each,

35 and

0 L in this case stands for straight-chain or branched alkoxy with up to 5 carbon atoms, or for cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, or cycloheptyloxy,

T stands for a radical of the formula



wherein

R^7 and R^8 are identical or different and

10 denote cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or adamantyl, or

denote phenyl, pyridyl, quinolyl, indolyl, naphthyl, benzothiazolyl, or benzoxazolyl, which are optionally substituted up to 2 times in an identical manner or differently by trifluoromethyl, trifluoromethoxy, fluorine, chlorine, bromine, hydroxy, carboxyl, by straight-chain or branched alkyl, alkoxy, or alkoxycarbonyl with up to 4 carbon atoms
15 —each, or by phenyl, phenoxy, or thiophenyl, which can in turn be substituted by fluorine, chlorine, bromine, trifluoromethyl, or trifluoromethoxy,

20 X denotes a straight or branched alkyl chain with 2 to 6 carbon atoms each, which are optionally substituted up to 2 times by hydroxy,

R^9 denotes hydrogen,

25 and

R^{10} denotes hydrogen, fluorine, chlorine, bromine, azido, amino, trifluoromethyl, hydroxy, mercapto, trifluoromethoxy, straight-chain or branched alkoxy with up to 3 carbon atoms,

30

or

R^9 and R^{10} form a carbonyl group together with the carbon atom,

35 and the salts thereof.

0

Compounds according to the invention of the general formula (IA) are most preferred, in which

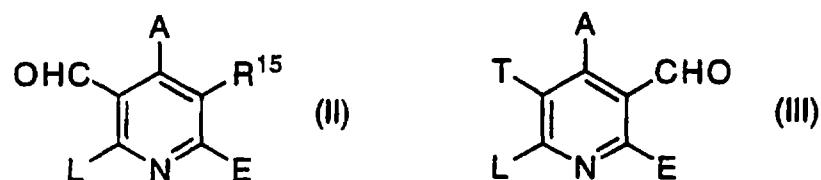
5

A stands for phenyl, which is optionally substituted by fluorine, chlorine, or methyl.

10

Furthermore, a process for the production of compounds according to the invention of the general formula (IA) has been discovered, characterized by the fact that

compounds of the general formula (II) or (III)



15 in which

A, E, L, and T have the above-mentioned meanings,

and

20

R¹⁵ stands for straight-chain or branched alkoxycarbonyl with up to 4 carbon atoms,

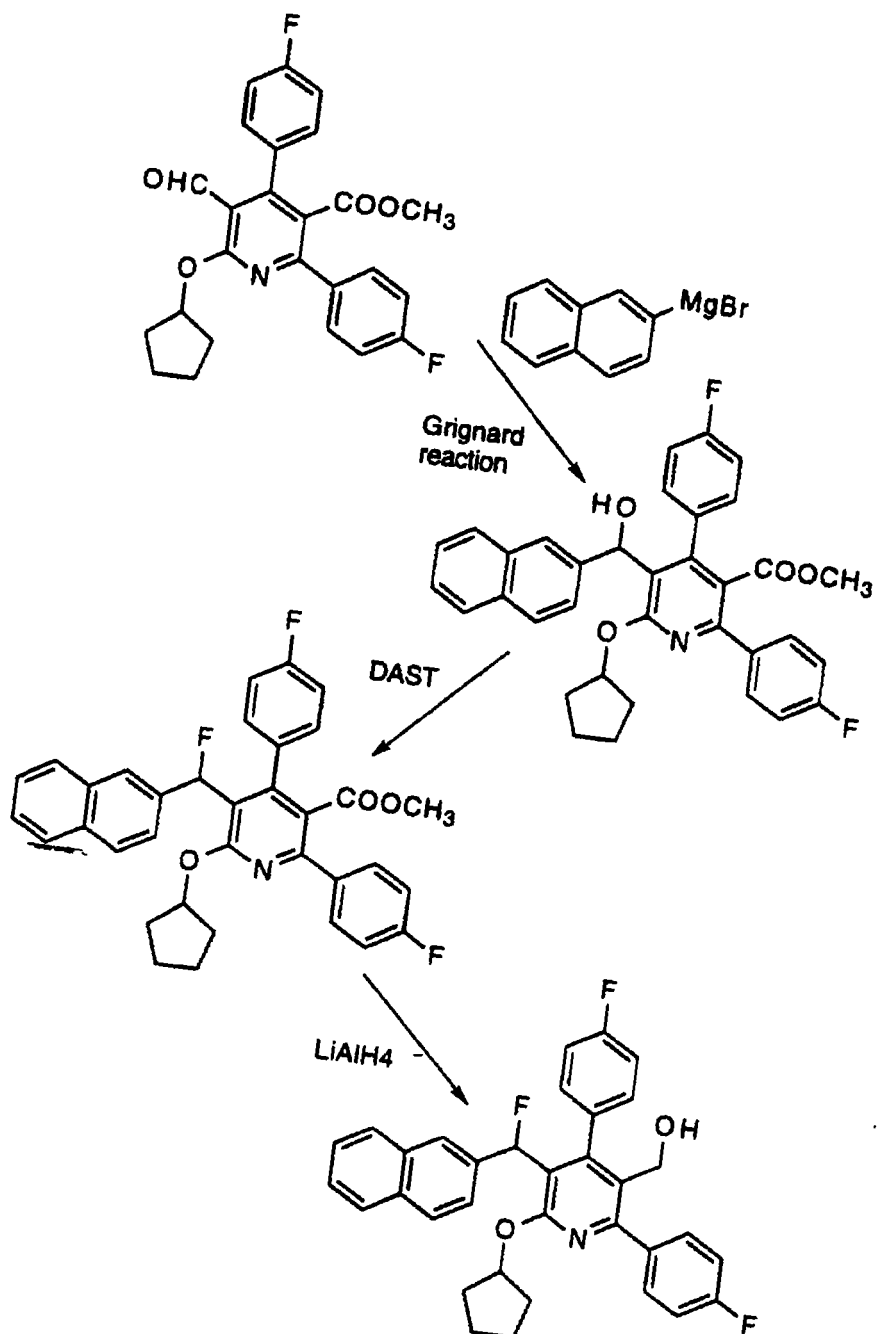
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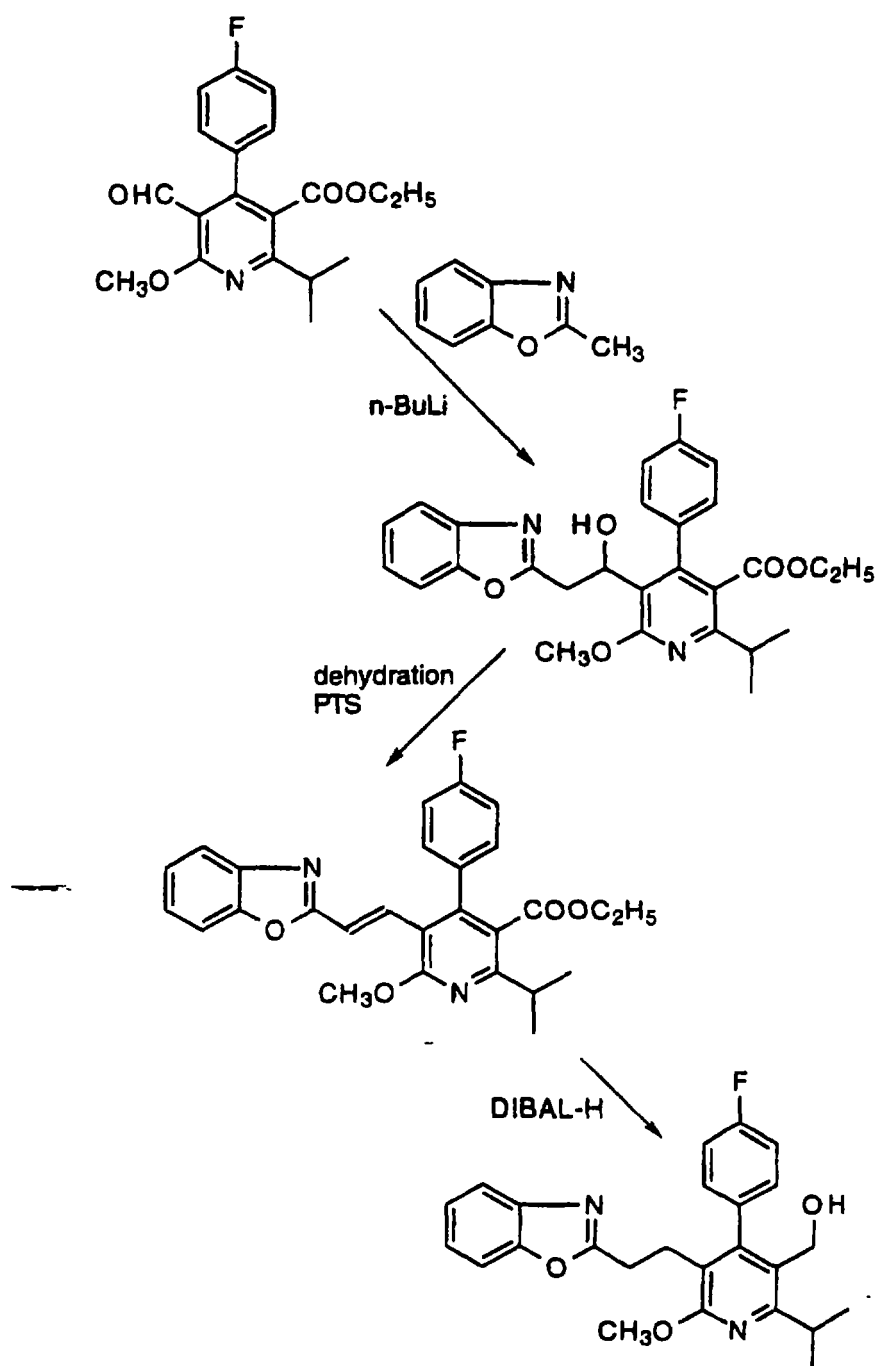
are either first reacted, using the Grignard or Wittig reaction, in an inert solvent, with further derivatization optionally being carried out according to the customary methods, and then are reduced in inert solvents,

or, in the case of compounds of the general formula (III), direct reductions are carried out, optionally via several steps.

30

The compounds according to the invention can be explained, for example, by means of the following reaction diagram:





0

Suitable solvents are ethers, such as diethyl ether, dioxane, tetrahydrofuran, or glycol dimethyl ether, or hydrocarbons, such as benzene, toluene, xylene, hexane, or cyclohexane, or petroleum fractions, or halocarbons, such as dichloromethane, trichloromethane, tetrachloromethane, dichloroethylene, or trichloroethylene, or chlorobenzene, or ethyl acetate, or triethylamine, pyridine, dimethyl sulfoxide, dimethyl formamide, hexamethylphosphoric triamide, acetonitrile, acetone, or nitromethane. It is likewise possible to use mixtures of said solvents. Dichloromethane is preferred.

0

Suitable organometallic reagents are systems such as Mg/bromobenzene trifluoride and p-trifluoromethylphenyllithium. The Mg/bromobenzene trifluoride system is preferred.

5 The reductions and derivatizations are carried out according to the above-mentioned methods.

In general, the reductions are carried out in ethers, such as dioxane, tetrahydrofuran, or diethyl ether, or in hydrocarbons, such as benzene, hexane, or
10 toluene. Toluene and tetrahydrofuran are preferred.

Suitable reductants are complex metal hydrides, such as lithium aluminum hydride, sodium cyanoborohydride, sodium aluminum hydride, diisobutylaluminum hydride, dimethoxymethylaluminate sodium salt, or sodium-
15 bis-(2-methoxyethoxy)-dihydroaluminate (Red-Al). Diisobutyl-aluminum hydride and dimethoxymethylaluminate sodium salt are preferred.

The reductant is generally added in a quantity ranging from 4 moles to 10 moles, preferably from 4 moles to 5 moles, relative to 1 mole of the compound to
20 be reduced.

The reduction generally takes place within a temperature range of -78°C to +50°C, preferably from -78°C to 0°C, and most preferably at -78°C, depending on the choice of both the reductant and the solvent.

25

The reduction generally takes place at normal pressure, but it is also possible to work at increased or reduced pressure.

However, the reductions can also be carried out with reductants that are
30 suitable for the reduction of ketones to hydroxy compounds. Particularly suitable in this regard is reduction using metal hydrides or complex metal hydrides in inert solvents, if appropriate in the presence of a trialkyl borane. Preferably, the reduction is carried out using complex metal hydrides, such as lithium borohydride, sodium borohydride, potassium borohydride, zinc borohydride, lithium trialkyl
35 borohydride, or lithium aluminum hydride. More particularly preferably, the reduction is carried out using sodium borohydride in the presence of triethylborane.

0

The reaction can also take place via hydrogenation. The hydrogenation takes place according to the customary methods using hydrogen in the presence of noble metal catalysts, such as Pd/C, Pt/C, or Raney nickel in one of the above-mentioned solvents, preferably in alcohols such as methanol, ethanol, or propanol, within a temperature range of -20°C to +100°C, preferably from 0°C to +50°C, at normal pressure or elevated pressure.

As derivatizations, the following types of reactions are cited by way of examples: oxidations, reductions, hydrogenations, halogenation, Wittig reactions/Grignard reactions, and amidation/sulfoamidation.

The customary strong basic compounds can be used as auxiliary agents. Among these are, preferably, organolithium compounds, such as n-butyllithium, sec-butyllithium, tert-butyllithium, or phenyllithium, or amides, such as lithium diisopropylamide, sodium amide, or potassium amide, or lithium hexamethylsilylamide, or alkali hydrides, such as sodium hydride or potassium hydride. Particularly preferably, n-butyllithium, or sodium hydride are used.

Furthermore, the customary inorganic bases are suitable bases. Among these are, preferably, alkali hydroxides or alkaline earth hydroxides, such as sodium hydroxide, potassium hydroxide, or barium hydroxide, or alkali carbonates, such as sodium carbonate, potassium carbonate, or sodium hydrogen carbonate. Particularly preferably, sodium hydroxide or potassium hydroxide are used.

25

Alcohols, such as methanol, ethanol, propanol, butanol, or tert-butanol, are also suitable solvents for the individual reaction steps. Tert-butanol is preferred.

It may possibly be necessary to carry out several reaction steps under a protective gas atmosphere.

30

The halogenation generally takes place in one of the above-mentioned chlorinated hydrocarbons, whereby methylene chloride is preferred.

Diethylamino sulfur trifluoride (DAST) or SOCl₂, for example, are suitable halogenation agents.

35

0 The halogenation generally takes place within a temperature range of -78°C to $+50^{\circ}\text{C}$, preferably from -78°C to 0°C , and most preferably at -78°C , depending on the choice of both the halogenation agent and the solvent.

5 The halogenation generally takes place at normal pressure, but it is also possible to work at increased or reduced pressure.

The customary reagents are suitable as Wittig reagents. 3-Trifluoromethylbenzyl triphenylphosphonium bromide is preferred.

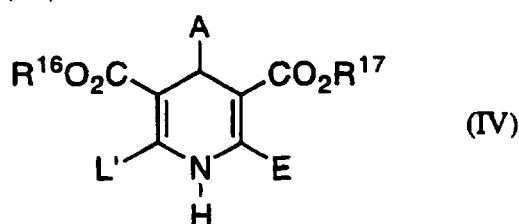
10 One of the above-mentioned bases are generally suitable as bases, preferably Li-bis-(triethylbutyl)amide.

15 The base is introduced in a quantity ranging from 0.1 mole to 5 moles, preferably from 0.5 mole to 2 moles, relative to 1 mole of the starting compound.

The reaction using Wittig reagents is generally carried out within a temperature range of 0°C to 150°C , preferably at 25°C to 40°C .

20 In general, the Wittig reactions are carried out at normal pressure. However, it is also possible to carry out the process at reduced pressure or high pressure (e.g., within a range from 0.5 to 5 bar).

25 Compounds of the general formula (II) in the case wherein L is other than alkoxy/cyclooxy (L') are known or can be produced by processing compounds of the general formula (IV)



in which

A, E, and L' have the above-mentioned meanings,

30

R^{16} and R^{17} are identical or different and

stand for straight-chain or branched alkyl with up to 4 carbon atoms,

0 in inert solvents with oxidants,

and

selectively reducing the alkoxycarbonyl function (CO_2R^{17}) to the hydroxy function
5 in a second step.

Suitable solvents for the oxidation are ethers, such as diethyl ether, dioxane, tetrahydrofuran, or glycol dimethyl ether, or hydrocarbons, such as benzene, toluene, xylol, hexane, or cyclohexane, or petroleum fractions, or halocarbons, such
10 as dichloromethane, trichloromethane, tetrachloromethane, dichloroethylene, or trichloroethylene, or chlorobenzene, or ethyl acetate, or triethylamine, pyridine, dimethyl sulfoxide, dimethyl formamide, hexamethylphosphoric triamide, acetonitrile, acetone, or nitromethane. It is likewise possible to use a mixture of said solvents. Dichloromethane is preferred.

15 Suitable oxidants are, for example, 2,3-dichloro-5,6-dicyanobenzoquinone, pyridinium chlorochromate (PCC), osmium tetroxide, and manganese dioxide. For the above-mentioned step, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is preferred.

20 The oxidant is introduced in a quantity ranging from 1 mole to 10 moles, preferably from 2 moles to 5 moles, relative to 1 mole of the compound of the general formula (IV).

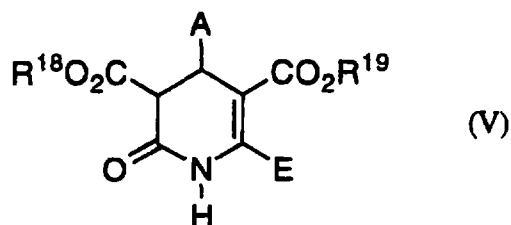
25 The oxidation generally takes place within a temperature range of -50°C to $+100^\circ\text{C}$, preferably from 0°C to room temperature.

The oxidation generally takes place at normal pressure. However, it is also possible to carry out the oxidation at increased or reduced pressure.

30 1,4-Dihydropyridine-3,5-dicarboxylic acid esters of the general formula (IV) are known and can be produced according to known methods.

35 The reaction is generally carried out at normal pressure. However, it is also possible to carry out the process at reduced pressure or high pressure (e.g., within a range of 0.5 to 5 bar).

- 0 Compounds of the general formula (II) in the case wherein L is alkoxy/cyclooxy (L') are known and can be produced by first oxidizing compounds of the general formula (V)



- 5 in which

A and E have the above-mentioned meanings

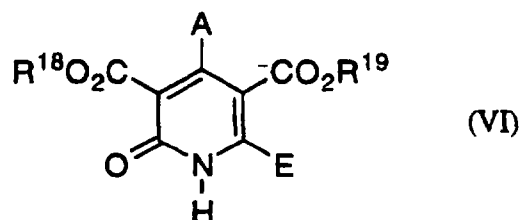
and

10

R¹⁸ and R¹⁹ have the meaning given above for R¹⁶ and R¹⁷ and are identical to or different from these,

with ceric(IV) ammonium nitrate into compounds of the general formula (VI)

15



in which

A, E, R¹⁸, and R¹⁹ have the above-mentioned meanings,

20

then, by reaction with alkylation agents of the general formula (VII)



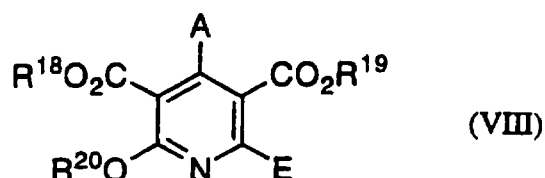
- 25 in which

R²⁰ stands for cycloalkyl with 3 to 8 carbon atoms, or stands for straight-chain or branched alkyl with up to 8 carbon atoms,

0 and

Y stands for halogen, preferably for bromine or iodine,

in inert solvents and in the presence of a base, converting them into compounds of
5 the general formula (VIII)



in which

10

A, E, R¹⁸, R¹⁹, and R²⁰ have the above-mentioned meanings,

and finally, as described above, carrying out a selective reduction with
diisobutylaluminum hydride of the alkoxycarbonyl group -CO₂R¹⁸ to the
15 hydroxymethylene function, followed by an oxidation to the corresponding
aldehyde, likewise as described above, preferably with PCC.

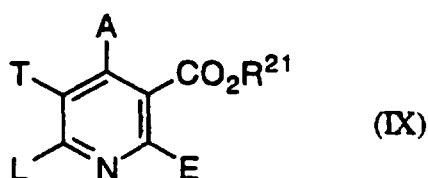
The individual reaction steps each take place in one of the above-mentioned
solvents and/or bases; preferably, the oxidation is carried out with ceric(IV)
20 ammonium nitrate in acetonitrile, the alkylation is carried out with dimethyl
formamide and sodium hydride, and the reduction is carried out in toluene within a
temperature range of -30°C to 100°C, at normal pressure, and, if applicable, under a
protective gas atmosphere.

25 Compounds of the general formulas (V) and (VII) are known in and of
themselves or can be produced according to the customary methods.

Compounds of the general formulas (VI) and (VIII) are known in part or are
novel and can therefore be produced according to the above-mentioned process.

30

Compounds of the general formula (III) are novel and are produced by
converting compounds of the general formula (IX)



0

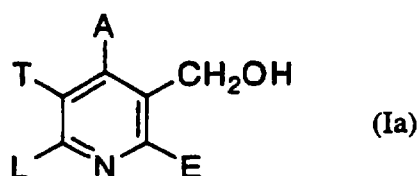
in which

A, E, L, and T have the above-mentioned meanings

5 and

R^{21} denotes a straight-chain or branched alkoxy carbonyl with up to 3 carbon atoms,

10 first by reduction of the alkoxy carbonyl function, into compounds of the general formula (Ia)



in which

15 A, E, L, and T have the above-mentioned meanings,

and in a second step, oxidizing the hydroxymethyl function into the aldehyde according to the above-mentioned conditions, preferably with pyridinium chlorochromate (PCC).

20

The individual reaction steps are generally carried out within a temperature range of -10°C to $+160^\circ\text{C}$, preferably 0°C to $+100^\circ\text{C}$, and at normal pressure.

25 Compounds of the general formula (IX) are produced analogously to the methods described above for the production of compounds of the general formula (II).

Compounds of the general formula (Ia) are also novel and can be produced as described above.

30

0 Compounds of the general formulas (IA) and (Ia) according to the invention have an unforeseeable pharmacological spectrum of action.

 Compounds of the general formulas (IA) and (Ia) according to the invention possess valuable pharmacological properties that are superior to those of the state
5 of the art; in particular, they are highly effective inhibitors of cholesterol ester transfer proteins (CETP) and stimulate reverse cholesterol transport. The active compounds according to the invention cause a reduction in LDL cholesterol levels in the blood, while at the same time increasing HDL cholesterol levels. They can therefore be used for the treatment of hyperlipoproteinemia or arteriosclerosis.

10 The invention additionally concerns the combination of compounds according to the invention with a glucosidase and/or amylase inhibitor for the treatment of familial hyperlipidemia, obesity (adiposis), and diabetes mellitus. Within the context of the invention, glucosidase and/or amylase inhibitors are, for
15 example, acarbose, adiposine, voglibose, miglitol, emiglitate, MDL-25637, camiglibose (MDL-73945), tendamistat, AI-3688, testatin, pradimicin-Q, and salbostatin.

 The combination of acarbose, miglitol, emiglitate, or voglibose and one of
20 the above-mentioned compounds of the general formula (IA) according to the invention is preferred.

 The pharmacological action of the substances according to the invention was determined in the following test:

25

CETP Inhibition Test

1. Obtaining CETP

30 CETP is obtained in partially purified form from human plasma by differential centrifugation and column chromatography and is used for testing. In so doing, human plasma is adjusted with NaBr to a density of 1.21 g per ml and is centrifuged for 18 h at 50,000 rpm at 4°C. The bottom fraction ($d > 1.21$ g/ml) is applied to a Sephadex® Phenyl-Sepharose 4B (Pharmacia) column, washed with
35 0.15 M NaCl/0.001 M TrisHCl, pH 7.4, and then eluted with dist. water. The CETP-active fractions were pooled, dialyzed against 50 mM Na acetate, pH 4.5, and applied to a CM-Sepharose® (Pharmacia) column. They were then eluted with a

0 linear gradient (0-1 M NaCl). The pooled CETP fractions were dialyzed against 10 mM TrisHCl, pH 7.4, and were then further purified by chromatography over a Mono Q[®] column (Pharmacia).

2. Obtaining Radioactively Tagged HDL

5

50 ml of fresh human EDTA plasma was adjusted with NaBr to a density of 1.12 and centrifuged at 4°C for 18 h at 50,000 rpm in the Ty 65 rotor. The upper phase was used to obtain cold LDL. The lower phase was dialyzed against 3x4 l of PDB buffer (10 mM Tris/HCl, pH 7.4, 0.15 mM NaCl, 1 mM EDTA, 0.02% NaN₃).

10 20 µl 3H cholesterol (Du Pont NET-725; 1 -µC/µl dissolved in ethanol) was subsequently added per 10 ml of dialysis residue volume and incubated for 72 h at 37°C under N₂.

The sediment was then adjusted with NaBr to a density of 1.21 and
15 centrifuged in the Ty 65 rotor for 18 h at 50,000 rpm at 20°C. The upper phase was obtained and the lipoprotein fractions were purified by gradient centrifugation. In so doing, the isolated, tagged lipoprotein fraction was adjusted with NaBr to a density of 1.26. Every 4 ml of this solution was covered in centrifuge tubes (SW 40 rotor) with 4 ml of a solution with a density of 1.21 and 4.5 ml of a solution with a
20 density of 1.063 (density solutions from PDB buffer and NaBr) and then centrifuged for 24 h at 38,000 rpm and 20°C in the SW 40 rotor. The intermediate layer between the densities 1.063 and 1.21 that contained the tagged HDL was dialyzed against 3x100 volumes of PDB buffer at 4°C.

The dialysis residue contained radioactively tagged ³H-CE-HDL, which was
25 adjusted to approx. 5x10⁶ cpm per ml and used for the test.

3. Conducting the Test

In order to test the CETP activity, the transfer of ³H cholesterol ester from
30 human HD lipoproteins to biotinylated LD lipoproteins was measured.

The reaction was ended by adding Streptavidin-SPA[®] beads (Amersham), and the transferred radioactivity was determined directly in the liquid scintillation counter.

In the test batch, 10 µl HDL-³H cholesterol ester (= 50,000 cpm) was
35 incubated for 18 h at 37°C with 10 µl biotin-LDL (Amersham) in 50 mM HEPES / 0.15 m NaCl / 0.1% bovine serum albumin / 0.05% NaN₃, pH 7.4, with 10 µl CETP (1 mg/ml) and 3 µl solution of the substance to be tested (dissolved in 10% DMSO /

0 1% BSA). Then 200 μ l of the SPA-Streptavidin bead solution (Amersham TRKQ 7005) was added, and the mixture was further incubated for 1 h under agitation and subsequently measured in the scintillation counter. Corresponding incubations with 10 μ l buffer, 10 μ l CETP at 4°C, and 10 μ l CETP at 37°C served as controls.

5 The transferred activity in the control batches with CETP at 37°C was assessed as 100% transfer. The substance concentration in which this transfer was reduced by half was indicated as an IC₅₀ value.

CETP inhibitory activity of the following compounds:

Example No.	IC ₅₀ (μ M)
7	0.6
24	1.0

10

Syrian golden hamsters from the company's own breeding were anesthetized after fasting for 24 h (0.80 mg/kg atropine, 0.80 mg/kg Ketavet® s.c., 30' later 50 mg/kg Nembutal i.p.). The jugular vein was then exposed and cannulated. The test substance was dissolved in a suitable solvent (as a rule, Adalat placebo solution: 60 g glycerin, 100 ml H₂O, ad 100 ml PEG-400) and administered to the animals via a PE catheter inserted into the jugular vein. The control animals received the same volume of solvent without any test substance. The vein was then ligated and the wound closed up. At different intervals — up to 24 hours after administration of the test substance — blood was drawn from the animals by puncture of the retroorbital venous plexus (approx. 250 μ l). Coagulation was completed by incubating at 4°C overnight, then the blood was centrifuged for 10 minutes at 6000 g. The cholesterol and triglyceride content in the serum obtained in this manner was determined using modified commercially available enzyme tests (cholesterol enzymatic 14366 Merck, triglyceride 14364 Merck). The serum was diluted in a suitable manner with physiological saline solution.

15
20
25

100- μ l serum dilution was mixed with 100 μ l test substance in 96-hole perforated plates and incubated 10 minutes at room temperature. The optical density was then determined with an automatic plate reader at a wavelength of 492 nm (SLT-Spectra). The triglyceride/cholesterol concentration contained in the samples was determined using a parallel-measured standard curve.

30

0 The determination of the HDL cholesterol content was carried out after precipitation of the lipoproteins containing Apo B by means of a reagent mixture (Sigma 352-4 HDL cholesterol reagent) according to the manufacturer's instructions.

5 In attempting to determine oral efficacy, the test substance, which was dissolved in DMSO and suspended in 0.5% methylcellulose, was administered orally to Syrian golden hamsters from the company's own breeding via a pharyngeal tube. The control animals received identical volumes of solvent without any test substance. Feed was then withheld from the animals and blood was drawn at
10 different intervals — up to 24 hours after administration of the substance — via puncture of the retroorbital venous plexus. It was further processed as described above.

15 The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions, and solutions, using inert, non-toxic, pharmaceutically suitable excipients or solvents. In this connection, the therapeutically active compound should be present in each case in a concentration of about 0.5% to 90% by weight, i.e., in amounts that are sufficient to achieve the
20 dosage range indicated.

 The formulations are prepared, for example, by extending the active compounds using solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, where, for example, in the case of the use of water as a diluent,
25 organic solvents can be used, if appropriate, as auxiliary solvents.

 The administration takes place in a customary manner, preferably orally or parenterally, in particular, perlingually or intravenously.

30 In the case of parenteral use, solutions of the active compound can be employed using suitable liquid excipients.

 In general, it has proved advantageous in intravenous administration to administer amounts of about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg
35 of body weight, to attain effective results, and in oral administration, the dosage is about 0.01 to 20 mg/kg, preferably 0.1 to 10 mg/kg of body weight.

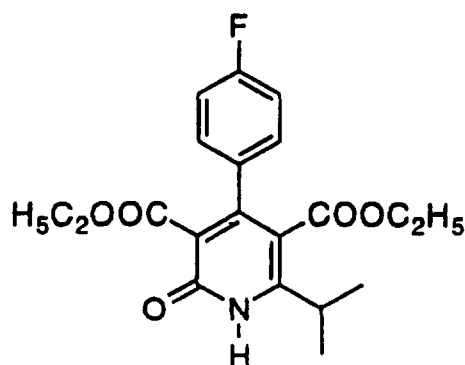
0 In spite of this, it may be necessary to deviate from the amounts mentioned, depending on the body weight or the type of administration route, individual behavior toward the medication, the type of formulation thereof, and the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the minimum amount previously mentioned, 5 whereas in other cases the upper limit mentioned must be exceeded. If larger amounts are administered, it may be advisable to divide these into several individual doses over the day.

10

Starting Compounds

Example I

15 Diethyl 4-(4-fluorophenyl)-6-isopropyl-(1H)-pyrid-2-one-3,5-dicarboxylate



20 149 g (0.395 mmol) of diethyl 3,4-dihydro-4-(4-fluorophenyl)-6-isopropyl-(1H)-pyrid-2-one-3,5-dicarboxylate is dissolved in 800 ml of acetonitrile, mixed with 475 g (0.867 mol) of ceric(IV) ammonium nitrate dissolved in 500 ml of H₂O, and subsequently stirred for 3 h. The aqueous phase is extracted two times with ethyl acetate. The combined ethyl acetate phases are washed with salt water, dried, and concentrated. The residue is mixed with isopropanol immediately thereafter, 25 whereby crystallization is started by cooling with ice. The product is drawn off by suction and dried in a high vacuum.

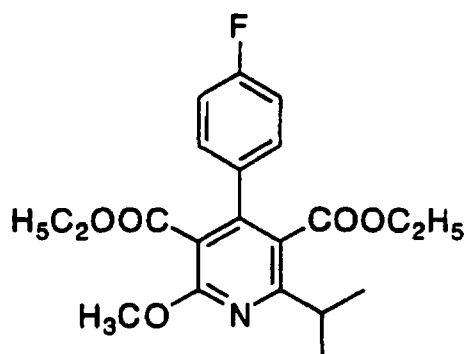
Yield: 58.8 g (39.6% of theory)

R_f = 0.5 (toluene / ethyl acetate 1:1)

30

0 Example II

Diethyl 4-(4-fluorophenyl)-6-isopropyl-2-methoxy-3,5-dicarboxylate



5

1.72 mg (42.9 mmol; 1.61 eq.) of sodium hydride (60% dispersion in mineral oil) is added to 10 g (26.6 mmol) of the compound from Example I dissolved in 40 g of DMF, and the mixture is suspended in 30 ml at -20°C. Afterwards, the suspension is heated to +30°C, 3.3 ml (53.2 mmol; 2 eq.) of methyl iodide is added, and it is heated for 2.5 hours to 80°C - 100°C. The reaction solution is mixed with 500 ml ethyl acetate and 300 ml H₂O, and the aqueous layer is separated off and extracted one time with ethyl acetate. The combined ethyl acetate phases are washed with water and saline solution, dried, and concentrated. The crude product is dissolved in 20 ml of toluene and chromatographed over 200 ml of silica gel 60 using toluene as the eluant.

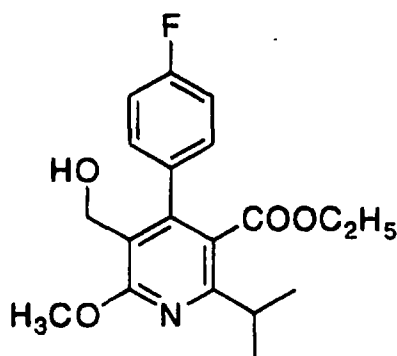
Yield: 10 g (96.4% of theory)

R_f = 0.28 (toluene)

Example III

20

Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methoxy-3-hydroxymethyl-pyridine-5-carboxylate



0

500 mg (1.284 mmol) of the compound from Example II in 40 g of toluene p.a. is mixed under argon at -78°C with 3.21 ml (3.852 mmol) of diisobutylaluminum hydride (DIBAL-H, 1.2 molar in toluene). The mixture is stirred 30 min at -78°C , and the batch is allowed to stand overnight at -30°C in the refrigerator. It is further cooled to -70°C , 20% potassium sodium tartrate solution is added, and the mixture is extracted with ethyl acetate. The organic layer is dried with Na_2SO_4 and concentrated.

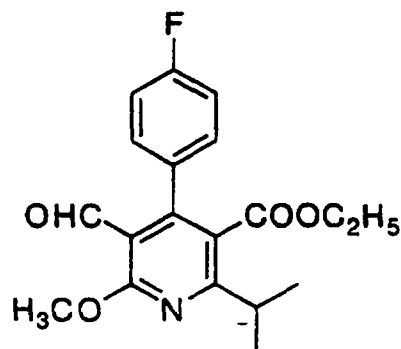
Yield: 287 mg (64.5% of theory)

$R_f = 0.41$ (toluene / ethyl acetate 9:1)

10

Example IV

Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methoxy-3-formyl-pyridine-5-carboxylate



15

21.3 g (0.0988 mol, 3.8 eq.) of pyridinium chlorochromate (PCC) is added to a solution of 9.07 g (0.026 mol) of the compound from Example III in 400 ml CH_2Cl_2 in the presence of neutral Al_2O_3 (10.07 g = 0.0988 mol), and the mixture is stirred for 1 h at room temperature. It is drawn off by suction over silica gel and subsequently washed with CH_2Cl_2 , then the filtrate is concentrated in a vacuum and chromatographed on silica gel 60 (500 ml) using toluene / ethyl acetate (8:2).

Yield: 8.88 g (98.4% of theory)

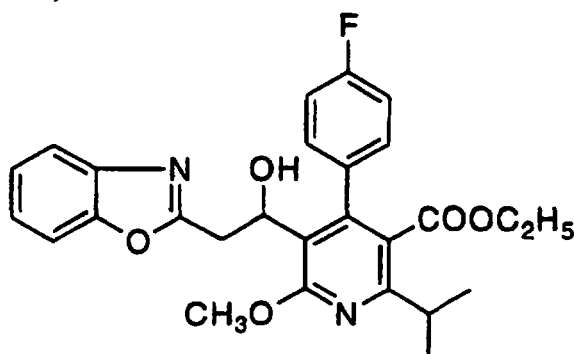
$R_f = 0.62$ (toluene / ethyl acetate 9:1)

25

30

0 Example V

Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methoxy-3-[2-(benzoxazol-2-yl)-1-hydroxy-ethyl]-pyridine-5-carboxylate



5

400 mg (3 mmol) of 2-methylbenzoxazole dissolved in 5 g THF p.a. is cooled under argon to -78°C . 1.83 ml (3 mmol) of n-butyllithium (1.6 molar in hexane) is added to this, and the mixture is stirred for 120 min at -78°C . 1.036 g (3 mmol) of the compound from Example IV is then added by drops at -78°C ; the mixture is stirred for 10 min at -78°C and overnight until it reaches room temperature. After adding 50 ml of water, it is extracted by shaking with 100 ml of ethyl acetate. The aqueous phase is separated off, washed two times with saline solution, dried over Na_2SO_4 , and concentrated. The residue is chromatographed on 60 ml of silica gel using toluene and toluene / ethyl acetate (8:2). The concentrated fractions are dried in a high vacuum.

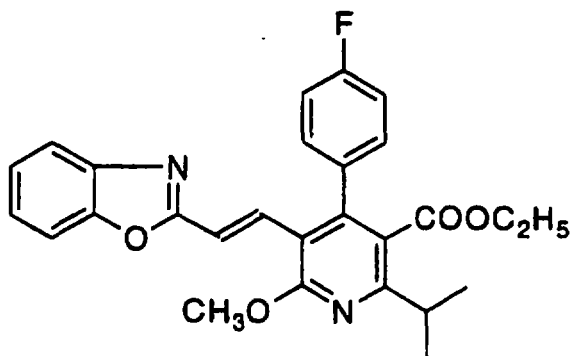
Yield: 450 mg (31.4% of theory)

$R_f = 0.22$ (toluene / ethyl acetate 9:1)

Example VI

20

Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methoxy-3-[2-(benzoxazol-2-yl)-ethenyl]-pyridine-5-carboxylate



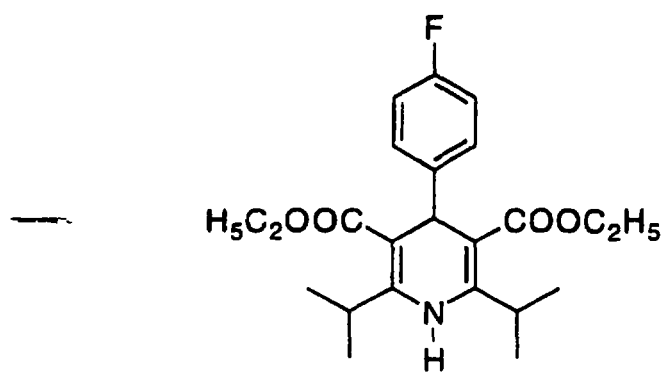
- 0 100 mg (0.209 mmol) of the compound from Example V is boiled in 10 g toluene p.a. under argon in the presence of 25 mg (0.131 mmol) of p-toluenesulfonic acid hydrate for 6 h under reflux, and afterwards the mixture is stirred at room temperature overnight. The reaction solution is then applied to a column filled with 40 ml of silica gel and consecutively eluted with toluene and
- 5 toluene / ethyl acetate (9.5:0.5). The desired fractions are concentrated and dried in a high vacuum.

Yield: 91 mg (94.6% of theory)

R_f = 0.59 (toluene / ethyl acetate 9:1)

10 Example VII

Diethyl 1,4-dihydro-2,6-diisopropyl-4-(4-fluorophenyl)pyridine-3,5-dicarboxylate



15

- 528 g (2 mol) of (E/Z)-4-carboxymethyl-5-(4-fluorophenyl)-2-methyl-pent-4-en-3-one and 350 g (2 mol) of 90% ethyl 3-amino-4-methyl-pent-2-enoate are stirred in 1800 ml ethanediol overnight at a bath temperature of 200°C. The mixture is cooled slowly and poured into a large glass beaker at approx. 80°C. After further
- 20 cooling to 0°C, the solution is drawn off by suction from the precipitated sediment, then the sediment is washed well with ice cold ethanol and dried in a desiccator. The ethanol solution is concentrated, and the residue together with the ethanediol mother liquor is extracted four times with 1.5 l ether each time. The combined ether phases are washed three times each with 500 ml of 10% hydrochloric acid and
- 25 once each with 500 ml of saturated sodium hydrogen carbonate solution and water, dried over magnesium sulfate, filtered, and allowed to stand overnight at room temperature. The solution is drawn off by suction from the precipitated sediment, subsequently washed with ice cold ethanol, and dried in a desiccator. The ethanol solution and the ether mother liquor are concentrated together in a vacuum to a

0 volume of approx. 2 l, allowed to stand overnight again, and drawn off by suction from the precipitated sediment.

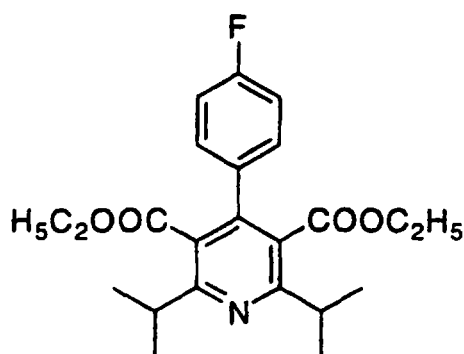
Total yield: 556.9 g (69.1% of theory)

$^1\text{H-NMR}$ (CDCl_3): $\delta = 1.1 - 1.3$ (m, 18H); 4.05 - 4.25 (m, 6H); 5.0 (s, 1H); 6.13 (s, 1H); 6.88 (m, 2OH); 7.2 (m, 2H) ppm.

5

Example VIII

Diethyl 2,6-diisopropyl-4-(4-fluorophenyl)-pyridine-3,5-dicarboxylate



10

171.7 g (0.757 mol) of 2,3-dichloro-5,6-dicyano-p-benzoquinone is added to a solution of 304.8 g (0.757 mol) of the compound from Example VII in 2 l of dichloromethane, and the mixture is stirred overnight at room temperature. The mixture is drawn off by suction over diatomaceous earth and subsequently washed well with dichloromethane. After concentration of the dichloromethane phase to a volume of approx. 800 ml, it is chromatographed on a column (2 kg of silica gel 70-230 mesh) with dichloromethane.

15

Yield: 222 g (73.4% of theory)

20

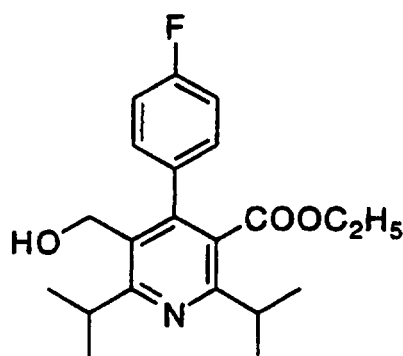
$^1\text{H-NMR}$ (CDCl_3): $\delta = 0.98$ (t, 6H); 1.41 (d, 12H); 3.1 (m, 2H); 4.11 (q, 4H); 7.04 (m, 2H); 7.25 (m, 2H) ppm.

25

30

0 Example IX

Ethyl 2,6-diisopropyl-4-(4-fluorophenyl)-3-hydroxymethylpyridine-5-carboxylate



5

257 ml (0.9 mol) of a 3.5 molar solution of sodium-bis-(2-methoxyethoxy)dihydroaluminate is steadily added by drops under nitrogen to a solution of 120 g (0.3 mol) of the compound from Example VIII in 800 ml of dried tetrahydrofuran at room temperature, and the mixture is subsequently stirred for 5 h. After cooling to 0°C, 500 ml of water is carefully added by drops, the phases are separated, and the aqueous phase is extracted three times with 250 ml ethyl acetate each time. The combined organic phases are washed with saturated sodium chloride solution, dried over magnesium sulfate, and evaporated in a vacuum. The residue is mixed with petroleum ether, drawn off by suction, and dried in a desiccator.

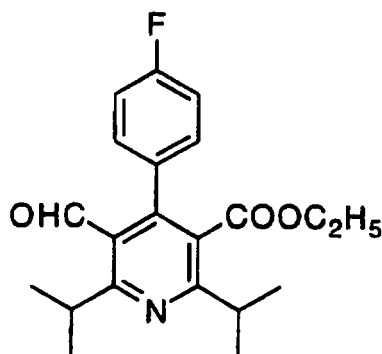
15

Yield: 69.1 g (64.2% of theory)

¹H-NMR (CDCl₃): δ = 0.95 (t, 3H); 1.31 (m, 12H); 3.05 (m, 1H); 3.48 (m, 1H); 3.95 (q, 2H); 4.93 (d, 2H); 7.05 - 7.31 (m, 4H) ppm.

20 Example X

Ethyl 2,6-diisopropyl-4-(4-fluorophenyl)-3-formyl-pyridine-5-carboxylate



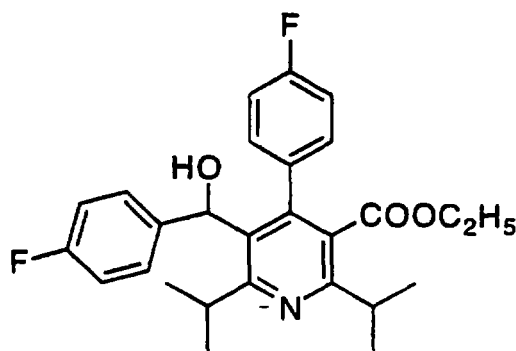
0 14.18 g (0.139 mol) of neutral Al_2O_3 and 29.96 g (0.13 mol) of pyridinium chlorochromate (PCC) are added to a solution of 25.0 g (0.0695 mol) of the compound from Example IX in 500 ml CH_2Cl_2 and the mixture is stirred for 1 h at room temperature. It is drawn off by suction over silica gel and subsequently washed with CH_2Cl_2 , and the filtrate is concentrated in a vacuum, whereby the
5 product precipitates out.

Yield: 20 g (80.48% of theory)

$^1\text{H-NMR}$ (DMSO-d_6): δ = 0.92 (t, 3H); 1.39 (dd, 6H); 3.02 - 3.13 (m, 1H); 3.75 - 3.86 (m, 1H); 3.95 - 4.05 (q, 2H); 7.32 (m, 4H); 9.8 (s, 1H) ppm.

10 Example XI

Ethyl 2,6-diisopropyl-4-(4-fluorophenyl)-3-[(4-fluorophenyl)hydroxymethyl]-pyridine-5-carboxylate



15

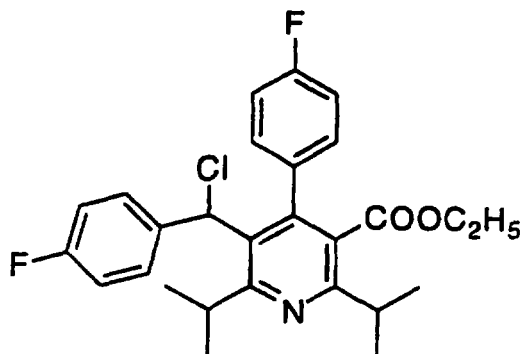
10.0 g (27.98 mmol) of aldehyde from Example X is cooled to -70°C in 100 g THF p.a. under argon, 33.6 ml (33.58 mmol, 1.2 eq.) of p-fluorophenyl magnesium bromide solution is added by drops at -70°C , and the mixture is then stirred for
20 another 2 h at -70°C . The reaction solution is mixed with 200 ml of conc. NH_4Cl solution, the cooling bath is removed, and the solution is adjusted with 1 molar HCl , $\text{pH} = 6$. After extraction with 400 ml of CH_2Cl_2 and drying over Na_2SO_4 , the organic phase is concentrated in a vacuum and the rigid foam is crystallized using n-heptane.

25 Yield: 8.97 g (70.7% of theory)
 R_f = 0.18 (toluene)

30

0 Example XII

Ethyl 2,6-diisopropyl-4-(4-fluorophenyl)-3-[(4-fluorophenyl)-chloromethyl]-pyridine-5-carboxylate



5

907 mg (2 mmol) of the compound from Example XI is dissolved in 20 g of CH_2Cl_2 p.a. and cooled under argon at -40°C , and 0.44 ml (6 mmol) SOCl_2 are added. The solution is stirred for 1.5 h from -40°C to -5°C and afterwards agitated in 50 ml of ethyl acetate / 40 ml of NaHCO_3 solution. The organic phase is separated off, dried over Na_2SO_4 , concentrated in a vacuum, and chromatographed on diatomaceous earth using toluene.

Yield: 899 mg (95% of theory)

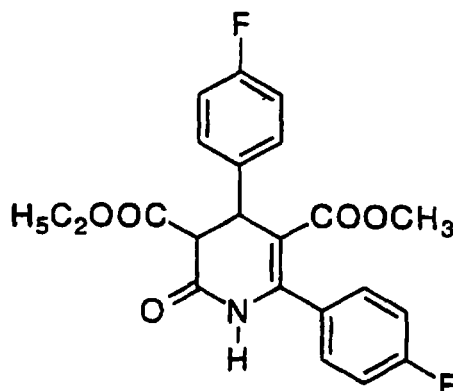
$R_f = 0.79$ (toluene)

15

Example XIII

3-Ethyl 5-methyl 3,4-dihydro-4-(4-fluorophenyl)-6-p-fluorophenyl-(1H)-pyrid-2-one-3,5-dicarboxylate

20



0

30.69 g (115.3 mmol) of ethyl 1-carboethoxy-2-(4-fluorophenyl)-propenate, 22.5 g (115.3 mmol) of methyl 3-amino-3-(4-fluorophenyl)-acrylate, 115 mg of sodium methylate, and 0.6 ml of ethanol are stirred for 48 h at a bath temperature of 140°C. The reaction mixture is absorbed in ethyl acetate, washed three times with water, dried over Na₂SO₄, and concentrated in a vacuum.

5

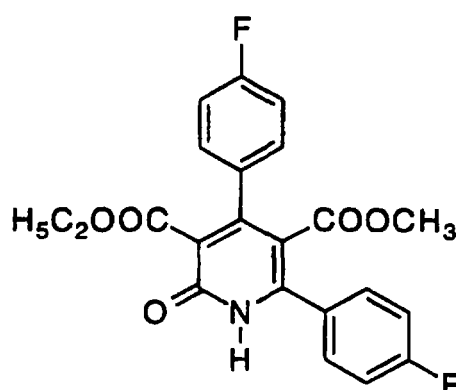
Yield: 43.2 g (90.2% of theory)

R_f = 0.26 (toluene / ethyl acetate 9:1)

Example XIV

10

3-Ethyl 5-methyl 4-(4-fluorophenyl)-6-p-fluorophenyl-(1H)-pyrid-2-one-3,5-dicarboxylate



15

Analogously to Example I, 1.00 g (0.2407 mol) of the compound from Example XIII is stirred with 277 g (0.506 mol) of ceric(IV) ammonium nitrate in 600 ml of acetonitrile and 600 ml of water for 3 h at room temperature. After extraction with ethyl acetate, the residue is crystallized from isopropanol.

Yield: 28.59 g (28.7% of theory)

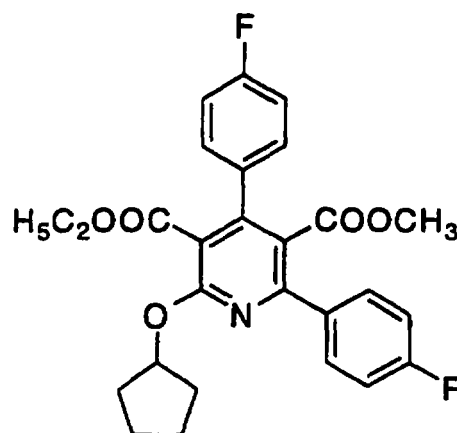
20

R_f = 0.16 (toluene / ethyl acetate 8:2)

25

0 Example XV

3-Ethyl 5-methyl 4-(4-fluorophenyl)-6-(4-fluorophenyl)-2-cyclopentoxy-3,5-dicarboxylate



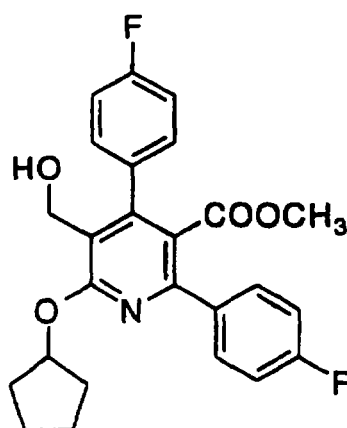
5

Following the instructions in Example II, 5.0 g (0.0121 mol) of the mixture from Example XIV in 20 ml of DMF is reacted in the presence of 0.783 g (0.0196 mol) of 60% NaH with 3.61 g (0.0242 mol) of cyclopentyl bromide. After chromatography on silica gel using toluene, 5.14 g (88.3% of theory) is obtained.

10 $R_f = 0.34$ (toluene)

Example XVI

15 Methyl 4-(4-fluorophenyl)-6-(4-fluorophenyl)-2-cyclopentoxy-3-hydroxymethyl-pyridine-5-carboxylate



20 Analogously to Example III, 3.719 g (7.72 mmol) of the compound from Example XV in 150 g of toluene is stirred with 11.58 ml (11.58 mmol) of DIBAL-H

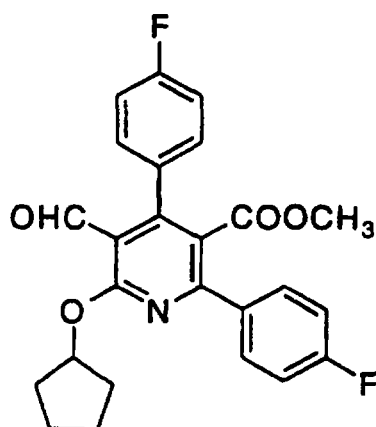
- 0 (1.0 molar) for 2.5 h at -78°C. The compound is chromatographed on silica gel first with toluene and then with toluene / ethyl acetate (9:1).

Yield: 1.648 g (48.5% of theory)

R_f = 0.45 (toluene / ethyl acetate 9:1)

5 Example XVII

Methyl 4-(4-fluorophenyl)-6-(4-fluorophenyl)-2-cyclopentoxo-3-formyl-pyridine-5-carboxylate



10

Following the instructions in Example IV, 1.636 g (3.72 mmol) of the compound from Example XVI in 150 ml of CH₂Cl₂ is stirred with 0.759 g (7.44 mmol) of Al₂O₃ (neutral) and 1.604 g (7.44 mmol) of PCC for 1.5 h. The crude product is purified by chromatography on silica gel using toluene.

15

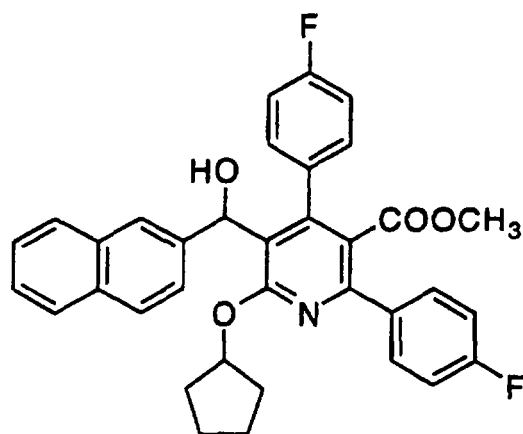
Yield: 1.484 g (91.2% of theory)

R_f = 0.59 (toluene / ethyl acetate 9:1)

Example XVIII

20

Methyl 4-(4-fluorophenyl)-6-(4-fluorophenyl)-2-cyclopentoxo-3-[(naphthyl-2)-hydroxy-methyl]-pyridine-5-carboxylate



0

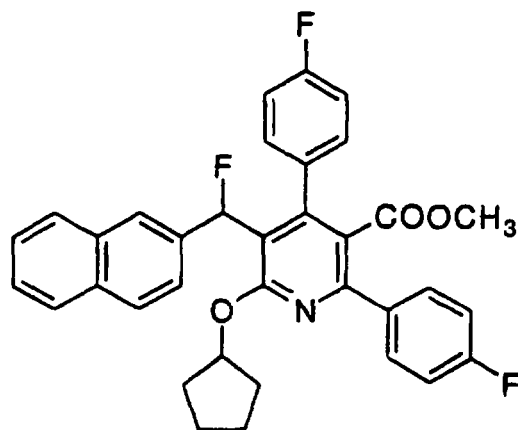
53.4 mg (2.2 mmol) of magnesium shavings is heated to reflux in 10 ml of THF p.a. under argon. 313 mg (1.51 mmol) of 2-bromonaphthalene dissolved in 15 ml of THF is added to this and the solution is boiled 75 min to reflux in the presence of iodine crystals (= Grignard reagent). 220 mg (0.503 mmol) of the compound from Example XVII is dissolved in 5 ml of THF p.a. and cooled under argon to -70°C, and the Grignard reagent is sprayed in. The batch is subsequently stirred for one hour without cooling. The reaction solution is distributed in ethyl acetate / ammonium chloride solution, and the organic phase is separated off, washed with NaCl solution, dried, and concentrated. Chromatography is then carried out on silica gel using toluene.

Yield: 261 mg (91.9% of theory)

R_f = 0.57 (toluene / ethyl acetate 9:1)

15 Example XIX

Methyl 4-(4-fluorophenyl)-6-(4-fluorophenyl)-2-cyclopentoxy-3-[(naphthyl-2)-fluoromethyl]-pyridine-5-carboxylate



20

0

0.08 mmol (0.602 mmol) of diethylamino sulfur trifluoride (DAST) is added to a solution of 227 mg (0.401 mmol) of the compound from Example XVIII in 10 g of CH_2Cl_2 at -40°C under argon, the cooling bath is removed, and the solution is stirred for 20 min. The reaction solution is subsequently distributed in ethyl acetate / NaHCO_3 solution, and the organic layer is dried with Na_2SO_4 and concentrated in a vacuum. The crude product is chromatographed on silica gel using toluene.

5

Yield: 224 mg (98.6% of theory)

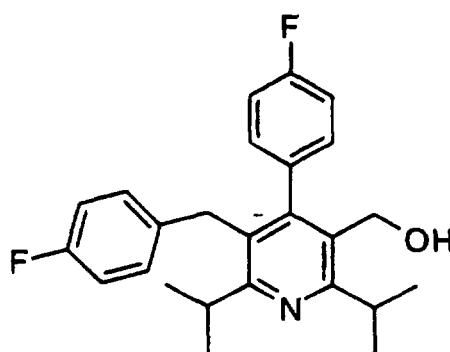
$R_f = 0.67$ (toluene)

10

Production Examples

Example 1

15 2,6-Diisopropyl-3-p-fluorobenzyl-4-p-fluorophenyl-5-hydroxymethyl-pyridine



5.7 g (150 mmol) of LiAlH_4 are suspended in 200 ml of THF, heated to 80°C , and mixed by drops with a solution of 23.7 g of the compound from Example XII in 150 ml of THF. After being stirred for 5 h, the mixture is cooled, carefully neutralized with 20% Na-K-tartrate solution, and extracted three times with ethyl acetate, and the organic phase is dried, concentrated, and chromatographed over silica gel 60 (toluene).

20

25

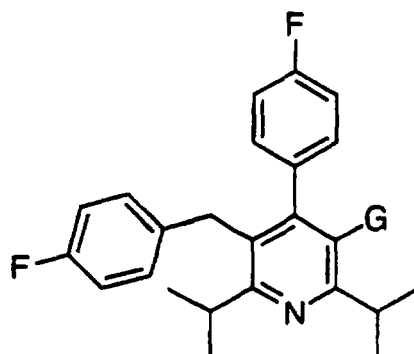
Yield: 13.6 g (69% of theory)

$R_f = 0.59$ (toluene / ethyl acetate = 9/1)

30

0 The compounds listed in Table 1(A) are produced in analogy to the instructions in Example I:

Table 1(A):



5

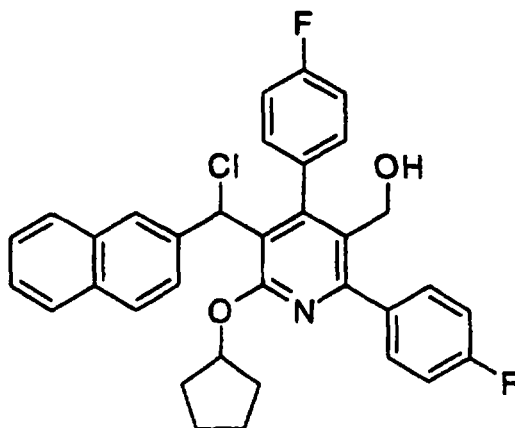
Ex. No.	G	R _f	Solvent
2		0.60	toluene / ethyl acetate 9:1
3		0.74	toluene / ethyl acetate 9:1
4		0.75	toluene / ethyl acetate 9:1

10

15

0 Example 5

4-(4-fluorophenyl)-6-(4-fluorophenyl)-2-cyclopentoxymethyl-3-[(naphthyl-2)-fluoromethyl]-5-hydroxymethyl-pyridine



5

Analogously to the instructions of Example 1, 182 mg (0.321 mmol) of the compound from Example XIX in 10 ml of THF p.a. is boiled with 18.3 mg (0.481 mmol) of LiAlH₄ for 1 h under reflux. The compound is purified by chromatography on silica gel first with toluene and then with toluene / ethyl acetate (9:1).

Yield: 86 mg (49.7% of theory)

R_f = 0.47

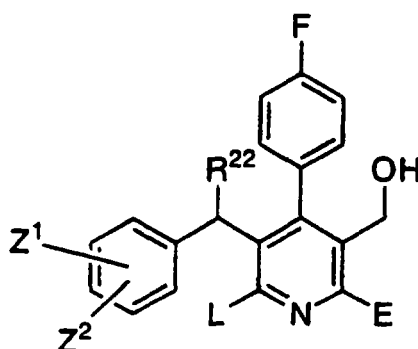
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20

25

0 The compounds listed in Table 2(B) are produced in analogy to the instructions of Example 5:

Table 2(B):



5

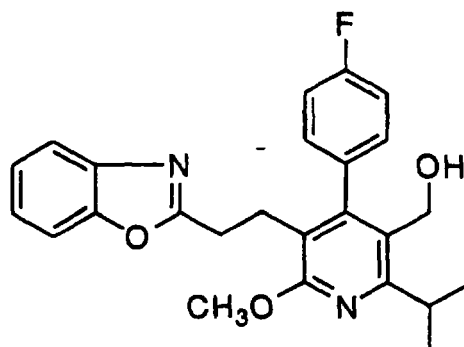
Ex. No.	E	R ²²	Z ¹ /Z ²	L	R _f (solvent)
6	cyclo-C ₆ H ₁₁	H	p-F / H	CH(CH ₃) ₂	0.59 toluene / ethyl acetate 9:1
7	CH(CH ₃) ₂	NH ₂	p-F / H	CH(CH ₃) ₂	0.60 toluene / ethyl acetate 1:1
8	CH(CH ₃) ₂	SH	p-F / H	CH(CH ₃) ₂	0.31 toluene / ethyl acetate 9:1
9	CH(CH ₃) ₂	Cl	p-CF ₃ / H	CH(CH ₃) ₂	0.54 toluene / ethyl acetate 9:1
10	CH(CH ₃) ₂	H	3,4-F ₂	CH(CH ₃) ₂	0.26 toluene
11	4-F-C ₆ H ₄	F	p-CF ₃ / H	-OCH ₃	0.48 toluene / ethyl acetate 9:1

0 Table 2(B), contd.

Ex. No.	E	R ²²	Z ¹ /Z ²	L	R _f (solvent)
12	CH(CH ₃) ₂	F	p-F / H	CH(CH ₃) ₂	0.21 toluene
13	4-F-C ₆ H ₄	F	p-CF ₃ / H	(cyclo-C ₇ H ₁₃)O	0.28 petroleum ether / ethyl acetate 5:1

Example 14

- 5 2-Isopropyl-6-methoxy-4-(4-fluorophenyl)-5-[2-(benzoxazol-2-yl)ethyl]-3-hydroxymethylpyridine



- 10 69 mg (0.15 mmol) of the compound from Example VI is dissolved in 5 g of toluene and mixed with 0.6 ml DIBAL-H (1.0 molar in toluene). The mixture is then stirred without a cooling bath for 4 h to +15°C. 30 ml of ethyl acetate and 15 ml of a 20% potassium sodium tartrate solution is added, and the solution is stirred for 10 min. The aqueous layer is separated off, and the organic phase is dried,
- 15 concentrated, and chromatographed. After chromatography on 20 ml of silica gel using toluene / ethyl acetate (9:1), 19 mg (30.2% of theory) is obtained.

R_f = 0.28 (toluene / ethyl acetate 9:1)

0 **Detailed description with reference to compounds of general formula (IB)**

The compounds according to the invention can also occur in the form of the salts thereof. In general, salts with organic or inorganic bases or acids are mentioned here.

5

Within the context of the present invention, physiologically safe salts are preferred. Physiologically safe salts from the compounds according to the invention can be salts of substances according to the invention with mineral acids, carboxylic acids, or sulfonic acids. Salts with, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalene disulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid, or benzoic acid are particularly preferred.

15 Physiologically safe salts can also be metallic or ammonium salts of the compounds according to the invention that possess a free carboxyl group. For example, sodium salts, potassium salts, magnesium salts, or calcium salts, as well as ammonium salts, that are derived from ammonia, or organic amines such as ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine, ethylenediamine, or 2-phenylethylamine are particularly preferred.

25 The compounds according to the invention can exist in stereoisomeric forms, which either behave like an image and mirror image (enantiomers) or do not behave like an image and mirror image (diastereomers). The invention concerns both enantiomers or diastereomers or the mixtures thereof. These mixtures of enantiomers and diastereomers can be separated in the known manner into stereoisomerically homogeneous components.

30 Within the context of the invention, the heterocyclic compound, which is optionally benzo-condensed, stands in general for a saturated or unsaturated, 5- to 7-member, and preferably 5- to 6-member, heterocyclic compound that can contain up to 3 heteroatoms from the series S, N, and/or O. Tetrazolyl, isoquinolyl, quinolyl, benzo[b]thiophene, benzo[b]furanyl, pyridyl, pyrimidinyl, pyrazinyl, thienyl, -furyl, pyriny, benzothiazolyl, phenoxathinyl, benzoxazolyl, tetrahydropyrimidyl, pyrazolopyrimidyl, pyrrolyl, thiazolyl, oxazolyl, and imidazolyl are cited as examples. Quinolyl, furyl, pyridyl, tetrahydropyrimidyl,

0 indolyl, benzothiazolyl, benzoxazolyl, pyrynyl, and pyrazolopyrimidyl are preferred.

This also includes 5- to 7-member saturated heterocyclic compounds bound via N, which can also contain up to 2 oxygen, sulfur, and/or nitrogen atoms as heteroatoms, such as piperidyl, morpholinyl, or piperazine or pyrrolidinyl. Piperidyl and pyrrolidinyl are particularly preferred.

Compounds of general formula (IB) are preferred, in which

10

A stands for naphthyl or phenyl, which are optionally substituted up to 3 times in an identical manner or differently by fluorine, chlorine, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or alkoxy with up to 6 carbon atoms each, or by a group of the formula -NR²R³ and/or by a group of the formula -W-R⁴,

15

wherein

R² and R³ are identical or different and

20

denote hydrogen, phenyl, or straight-chain or branched alkyl with up to 4 carbon atoms,

W denotes an oxygen or sulfur atom,

25

R⁴ denotes phenyl or benzyl, which are optionally substituted up to 3 times in an identical manner or differently by fluorine, chlorine, trifluoromethyl, trifluoromethoxy, hydroxy, or by straight-chain or branched alkyl or alkoxy with up to 5 carbon atoms each,

30

D and E are identical or different and

stand for a straight-chain or branched alkyl chain with up to 6 carbon atoms,

or

35

E stands for a bond,

V stands for an oxygen or sulfur atom or for a group of the formula -NR⁵,

0

wherein

R⁵ denotes hydrogen or straight-chain or branched alkyl with up to 4 carbon atoms or phenyl,

5

R¹ stands for cyclopropyl, cyclopentyl, or cyclohexyl, or tetrahydropyrimidyl stands for phenyl, naphthyl, pyridyl, tetrazolyl, pyrimidinyl, pyrazinyl, pyrrolidinyl, tetrahydropyrimidinyl, indolyl, morpholinyl, imidazolyl, benzothiazolyl, phenoxathiin-2-yl, benzoxazolyl, furyl, quinolyl, pyrazolopyrimidyl, or purine-yl,

10

with the rings, also via the N function in the case of nitrogen-containing rings, being optionally substituted up to 3 times in an identical manner or differently by fluorine, chlorine, bromine, trifluoromethyl, hydroxy, cyano, carboxyl, trifluoromethoxy, straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy, or alkoxycarbonyl with up to 4 carbon atoms each, triazolyl, tetrazolyl, benzoxathiazolyl, or phenyl, and/or by a group of the formula -OR⁶, -SR⁷, or -SO₂R⁸,

15

wherein

20

R⁶, R⁷, and R⁸ are identical or different and

denote phenyl, which in turn is substituted up to 2 times in an identical manner or differently by phenyl, fluorine, chlorine, or by straight-chain or branched alkyl with up to 4 carbon atoms,

25

L and T are identical or different and

stand for trifluoromethyl, pyrrolidinyl, or for straight-chain or branched alkyl with up to 7 carbon atoms, which is optionally substituted by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, naphthyl, or phenyl, which in turn can be substituted up to 2 times in an identical manner or differently by fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or alkoxy with up to 6 carbon atoms each,

30

35 or

0 L and/or T stand for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or
 cycloheptyl, or
 for naphthyl, phenyl, pyridyl, or furyl, which optionally can be substituted
 up to 3 times in an identical manner or differently by fluorine, chlorine,
 5 bromine, nitro, trifluoromethyl, trifluoromethoxy, or by straight-chain or
 branched alkyl, acyl, or alkoxy with up to 6 carbon atoms each,

and the salts thereof.

10 Compounds of general formula (IB) are particularly preferred,

in which

15 A stands for phenyl, which is optionally substituted up to 2 times in an identical
 manner or differently by fluorine, chlorine, hydroxy, trifluoromethyl,
 trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or alkoxy
 with up to 4 carbon atoms each or by benzyloxy, which in turn can be
 substituted by fluorine or chlorine.

20 D and E are identical or different and
 stand for a straight-chain or branched alkyl chain with up to 3 carbon atoms,

or

25 E stands for a bond,

V stands for an oxygen or sulfur atom or for a group of the formula -NR⁵,

wherein

30 R⁵ denotes hydrogen or straight-chain or branched alkyl with up to 3
 carbon atoms,

35 R¹ stands for cyclopropyl, cyclopentyl, or cyclohexyl, or tetrahydropyridinyl
 stands for phenyl, naphthyl, pyridyl, tetrazolyl, pyrimidyl, pyrazinyl,
 tetrahydropyrimidyl, phenoxathiin-2-yl, indolyl, imidazolyl, pyrrolidinyl,

0 morpholiny, benzothiazoly, benzoxazoly, furyl, quinoly,
pyrazolopyrimidyl, or purine-yl,
with the rings, also via the N-function in the case of nitrogen-containing
rings, optionally being substituted up to 3 times in an identical manner or
differently by fluorine, chlorine, trifluoromethyl, hydroxy, cyano, carboxyl,
5 trifluoromethoxy, straight-chain or branched alkyl, alkylthio, alkylalkoxy,
alkoxy, or alkoxycarbonyl with up to 3 carbon atoms each, triazolyl,
tetrazolyl, benzoxathiazolyl, or phenyl,
and/or substituted by a group of the formula -OR⁶, -SR⁷, or -SO₂R⁸,

10 wherein

R⁶, R⁷, and R⁸ are identical or different and
denote phenyl, which in turn is substituted up to 2 times in an
identical manner or differently by phenyl, fluorine, chlorine, or is
15 substituted by straight-chain or branched alkyl with up to 3 carbon
atoms,

L and T are identical or different and
stand for trifluoromethyl, pyrrolidinyl, or for straight-chain or branched
20 alkyl with up to 6 carbon atoms, which are optionally substituted by
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or phenyl,
which in turn may be substituted up to 2 times in an identical manner or
differently by fluorine, chlorine, trifluoromethyl, trifluoromethoxy, or by
straight-chain or branched alkyl or alkoxy with up to 4 carbon atoms each,

25

or

L and/or T stand for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or
cycloheptyl, or stand for naphthyl, phenyl, or furyl, which are optionally
30 substituted up to 2 times in an identical manner or differently by fluorine,
chlorine, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched
alkyl or alkoxy with up to 3 carbon atoms each,

and the salts thereof.

35

WO 98/04528

PCT/US97/13248

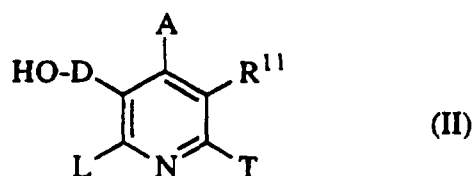
0 The compounds according to the invention of general formula (IB) are particularly preferred, in which

A stands for phenyl, which is optionally substituted up to 2 times in an identical
 5 manner or differently by fluorine, chlorine, trifluoromethyl, methoxy, methyl, or by fluorine- or chlorine-substituted benzyloxy.

Moreover, a process for the production of compounds according to the invention of general formula (IB) has been discovered, characterized in that

10

[A] in the case of $V = O$
 compounds of general formula (II)



15

in which

A, D, L, and T have the indicated meaning,

20 and

R^{11} stands for straight-chain or branched alkoxy carbonyl with up to 4 carbon atoms or for the group of the formula $-CH_2-O-Si(CH_3)_2C(CH_3)_3$,

25 are reacted with compounds of general formula (III)



in which

30

R^1 and E have the indicated meaning

and

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0 Z stands for halogen, preferably chlorine or bromine,

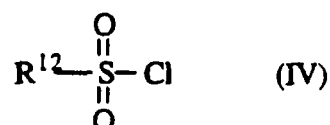
in inert solvents, optionally in the presence of bases and/or auxiliary agents, and reductive separation is then carried out, depending on the meaning of the group R¹¹,

5

or

[B] compounds of general formula (II) are first converted by reactions with compounds of general formula (IV)

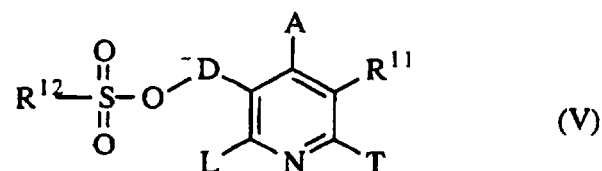
10



in which

15 R¹² stands for straight-chain alkyl with up to 4 carbon atoms,

into compounds of general formula (V)



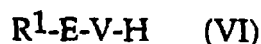
20

in which

A, D, L, T, R¹¹, and R¹² have the indicated meaning,

and these are then reacted with compounds of general formula (VI)

25



in which

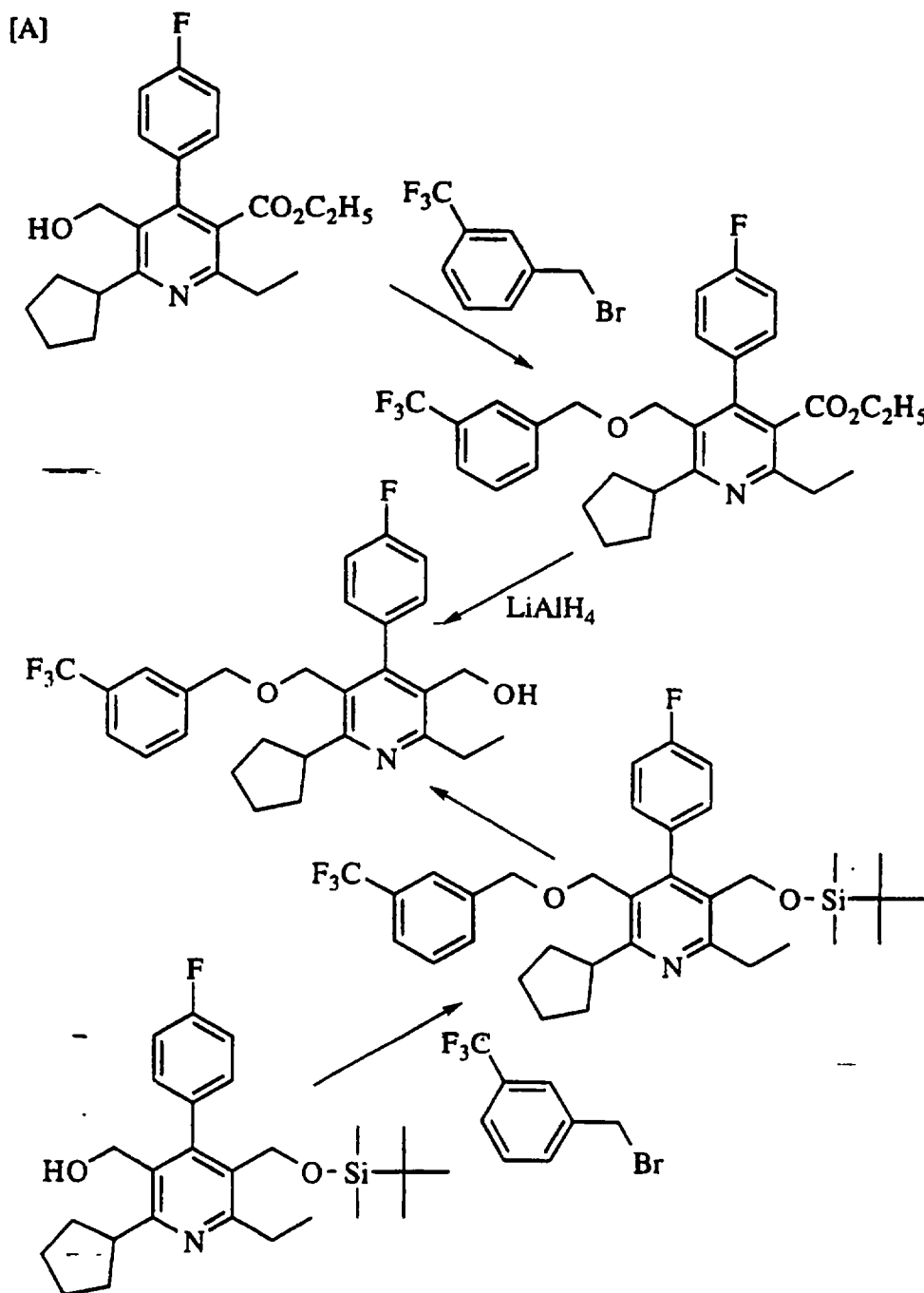
30 R¹, E, and V have the indicated meaning,

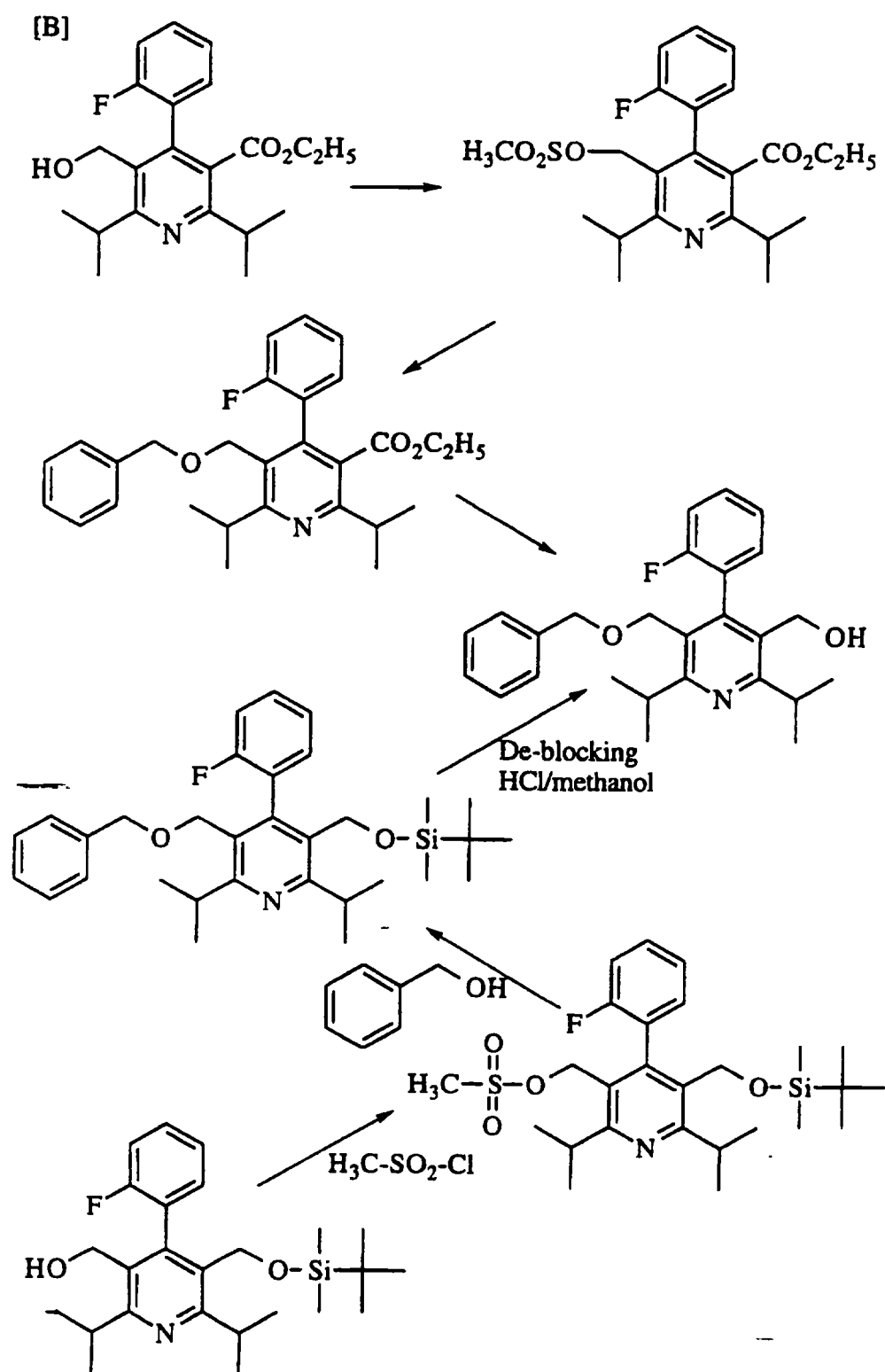
and reductive separation is carried out,

0

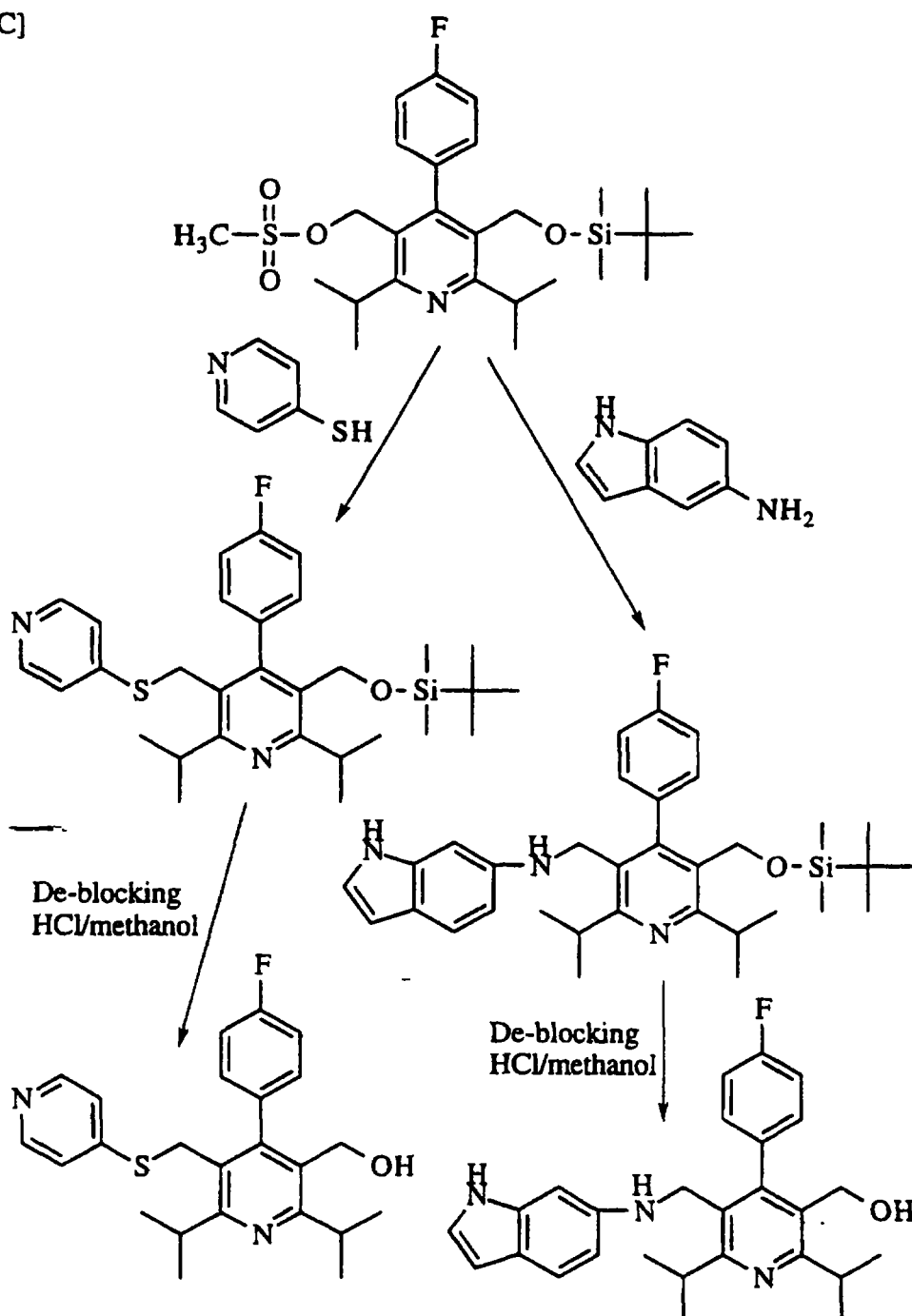
and optionally, the groups listed under substituents A, L, T, and R¹ are introduced or varied according to customary methods.

5 The processes according to the invention can be explained, for example, by means of the following reaction diagrams:





[C]



0

Suitable solvents for this process are inert organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether or tetrahydrofuran, halocarbons such as dichloromethane, trichloromethane, 5 tetrachloromethane, 1,2-dichloroethane, trichloroethane, tetrachloroethane, 1,2-dichloroethane, or trichloroethylene, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane, or petroleum fractions, nitromethane, dimethylformamide, acetone, acetonitrile, or hexamethylphosphoric triamide. It is

- 0 also possible to use mixtures of the solvents. Dichloromethane, tetrahydrofuran, toluene, or dimethylformamide are particularly preferred.

In general, as auxiliary agents for the process according to the invention, inorganic or organic bases may be used. These preferably include alkali hydroxides
5 such as sodium hydroxide or potassium hydroxide, alkaline earth hydroxides such as barium hydroxide, alkali carbonates such as sodium carbonate or potassium carbonate, alkaline earth carbonates such as calcium carbonate, or alkali or alkaline earth alcoholates such as sodium or potassium ethanolate, sodium or potassium methanolate, or potassium tert-butylate, or organic amines (trialkyl(C₁-C₆)amines)
10 such as triethylamine, or heterocyclic compounds such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, diaminopyridine, methylpiperidine, or morpholine. It is also possible to use alkali metals such as sodium and hydrides thereof such as sodium hydride as bases. Sodium and potassium carbonate and triethylamine are preferred.

15 As bases, the usual strongly basic compounds can be used for the individual steps. These preferably include lithium organic compounds such as n-butyl lithium, sec-butyl lithium, tert-butyl lithium, or phenyl lithium, or amides such as lithium diisopropylamide, sodium amide or potassium amide, or lithiumhexamethylsilyl
20 amide, or alkali hydrides such as sodium hydride or potassium hydride. N-butyl lithium or sodium hydride should preferably be used.

The bases are used in a mixture of 1 mole to 5 moles, and preferably 1 mole to 3 moles, relative to 1 mole of the compound of general formula (II).

25 In general, the reaction is carried out in a temperature range of 0°C to 150°C, and preferably from +20°C to +110°C.

The reaction can be carried out at normal, increased, or reduced pressure
30 (for example, 0.5 to 5 bar). In general, the reaction is carried out at normal pressure.

As derivatizations, the following types of reactions are cited as examples: oxidations, reductive separation, reductions, hydrogenations, halogenation,
35 Wittig/Grignard reactions, and amidation/sulfoamidation.

0 Suitable solvents are ethers such as diethyl ether, dioxane, tetrahydrofuran,
or glycol dimethyl ether, or hydrocarbons such as benzene, toluene, xylene,
hexane, or cyclohexane, or petroleum fractions, or halocarbons such as
dichloromethane, trichloromethane, tetrachloromethane, dichloroethylene, or
5 trichloroethylene, or chlorobenzene, or ethyl acetate, or triethylamine, pyridine,
dimethyl sulfoxide, dimethyl formamide, hexamethylphosphoric triamide,
acetonitrile, acetone, or nitromethane. It is also possible to use mixtures of said
solvents. Dichloromethane is preferred.

10 Suitable organometallic reagents are Grignard systems such as
Mg/bromobenzotrifluoride and p-trifluoromethylphenyl lithium. The
Mg/bromobenzotrifluoride system is preferred.

15 The reductions and derivatizations are carried out according to the
above-mentioned methods.

20 In general, the reductions are carried out in ethers such as dioxane,
tetrahydrofuran, or diethyl ether, or in hydrocarbons such as benzene, hexane, or
toluene. Toluene and tetrahydrofuran are preferred.

25 Suitable reductants are complex metal hydrides such as lithium aluminum
hydride, sodium cyanoborohydride, sodium aluminum hydride, diisobutyl
aluminum hydride, dimethoxymethyl aluminate sodium salt, or
sodium-bis(2-methoxyethoxy) dihydroaluminate (Red-Al). Diisobutyl aluminum
hydride and dimethoxymethylaluminate sodium salt are preferred.

30 The reductant is generally added in the amount of 4 moles to 10 moles, and
preferably from 4 moles to 5 moles, relative to 1 mole of the compound to be
reduced.

35 The reduction generally takes place within a temperature range of -78°C to
+50°C, preferably from -78°C to 0°C, and particularly preferably at -78°C,
depending on the choice of both the reductant and the solvent.

40 The reduction generally takes place at normal pressure, but it is also possible
to work at increased or reduced pressure.

0 However, the reductions can also be carried out with reductants that are
suitable for the reduction of ketones to hydroxy compounds. Particularly suitable
in this regard is reduction using metal hydrides or complex metal hydrides in inert
solvents, if appropriate, in the presence of a trialkyl borane. Preferably, the
reduction is carried out using complex metal hydrides such as lithium borohydride,
5 sodium borohydride, potassium borohydride, zinc borohydride, lithium
trialkylborohydride, or lithium aluminum hydride. More preferably, the reaction is
carried out using sodium borohydride in the presence of triethyl borane.

10 The hydrogenation takes place according to the customary methods using
hydrogen in the presence of noble metal catalysts such as Pd/C, Pt/C, or Raney
nickel in one of the above-mentioned solvents, preferably in alcohols such as
methanol, ethanol, or propanol, within a temperature range of -20°C to +100°C,
preferably from 0°C to 50°C, at normal pressure or elevated pressure.

15 As derivatizations, the following types of reactions are cited by way of
examples: oxidations, reductions, hydrogenations, halogenation, Wittig/Grignard
reactions, and amidation/sulfoamidation.

20 The customary strongly basic compounds can be used as bases for the
individual steps. These preferably include organolithium compounds such as
n-butyl lithium, sec-butyl lithium, tert-butyl lithium, or phenyl lithium, or amides
such as lithium diisopropylamide, sodium amide, or potassium amide, or lithium
hexamethylsilyl amide, or alkali hydrides such as sodium hydride or potassium
hydride. n-butyl lithium or sodium hydride are particularly preferred.

25 Furthermore, the customary inorganic bases are suitable bases. These
preferably include alkali hydroxides or alkaline earth hydroxides such as sodium
hydroxide, potassium hydroxide, or barium hydroxide, or alkali carbonates such as
sodium carbonate, potassium carbonate, or sodium hydrogencarbonate. Sodium
30 hydroxide or potassium hydroxide are particularly preferred.

 Alcohols such as methanol, ethanol, propanol, or tert-butanol are also
suitable solvents for the individual reaction steps. Tert butanol is preferred.

35 It may possibly be necessary to carry out several reaction steps under a
protective gas atmosphere.

0 The halogenations generally take place in one of the above-mentioned chlorinated hydrocarbons, with methylene chloride being preferred.

Diethylamino sulfur trifluoride (DAST) or SOCl_2 , for example, are suitable halogenation agents.

5 The halogenation generally takes place within a temperature range of -78°C to $+50^\circ\text{C}$, preferably from -78°C to 0°C , and particularly preferably at -78°C , depending on the choice of both the halogenation agent and the solvent.

10 The halogenation generally takes place at normal pressure, but it is also possible to work at increased or reduced pressure.

The customary reagents are suitable as Wittig reagents. 3-Trifluoromethylbenzyltriphenylphosphonium bromide is preferred.

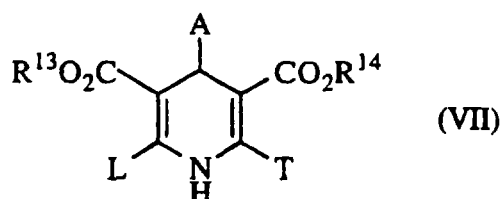
15 In general, one of the above-mentioned bases is suitable as a base, preferably Li-bis-(triethylbutyl)amide.

20 The base is used in an amount of 0.1 moles to 5 moles, preferably 0.5 moles to 2 moles, in relation to 1 mole of the parent compound.

The reaction with Wittig reagents is generally carried out in a temperature range of 0°C to 150°C , preferably at 25°C to 40°C .

25 The Wittig reactions are generally carried out at normal pressure. However, it is also possible to carry out the process at reduced or high pressure (e.g., within a range of 0.5 to 5 bar).

30 The compounds of general formula (II) are known in part or new and can then be produced from the corresponding dihydropyridines of general formula (VII)



0 in which

A, L, and T have the above-indicated meaning,

and

5

R¹³ and R¹⁴ are identical or different and denote straight-chain or branched alkyl with up to 4 carbon atoms,

10 through oxidation into the corresponding pyridines and finally depending on the substituents a reduction according to conventional methods can be carried out.

Suitable solvents for the oxidation are ethers such as diethyl ether, dioxane, tetrahydrofuran, or glycol dimethyl ether; or hydrocarbons such as benzene, 15 toluene, xylene, hexane, or cyclohexane, or petroleum fractions, or halocarbons such as dichloromethane, trichloromethane, tetrachloromethane, dichloroethylene, or trichloroethylene, or chlorobenzene, or ethyl acetate, or triethylamine, pyridine, dimethylsulfoxide, dimethylformamide, hexamethylphosphoric triamide, acetonitrile, acetone, or nitromethane. It is also possible to use a mixture of said 20 solvents. Dichloromethane is preferred.

Suitable oxidants are, for example, 2,3-dichloro-5,6-dicyanobenzoquinone, pyridinium chlorochromate (PCC), osmium tetroxide, and manganese dioxide. For the above-mentioned step, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is 25 preferred.

The oxidant is introduced in an amount of 1 mole to 10 moles, preferably 2 moles to 5 moles, relative to 1 mole of the compound of general formula (VII).

30 The oxidation generally takes place within a temperature range of -50°C to +100°C, preferably from 0°C to room temperature.

The oxidation generally takes place at normal pressure. However, it is also possible to carry out the oxidation at increased or reduced pressure.

35

The dihydropyridines of general formula (VII) are known per se or can be produced by customary methods.

0

The compounds of general formulas (III), (IV), and (VI) are known per se or can be produced by customary methods.

5

The compounds of general formula (V) are new or can be manufactured as described above.

10

The 3-heteroalkyl-aryl-substituted pyridines according to the invention possess valuable pharmacological properties that are superior to those of the state of the art; in particular, they are highly effective inhibitors of cholesterol ester transfer proteins (CETP) and stimulate reverse cholesterol transport. The active compounds according to the invention cause a reduction in LDL cholesterol levels in the blood, while at the same time increasing HDL cholesterol levels. They can therefore be used for the treatment of hyperlipoproteinemia or arteriosclerosis.

15

20

The invention additionally concerns the combination of compounds according to the invention with a glucosidase and/or amylase inhibitor for the treatment of familial hyperlipidemia, obesity (adiposis), and diabetes mellitus. Within the context of the invention, glucosidase and/or amylase inhibitors are, for example, acarbose, adiposine, voglibose, miglitol, emiglitate, MDL-25637, camiglibose (MDL-73945), tendamistate, AI-3688, tetratin, pradimicin-Q, and salbostatin.

25

The combination of acarbose, miglitol, emiglitate, or voglibose and one of the above-mentioned compounds of general formula (IB) according to the invention is preferred.

CETP Inhibition Test

1. Obtaining CETP

30

35

CETP was obtained in partially purified form from human plasma by differential centrifugation and column chromatography and was used for testing. In so doing, human plasma was adjusted with NaBr to a density of 1.21 g/ml and was centrifuged for 18 h at 50,000 rpm at 4°C. The bottom fraction ($d > 1.21$ g/ml) was applied to a Sephadex® Phenyl-Sepharose 4B (Pharmacia) column, washed with 0.15 M NaCl/0.001 M Tris HCl, pH 7.4, and then eluted with dist. water. The CETP-active fractions were pooled, dialyzed against 50 mM Na acetate, pH 4.5, and applied to a CM-Sepharose®

0 (Pharmacia) column. They were then eluted with a linear gradient (0-1 M NaCl). The pooled CETP fractions were dialyzed against 10 mM Tris HCl, pH 7.4, and were then further purified by chromatography over a Mono Q[®] column (Pharmacia).

5 2. Obtaining radioactively-labeled HDL

50 ml of fresh human EDTA plasma was adjusted with NaBr to a density of 1.12 and centrifuged at 4°C for 18 h at 50,000 rpm in the Ty 65 rotor. The upper phase was used to obtain cold LDL. The lower phase was dialyzed against 3 x 4 l PDB buffer (10 mM Tris/HCl, pH 7.4, 0.15 mM NaCl, 1 mM EDTA, 0.02% NaN₃). 20 µl of 3H cholesterol (Du Pont NET-725; 1 µC/µl dissolved in ethanol) was subsequently added per 10 ml of dialysis residue volume and incubated for 72 h at 37°C under N₂.

The sediment was then adjusted with NaBr to a density of 1.21 and centrifuged in the Ty 65 rotor for 18 h at 50,000 rpm at 20°C. The upper phase was obtained, and the lipoprotein fractions were purified by gradient centrifugation. In so doing, the isolated, tagged lipoprotein fraction was adjusted with NaBr to a density of 1.26. Every 4 ml of this solution was covered in centrifuge tubes (SW 40 rotor) with 4 ml of a solution with a density of 1.21 and 4.5 ml of a solution with a density of 1.063 (density solutions from PDB buffer and NaBr) and then centrifuged for 24 h at 38,000 rpm and 20°C in the SW 40 rotor. The intermediate layer between the density of 1.063 and 1.21 that contained the labeled HDL was dialyzed against 3 x 100 volumes of PDB buffer at 4°C.

The dialysis residue contained radioactively-labeled ³H-CE-HDL, which was adjusted to approx. 5 x 10⁶ cpm per ml and used for the test.

3. Conducting the test

In order to test the CETP activity, the transfer of ³H cholesterol ester from human HD lipoproteins to biotinylated LD lipoproteins was measured.

The reaction was ended by adding Streptavidin-SPA[®] beads (Amersham), and the transferred radioactivity was determined directly in the liquid scintillation counter.

In the test batch, 10 µl of HDL-³H cholesterol ester (~50,000 cpm) was incubated for 18 h at 37°C with 10 µl of biotin-LDL (Amersham) in 50 mM HEPES / 0.15 m NaCl / 0.1% bovine serum albumin / 0.05% NaN₃, pH 7.4, with 10 µl of CETP (1 mg/ml) and 3 µl solution of the substance to be tested

0 (dissolved in 10% DMSO / 1% BSA). Then, 200 μ l of the SPA-Streptavidin bead solution (Amersham TRKQ 7005) was added, and the mixture was further incubated for 1 h under agitation and subsequently measured in the scintillation counter. Corresponding incubations with 10 μ l buffer, 10 μ l CETP at 4°C, and 10 μ l CETP at 37°C served as controls.

5 The transferred activity in the control batches with CETP at 37°C was assessed as 100% transfer. The substance concentration in which this transfer was reduced by half was indicated as the IC₅₀ value.

10 Syrian golden hamsters from the company's own breeding were anesthetized after fasting for 24 h (0.88 mg/kg atropine, 0.80 mg/kg Ketavet® s.c., 30' later 50 mg/kg Nembutal i.p.). The jugular vein was then exposed and cannulated. The test substance was dissolved in a suitable solvent (as a rule, Adalat placebo solution: 60 g glycerin, 100 ml H₂O, ad 100 ml PEG-400) and administered to the animals via a PE catheter inserted into the jugular vein. The control animals
15 received the same volume of solvent without any test substance. The vein was then ligated and the wound closed up. At different intervals--up to 24 h after administration of the test substance blood was drawn from the animals by puncture of the retroorbital venous plexus (approx. 250 μ l). Coagulation was completed by incubating at 4°C overnight, and the blood was then centrifuged for
20 10 minutes at 6,000 g. The cholesterol and triglyceride content in the serum obtained in this manner was determined using modified commercially-available enzyme tests (cholesterol enzymatic 14366 Merck, triglyceride 14364 Merck). The serum was diluted in a suitable manner with physiological saline solution. 100 μ l serum dilution was mixed with 100 μ l of test substance in 96-well plates and
25 incubated for 10 minutes at room temperature. The optical density was then determined with an automatic plate reader at a wavelength of 492 nm (SLT-Spectra). The triglyceride/cholesterol concentration contained in the samples was determined using a parallel-measured standard curve.

30 The determination of the HDL cholesterol content was carried out after precipitation of the lipoproteins containing Apo B by means of a reagent mixture (Sigma 352-4 HDL cholesterol reagent) according to the manufacturer's instructions.

35 In attempting to determine oral efficacy, the test substance, which was dissolved in DMSO and suspended in 0.5% methylcellulose, was administered orally to Syrian golden hamsters from the company's own breeding via a pharyngeal

0 tube. The control animals received identical volumes of solvent without any test substance. Feed was then withheld from the animals, and blood was drawn at different intervals--up to 24 h after administration of the substance--via puncture of the retroorbital venous plexus. Further processing was carried out as described above.

5

The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions, and solutions, using inert, nontoxic, pharmaceutically-suitable excipients or solvents. In this connection, the therapeutically-active compound should be present in each case in a concentration of about 0.5% to 90% by weight, i.e., in amounts that are sufficient to achieve the dosage range indicated.

15 The formulations are prepared, for example, by extending the active compounds using solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, with it being possible, for example, in the case of the use of water as a diluent, to use organic solvents, if appropriate, as auxiliary solvents.

20 Administration takes place in a customary manner, preferably orally or parenterally, in particular, perlingually or intravenously.

In the case of parenteral use, solutions of the active compound can be employed using suitable liquid excipients.

25 In general, it has proved to be advantageous in intravenous administration to administer amounts of about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg of body weight, to obtain effective results, and in oral administration, the dosage is about 0.01 to 20 mg/kg, preferably 0.1 to 10 mg/kg of body weight.

30 In spite of this, it may be necessary to deviate from the amounts mentioned, depending on the body weight or the type of administration route, individual response to the medication, the type of formulation thereof, and the time or interval at which administration takes place. Thus in some cases, it may be sufficient to manage with less than the minimum amount previously mentioned, whereas in other cases, the upper limit mentioned must be exceeded. If larger amounts are administered, it may be advisable to divide these into several individual doses over the day.

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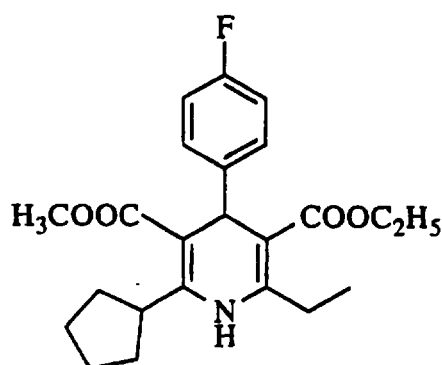
I. Mobile solvents for thin-layer chromatography

	A ₁	=	PE 98 : EE 2	
	A ₂	=	PE 95 : EE 5	
5	A ₃	=	PE 9 : EE 1	
	A ₄	=	PE 85 : EE 15	
	A ₅	=	PE 8 : EE 2	
	A ₆	=	PE 75 : EE 25	
	A ₇	=	PE 7 : EE 3	
10	A ₈	=	PE 65 : EE 35	
	A ₉	=	PE 6 : EE 4	
	A ₁₀	=	PE 55 : EE 45	
	A ₁₁	=	PE 1 : EE 1	
	A ₁₂	=	Toluene/ethyl acetate	1/1
15	A ₁₃	=	Toluene/ethyl acetate	8/2
	A ₁₄	=	Acetonitrile/water	9/1

PE = petroleum ether; EE = ethyl acetate

20 Example I

1,4-Dihydro-2-cyclopentyl-6-ethyl-4-(4-fluorophenyl)pyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester



25

6.2 g (50 mmol) of 4-fluorobenzaldehyde, 8.5 g (50 mmol) of 3-amino-cyclopentylprop-2-ene-carboxylic methylester, and 7.2 g (50 mmol) of 4-methylacetoacetic ethylester are heated for 18 hours to 130°C while stirring.

30 After cooling to room temperature, chromatography is carried out over silica gel

0 (200 g of silica gel, 230-400 mesh; d 3.5 cm, mobile solvent ethyl acetate/petroleum ether 1 : 9).

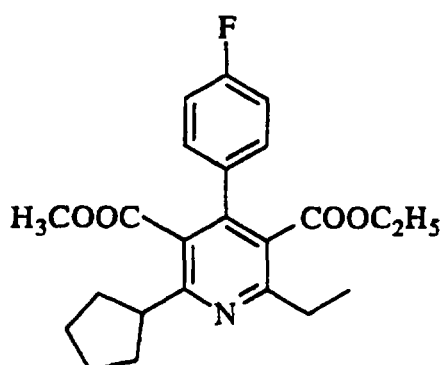
Yield: 2.8 g (14% of theory)

R_f (ethyl acetate / petroleum ether 2 : 8) = 0.31

5

Example II

2-Cyclopentyl-6-ethyl-4-(4-fluorophenyl)pyridine-3,5-dicarboxylic acid-3-methylester- 5-ethylester



10

2.8 g (6.98 mmol) of 1,4-dihydro-2-cyclopentyl-6-ethyl-4-(4-fluorophenyl)pyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester is dissolved in 100 ml of absol. methylene chloride, and after addition of 1.6 g (6.98 mmol) of 2,3-dichloro-5,6-dicyano- p-benzoquinone (DDQ), the mixture is stirred for 1 hour at room temperature. After this, it is drawn off by suction over diatomaceous earth and concentrated in a vacuum. The residue is chromatographed over silica gel (100 g of silica gel, 230-400 mesh, d 3.5 cm, mobile solvent ethyl acetate / petroleum ether 5:95).

20 Yield: 2.1 g (75.4% of theory)

R_f (ethyl acetate / petroleum ether 1:9) = 0.56

$^1\text{H-NMR}$ (CDCl_3): δ = 0.95 (t, 3H); 1.32 (t, 3H); 1.6 - 2.1 (m, 8H); 2.83 (q, 2H);

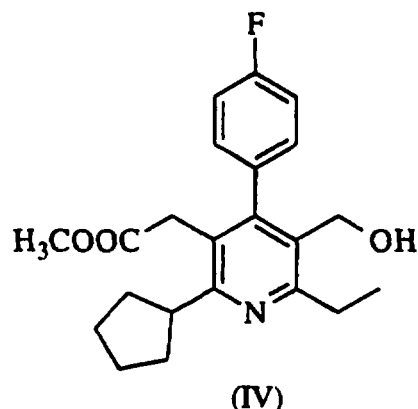
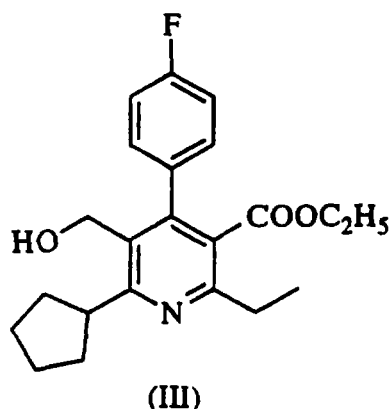
3.14 (m, 1H); 3.53 (s, 3H); 4.02 (q, 2H); 7.0-7.3 (m, 4H) ppm.

25 Example III and Example IV

2-Cyclopentyl-6-ethyl-4-(4-fluorophenyl)-3-hydroxymethylpyridine-5-carboxylic acid ethylester (Example III) and

30 2-Cyclopentyl-6-ethyl-4-(4-fluorophenyl)-5-hydroxymethylpyridine-3-carboxylic acid methylester (Example IV)

0



Under argon, 2.1 g (5.26 mmol) of 2-cyclopentyl-6-ethyl-4-(4-fluorophenyl)pyridine-3,5-dicarboxylic acid-3-methylester5-ethylester is dissolved in 50 ml of absol. toluene. 26.6 ml of diisobutyl aluminum hydride (1 M solution in toluene) is added dropwise to this solution at -60°C. After this, the mixture is stirred for 15 minutes at -60°C, and the reaction solution is then cooled at -30°C for 18 h. After heating to 0°C, 50 ml of water is added, and the resulting sediment is drawn off by suction and washed 4 times with 50 ml of ethyl acetate. The aqueous phase is washed with 100 ml of ethyl acetate, and the combined organic phases are shaken out with 150 ml of saturated sodium chloride solution, dried with sodium sulfate, and concentrated in a vacuum. The residue is chromatographed over silica gel (100 g of silica gel, 230-400 mesh, d 3.5 cm, mobile solvent ethyl acetate / petroleum ether 15:85).

Yield (Example III): 0.263 g (13.5% of theory)

R_f (ethyl acetate / petroleum ether 2:8) = 0.42

$^1\text{H-NMR}$ (CDCl_3): δ = 0.95 (t, 3H); 1.28 (t, 3H); 1.6-2.1 (m, 8H); 2.76 (q, 4H); 3.55 (m, 1H); 3.97 (q, 4H); 4.48 (d, 2H); 7.0-7.3 (m, 4H) ppm.

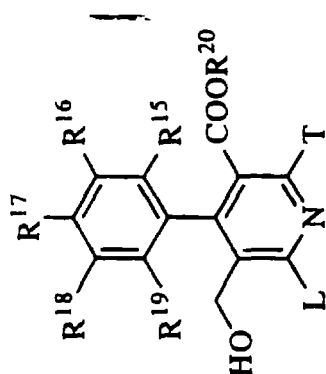
Yield (Example IV): 0.907 g (48.3% of theory)

R_f (ethyl acetate / petroleum ether 2:8) = 0.32

$^1\text{H-NMR}$ (CDCl_3): δ = 1.32 (t, 3H); 1.6-2.1 (m, 8H); 2.97 (t, 3H); 3.06 (m, 1H); 3.45 (s, 3H); 4.45 (d, 2H) ppm.

The compounds shown in Table I(B) are produced analogously to the instructions for Examples I-IV:

Table I(B)



Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
V	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH(CH ₃) ₂	0.51 (A5)
VI	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH ₃	0.28 (A5)
VII	H	H	F	H	H	CH ₃	CH ₃	CH ₃	0.33 (A7)
VIII	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	cyclo-C ₃ H ₅	0.41 (A5)
IX	H	H	F	H	H	C ₂ H ₅	cyclo-C ₃ H ₅	cyclo-C ₃ H ₅	0.44 (A5)
X	H	H	H	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH(CH ₃) ₂	0.41 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
XI	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	cyclo-C ₄ H ₇	0.45 (A5)
XII	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	cyclo-C ₅ H ₉	0.46 (A5)
XIII	H	H	F	H	H	CH ₃	cyclo-C ₅ H ₉	CH(CH ₃) ₂	0.41 (A5)
XIV	H	CH ₃	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH(CH ₃) ₂	0.26 (A3)
XV	CH ₃	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH(CH ₃) ₂	0.48 (A5)
XVI	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	sec-C ₄ H ₉	0.58 (A5)
XVII	H	H	F	H	H	CH ₃	sec-C ₄ H ₉	CH(CH ₃) ₂	0.53 (A5)
XVIII	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH(OCH ₃) ₂	0.45 (A5)
XIX	H	H	F	H	H	C ₂ H ₅	CH ₂ CH ₃	CH(CH ₃) ₂	0.49 (A5)
XX	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH ₂ CH ₃	0.44 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
XXI	H	H	OH	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH(CH ₃) ₂	0.21 (A7)
XXII	H	H	CH ₃	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH(CH ₃) ₂	0.25 (A3)
XXIII	H	H	F	H	H	CH ₃	CH ₃	cyclo-C ₃ H ₅	0.43 (A7)
XXIV	H	H	F	H	H	CH ₃	cyclo-C ₃ H ₅	CH ₃	0.36 (A7)
XXV	H	H	F	H	H	C ₂ H ₅	thiophen-2-yl	CH(CH ₃) ₂	0.5 (A5)
XXVI	H	H	F	H	H	C ₂ H ₅	C ₆ H ₅	CH(CH ₃) ₂	0.42 (A5)
XXVII	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	4-F-C ₆ H ₄	0.49 (A5)
XXVIII	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.34 (A5)
XXIX	H	H	F	H	H	C ₂ H ₅	furan-2-yl	CH(CH ₃) ₂	0.36 (A5)
XXX	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	C ₆ H ₅ CH ₂ CHCH ₃	0.42 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
XXXI	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH(C ₂ H ₅) ₂	0.47 (A5)
XXXII	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	C ₆ H ₅ CHCH ₃	0.45 (A5)
XXXIII	H	H	H	H	H	C ₂ H ₅	CH(CH ₃) ₂	cyclo-C ₃ H ₅	0.37 (A5)
XXXIV	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	n-C ₃ H ₇	0.24 (A3)
XXXV	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	n-C ₄ H ₉	0.27 (A3)
XXXVI	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	C ₆ H ₅ (CH ₂) ₂	0.4 (A5)
XXXVII	H	H	F	H	H	CH ₃	4-CH ₃ O-C ₆ H ₄	CH(CH ₃) ₂	0.52 (A7)
XXXVIII	H	H	F	H	H	C ₂ H ₅	2-F-C ₆ H ₄	CH(CH ₃) ₂	0.34 (A5)
XXXIX	H	H	F	H	H	C ₂ H ₅	pyrrolidin-1-yl	CH(CH ₃) ₂	0.35 (A5)
XL	H	H	F	H	H	C ₂ H ₅	piperidin-1-yl	CH(CH ₃) ₂	0.47 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
XLI	H	H	F	H	H	C ₂ H ₅	cyclo-C ₆ H ₁₁	CH(CH ₃) ₂	0.53 (A5)
XLII	H	H	F	H	H	C ₂ H ₅	pyridin-4-yl	CH(CH ₃) ₂	0.38 (A11)
XLIII	H	H	F	H	H	C ₂ H ₅	pyridin-3-yl	CH(CH ₃) ₂	0.44 (A11)
XLIV	H	H	F	H	H	C ₂ H ₅	3-CH ₃ O-C ₆ H ₄	CH(CH ₃) ₂	0.30 (A5)
XLV	H	H	F	H	H	C ₂ H ₅	4-NO ₂ -C ₆ H ₄	CH(CH ₃) ₂	0.38 (A5)
XLVI	H	H	F	H	H	C ₂ H ₅	CH(CH ₃) ₂	C ₆ F ₅	0.22 (A3)
XLVII	H	H	F	H	H	C ₂ H ₅	2-CH ₃ -C ₆ H ₄	CH(CH ₃) ₂	0.44 (A5)
XLVIII	H	H	F	H	H	C ₂ H ₅	4-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.21 (A3)
XLIX	H	H	H	H	H	C ₂ H ₅	CH(CH ₃) ₂	4-F-C ₆ H ₄	0.37 (A3)
L	H	H	H	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.2 (A3)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
LI	C ₆ H ₅ CH ₂ O	H	H	H	H	C ₂ H ₅	CH(CH ₃) ₂	4-F-C ₆ H ₄	0.27 (A4)
LI	C ₆ H ₅ CH ₂ O	H	H	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.18 (A4)
LI	2-F-C ₆ H ₄ CH ₂ O	H	H	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH(CH ₃) ₂	0.23 (A3)
LIV	4-F-C ₆ H ₄ CH ₂ O	H	H	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH(CH ₃) ₂	0.21 (A4)
LV	4-Cl-C ₆ H ₄ CH ₂ O	H	H	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH(CH ₃) ₂	0.12 (A4)
LVI	H	2-F-C ₆ H ₄ CH ₂ O	H	H	H	C ₂ H ₅	CH(CH ₃) ₂	CH(CH ₃) ₂	0.17 (A3)
LVI	H	H	H	H	H	CH ₃	4-F-C ₆ H ₄	CH ₃	0.21 (A7)
LVIII	H	H	F	H	H	C ₂ H ₅	3-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.4 (A5)
LIX	H	H	F	H	H	CH ₃	CH(CH ₃) ₂	4-F-C ₆ H ₄ CH ₂	0.19 (A3)
LX	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	0.28 (A4)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
LXI	H	H	F	H	H	CH ₃	CH(CH ₃) ₂	4-F-C ₆ H ₄ CH ₂	0.23 (A4)
LXII	H	H	OCH ₃	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.18 (A5)
LXIII	H	H	Cl	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.16 (A3)
LXIV	H	Cl	H	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.28 (A3)
LXV	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄	CH(C ₂ H ₅) ₂	0.32 (A4)
LXVI	H	Cl	Cl	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.29 (A4)
LXVII	H	CF ₃	H	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.44 (A5)
LXVIII	H	CH ₃	H	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.34 (A5)
LXIX	H	H	CH ₃	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.31 (A5)
LXX	H	Cl	H	Cl	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.22 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
LXXI	F	H	H	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.22 (A5)
LXXII	H	OCH ₃	H	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.25 (A5)
LXXIII	OCH ₃	H	H	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.2 (A5)
LXXIV	Cl	Cl	H	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.14 (A4)
LXXV	H	CF ₃	Cl	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.21 (A4)
LXXVI	H	CF ₃	F	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.24 (A4)
LXXVII	H	Cl	CF ₃	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.23 (A3)
LXXVIII	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.39 (A5)
LXXIX	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄	cyclo-C ₃ H ₅	0.28 (A5)
LXXX	H	F	H	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.28 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
LXXXI	H	H	CF ₃	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.39 (A5)
LXXXII	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄	4-F-C ₆ H ₄	0.3 (A5)
LXXXIII	H	H	F	H	H	CH ₃	cyclo-C ₃ H ₅	cyclo-C ₃ H ₅	0.3 (A5)
LXXXIV	Cl	Cl	H	H	H	CH ₃	4-F-C ₆ H ₄	4-F-C ₆ H ₄	0.36 (A7)
LXXXV	H	CF ₃	F	H	H	CH ₃	CH(CH ₃) ₂	CH(CH ₃) ₂	0.41 (A5)
LXXXVI	H	CF ₃	F	H	H	CH ₃	4-F-C ₆ H ₄	4-F-C ₆ H ₄	0.25 (A5)
LXXXVII	CH ₃	H	H	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.32 (A5)
LXXXVIII	Cl	H	H	H	H	CH ₃	CH(CH ₃) ₂	CH(CH ₃) ₂	0.21 (A5)
LXXXIX	Cl	H	H	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.13 (A5)
XC	Cl	H	H	H	H	CH ₃	4-F-C ₆ H ₄	4-F-C ₆ H ₄	0.35 (A7)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
XCI	Cl	H	Cl	H	H	CH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.23 (A5)
XCII	Cl	H	Cl	H	H	CH ₃	4-F-C ₆ H ₄	4-F-C ₆ H ₄	0.31 (A5)
XCIII	H	H	F	H	H	CH ₃	3-CF ₃ -C ₆ H ₄	CH(CH ₃) ₂	0.31 (A5)
XCIV	H	H	F	H	H	CH ₃	3-CH ₃ -C ₆ H ₄	CH(CH ₃) ₂	0.31 (A5)
XCV	H	H	F	H	H	CH ₃	4-CH ₃ -C ₆ H ₄	CH(CH ₃) ₂	0.27 (A5)
XCVI	H	H	F	H	H	CH ₃	2-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.27 (A5)
XCVII	H	H	F	H	H	CH ₃	4-CH ₃ O-C ₆ H ₄	CH(CH ₃) ₂	0.22 (A5)
XCVIII	H	H	F	H	H	CH ₃	2-CH ₃ O-C ₆ H ₄	CH(CH ₃) ₂	0.43 (A7)
XCIX	H	H	F	H	H	CH ₃	3-CH ₃ O-C ₆ H ₄	CH(CH ₃) ₂	0.25 (A5)
C	H	H	F	H	H	C ₂ H ₅	cyclo-C ₆ H ₁₁	4-F-C ₆ H ₄	0.45 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
CI	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄	cyclo-C ₆ H ₁₁	0.33 (A5)
CII	H	H	F	H	H	C ₂ H ₅	4-Cl-C ₆ H ₄	cyclo-C ₅ H ₉	0.22 (A4)
CIII	H	H	F	H	H	CH ₃	3-CF ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.29 (A5)
CTV	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄	cyclo-C ₄ H ₇	0.2 (A5)
CV	H	H	F	H	H	C ₂ H ₅	cyclo-C ₇ H ₁₃	4-F-C ₆ H ₄	0.4 (A5)
CVI	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄	cyclo-C ₇ H ₁₃	0.3 (A5)
CVII	H	H	F	H	H	C ₂ H ₅	furan-2-yl	4-F-C ₆ H ₄	0.32 (A6)
CVIII	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄	furan-2-yl	0.21 (A6)
CIX	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄	(cyclo-C ₅ H ₉)CH ₂	0.11 (A4)
CX	H	H	F	H	H	C ₂ H ₅	(cyclo-C ₆ H ₁₁)CH ₂	4-F-C ₆ H ₄	0.31 (A5)

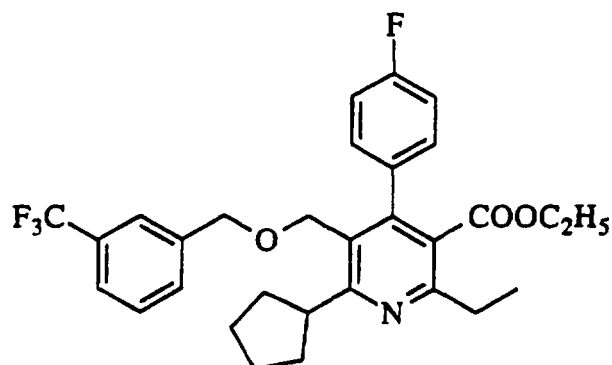
Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
CXI	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄	(cyclo-C ₆ H ₁₁)CH ₂	0.21 (A5)
CXII	H	H	F	H	H	C ₂ H ₅	CF ₃	4-F-C ₆ H ₄	0.26 (A5)
CXIII	H	H	F	H	H	CH ₃	cyclo-C ₅ H ₉	4-CF ₃ -C ₆ H ₄	0.30 (A4)
CXIV	H	H	F	H	H	C ₂ H ₅	4-CF ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.19 (A4)
CXV	H	H	F	H	H	C ₂ H ₅	1-naphthyl	cyclo-C ₅ H ₉	0.21 (A4)
CXVI	H	H	F	H	H	CH ₃	cyclo-C ₅ H ₉	3,5-(CF ₃) ₂ -C ₆ H ₃	0.25 (A3)
CXVII	H	H	F	H	H	C ₂ H ₅	2-naphthyl	cyclo-C ₅ H ₉	0.23 (A3)
CXVIII	H	H	F	H	H	CH ₃	3-CH ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.32 (A5)
CXIX	H	H	F	H	H	CH ₃	2-CF ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.2 (A5)
CXX	H	H	F	H	H	CH ₃	cyclo-C ₅ H ₉	2-CF ₃ -C ₆ H ₄	0.17 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
CXXI	H	H	F	H	H	C ₂ H ₅	4-F-C ₆ H ₄ CH ₂	cyclo-C ₅ H ₉	0.4 (A5)
CXXII	H	H	F	H	H	CH ₃	cyclo-C ₅ H ₉	4-F-C ₆ H ₄ CH ₂	0.32 (A5)
CXXIII	H	H	F	H	H	C ₂ H ₅	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	0.28 (A5)
CXXIV	H	H	F	H	H	CH ₃	cyclo-C ₅ H ₉	2,4-F ₂ -C ₆ H ₃	0.32 (A5)
CXXV	H	H	F	H	H	C ₂ H ₅	3,4-F ₂ -C ₆ H ₄ CH ₂	cyclo-C ₅ H ₉	0.23 (A4)
CXXVI	H	H	F	H	H	CH ₃	cyclo-C ₅ H ₉	cyclo-C ₅ H ₉	0.34 (A4)
CXXVII	H	H	F	H	H	C ₂ H ₅	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄ CH ₂	0.4 (A7)
CXXVIII	H	H	F	H	H	C ₂ H ₅	3-CF ₃ -C ₆ H ₄ (CH ₂) ₂	cyclo-C ₅ H ₉	0.36 (A5)
CXXIX	H	H	F	H	H	CH ₃	cyclo-C ₅ H ₉	3-CF ₃ -C ₆ H ₄ (CH ₂) ₂	0.34 (A5)
CXXX	H	H	F	H	H	C ₂ H ₅	3-CF ₃ -C ₆ H ₄ CH ₂	3-CF ₃ -C ₆ H ₄ (CH ₂) ₂	0.35 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ²⁰	T	L	R _f (solvent)
CXXXI	H	H	F	H	H	C ₂ H ₅	C ₂ H ₅	cyclo-C ₅ H ₉	0.41 (A5)
CXXXII	H	H	F	H	H	CH ₃	cyclo-C ₅ H ₉	C ₂ H ₅	0.32 (A5)
CXXXIII	H	H	F	H	H	C ₂ H ₅	C ₂ H ₅	C ₂ H ₅	0.22 (A7)
CXXXIV	H	H	F	H	H	C ₂ H ₅	3-CF ₃ -C ₆ H ₄ CH ₂	cyclo-C ₅ H ₉	
CXXXV	H	H	F	H	H	CH ₃	cyclo-C ₅ H ₉	4-F-C ₆ H ₄ CH ₂	
CXXXVI	H	H	F	H	H	C ₂ H ₅	(cyclo-C ₅ H ₉)(CH ₂) ₂	(cyclo-C ₅ H ₉)(CH ₂) ₂	
CXXXVII	H	H	F	H	H	C ₂ H ₅	(cyclo-C ₅ H ₉)(CH ₂) ₂	4-F-C ₆ H ₄	
CXXXVIII	H	H	F	H	H	CH ₃	4-F-C ₆ H ₄	(cyclo-C ₅ H ₉)(CH ₂) ₂	

0 Example CXXXIX

2-Cyclopentyl-6-ethyl-4-(4-fluorophenyl)-3-(3-trifluoromethylbenzyloxy-methyl)-pyridine-5-carboxylic acid ethylester



5

186 mg (0.5 mmol) of 2-cyclopentyl-6-ethyl-4-(4-fluorophenyl)-3-hydroxy-methylpyridine-5-carboxylic acid ethylester dissolved in 5 ml of absol. dimethyl formamide is added dropwise at 0°C while stirring to a suspension of 18 mg (0.5 mmol) of sodium hydride (80%) in 5 ml of dimethyl formamide and subsequently stirred for 30 minutes. After this, 143 mg (0.6 mmol) of trifluoromethylbenzylbromide dissolved in 3 ml of dimethyl formamide is added, and the mixture is stirred for 18 h at room temperature. After addition of 25 ml of water, the mixture is extracted twice with 50 ml of ethyl acetate each time, and the combined ethyl acetate phases are shaken out with 10 ml of saturated sodium chloride solution, dried with sodium sulfate, and concentrated in a vacuum. The residue is chromatographed over silica gel (100 g of silica gel, 230-400 mesh, diameter 3.5 cm, mobile solvent ethyl acetate / petroleum ether 1:9).

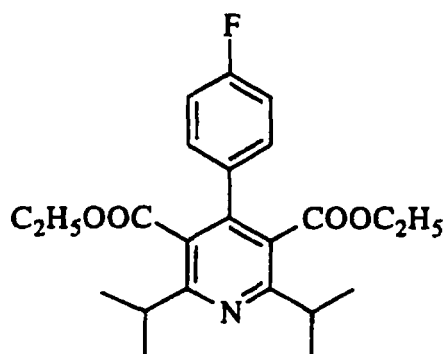
Yield: 0.246 g (93.1% of theory)

R_f value (ethyl acetate / petroleum ether 1:9) = 0.35

¹H-NMR (CDCl₃): δ = 0.95 (t, 3H); 1.32 (t, 3H); 1.6-2.1 (m, 8H); 2.78 (q, 4H); 3.44 (m, 1H); 3.95 (q, 4H); 4.28 (s, 2H); 4.42 (s, 2H); 7.0-7.6 (m, 8H) ppm.

25

30

0 **Example CXL****2,6-Diisopropyl-4-(4-fluorophenyl)pyridine-3,5-dicarboxylic acid diethylester**

5

3.8 g (16.4 mmol) of 2,3-dichloro-5,6-dicyano-p-benzoquinone is added to a solution of 6.6 g (16.4 mmol) of 1,4-dihydro-2,6-diisopropyl-4-(4-fluorophenyl)pyridine-3,5-dicarboxylic acid diethylester in 200 ml of analysis grade methylene chloride, and the mixture is then stirred for 1 h at room temperature. After this, it is drawn off by suction over diatomaceous earth, and the methylene-chloride phase is extracted 3 times with 100 ml of water each time and dried on magnesium sulfate. After concentrating in a vacuum, the residue is chromatographed on a column (100 g of silica gel, 70-230 mesh, diameter 3.5 cm, with ethyl acetate / petroleum ether 1:9).

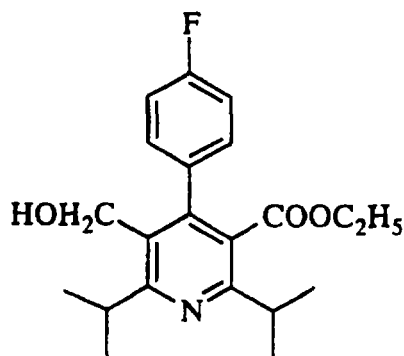
15

Yield: 5.8 g (87.9% of theory)

$^1\text{H-NMR}$ (CDCl_3): δ = 0.98 (t, 6H); 1.41 (d, 12H); 3.1 (m, 2H); 4.11 (q, 4H); 7.04 (m, 2H); 7.25 (m, 2H) ppm.

Example CXLI

20

2,6-Diisopropyl-4-(4-fluorophenyl)-5-hydroxymethyl-pyridine-3,5-carboxylic acid ethylester

0

Under nitrogen, 21 ml (80.5 mmol) of a 3.5 molar solution of sodium bis(2-methoxyethoxy)dihydroaluminate in toluene is added to a solution of 9.2 g (23 mmol) of the compound from Example CXL in 100 ml of dried tetrahydrofuran at -10°C to -5°C, and the mixture is stirred for 5 h at room temperature. After cooling to 0°C, 100 ml of water is carefully added dropwise, and extraction is carried out 3 times with 100 ml of ethyl acetate each time. The combined organic phases are washed with saturated sodium chloride solution, dried over magnesium sulfate, and evaporated in a vacuum. The residue is chromatographed on a column (200 g of silica gel, 70-230 mesh, diameter 4.5 cm, with ethyl acetate / petroleum ether 3:7).

10

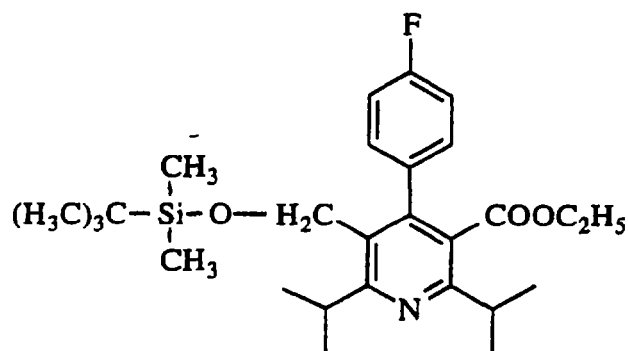
Yield: 7.2 g (87.2% of theory)

$^1\text{H-NMR}$ (CDCl_3): δ = 0.95 (t, 3H); 1.31 (m, 12H); 3.05 (m, 1H); 3.48 (m, 1H); 3.95 (q, 2H); 4.93 (d, 2H); 7.05-7.31 (m, 4H) ppm.

Example CXLII

15

5-(*tert*-Butyldimethylsilyloxymethyl)-2,6-diisopropyl-4-(4-fluorophenyl)-pyridine-3-carboxylic acid ethylester



20

2.1 g (13.8 mmol) of *tert*-Butyldimethylsilyl chloride, 1.8 g (27.5 mmol) of imidazole, and 0.05 g of 4-dimethyl-aminopyridine are added to a solution of 4.5 g (12.5 mmol) of the compound from Example CXLI in 50 ml of dimethyl formamide at room temperature. The mixture is stirred overnight at room temperature, 200 ml of water is added, and the mixture is adjusted to a pH of 3 with 1 N hydrochloric acid. The mixture is extracted 3 times with 100 ml of ether each time, and the combined organic phases are washed once with saturated sodium chloride solution, dried over magnesium sulfate, and concentrated in a vacuum. The residue is chromatographed on a column (150 g of silica gel, 70-230 mesh, diameter 4 cm, with ethyl acetate / petroleum ether 1:9).

30

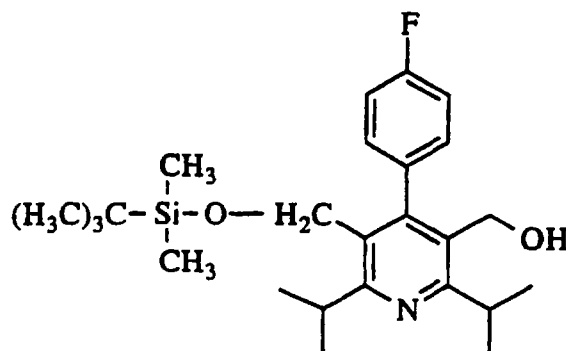
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0 Yield: 4.2 g (73.7% of theory)
 R_f = 0.75 (A3)

5 Example CXLIII

3-(*tert*-Butyldimethylsilyloxymethyl)-2,6-diisopropyl-4-(4-fluorophenyl)-5-hydroxymethylpyridine



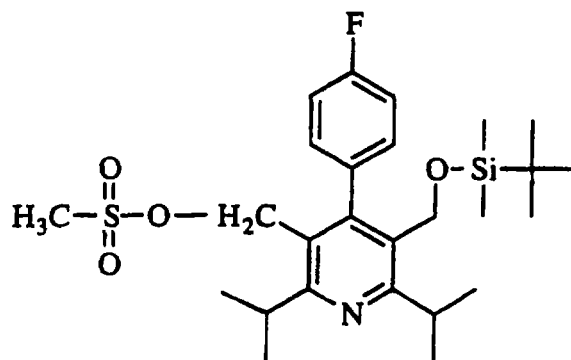
10 Under argon, 76.0 ml (0.266 mmol; 3.6 eq.) of a 3.5 molar solution of sodium bis(2methoxyethoxy)dihydroaluminate (Red-Al) in toluene is slowly added to a solution of 35.0 g (0.0738 mmol) of the compound from Example CXLII in 500 ml of analysis-grade THF at room temperature, and stirring is then carried out for 3 h. The reaction solution is mixed under ice cooling with 50 ml of a 20% potassium

15 sodium tartrate solution and extracted with 200 ml of ethyl acetate. The organic phase is washed once with a saturated NaCl solution, dried over Na₂SO₄, and concentrated in a vacuum. The residue is chromatographed over silica gel 60 with toluene / ethyl acetate (8:2).

Yield: 30.2 g (94.7% of theory)
 20 R_f = 0.71 (toluene / ethyl acetate 8:2)

Example CXLIV

25 3-(*tert*-Butyldimethylsilyloxymethyl)-2,6-diisopropyl-4-(4-fluorophenyl)-5-methylsulfonyloxymethylpyridine



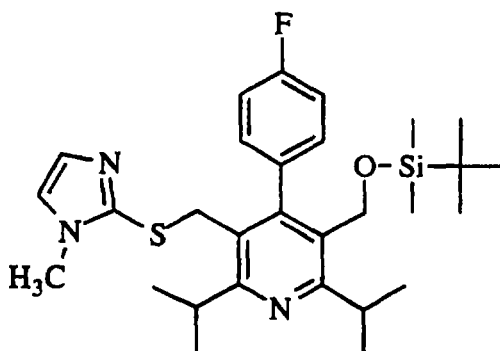
0

16.94 g (39.24 mmol) of 3-(tert-butyldimethylsilyloxymethyl)-2,6-diisopropyl-4-(4-fluorophenyl)-5-hydroxymethylpyridine is dissolved in 220 g of analysis grade CH_2Cl_2 , cooled to -60°C , and mixed dropwise with 11.0 ml (78.48 mmol; 2 eq.) of triethylamine and 6.1 ml (78.48 mmol; 2 eq.) of methanesulfonyl chloride under nitrogen while stirring. Stirring is carried out for 1 h at -60°C to -20°C and for 30 minutes at 0°C . After this, the reaction solution is washed with cold NaHCO_3 solution, dried over Na_2SO_4 , concentrated, dried for 60 min. in a high vacuum, and then stored at -20°C .

Yield: 19.8 g (99% of theory)
 $R_f = 0.77$ (toluene / ethyl acetate 8:2)

Example CXLV

3-(tert-Butyldimethylsilyloxymethyl)-2,6-diisopropyl-4-(4-fluorophenyl)-5-(1-methylimidazole-2-thiomethyl)pyridine



1.0 g (1.96 mmol) of 3-(tert-butyldimethylsilyloxymethyl)-2,6-diisopropyl-4-(4-fluorophenyl)-5-methylsulfonyloxymethylpyridine is placed in 15 ml of analysis-grade DMF. 0.256 g (2.25 mmol; 1.15 eq.) of 2-mercapto-1-methylimidazole and 0.41 ml (2.35 mmol; 1.2 eq.) of N,N-diisopropylamine are added, and the

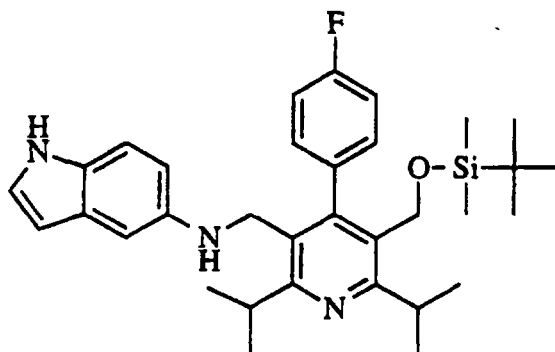
0 mixture is stirred overnight at 60°C. After this, 80 ml of ethyl acetate is added, and the mixture is then successively washed with saturated NaHCO₃ solution, 1 N H₂SO₄, and saturated NaCl solution. The organic phase is dried over Na₂SO₄, filtered, and concentrated.

Yield: 0.93 g (89.8% of theory)

5 R_f = 0.35 (toluene / ethyl acetate 8:2)

Example CXLVI

10 3-(*tert*-Butyldimethylsilyloxymethyl)-2,6-diisopropyl-4-(4-fluorophenyl)-5-(indolyl-5-aminomethyl)pyridine



15 2.0 g (3.92 mmol) of 3-(*tert*-butyldimethylsilyloxymethyl)-2,6-diisopropyl-4-(4-fluorophenyl)-5-methylsulfonyloxymethylpyridine is reacted in 20 ml of analysis grade DMF under nitrogen with 0.674 g (5.1 mmol; 1.3 eq.) of 5-aminoindole and 0.82 ml (4.71 mmol) of *N,N*-diisopropylethylamine analogously to the instructions of Example CXLII.

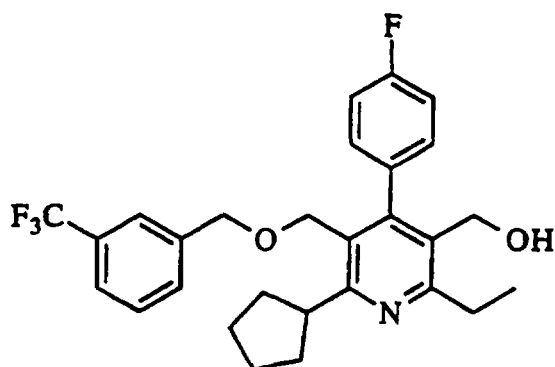
Yield: 2.05 g (95.8% of theory)

20 R_f = 0.75 (toluene / ethyl acetate 8:2)

Production Examples

25 Example 1

2-Cyclopentyl-6-ethyl-4-(4-fluorophenyl)-5-hydroxymethyl-3-(3-trifluoromethylbenzyloxymethyl)pyridine



0

A suspension of 30 mg (0.8 mmol) of lithium aluminum hydride in 10 ml of absol. tetrahydrofuran is heated under argon. After this, 212 mg (0.4 mmol) of 2-cyclopentyl-6-ethyl-4-(4-fluorophenyl)-3-(3-(trifluoromethyl)benzyloxymethyl)-pyridine-5-carboxylic acid ethylester dissolved in 10 ml of absolute tetrahydrofuran is added. Next, the mixture is refluxed for 1 h. After cooling to room temperature, 10 ml of a 10% potassium hydroxide solution is added. The resulting sediment is drawn off by suction and boiled off several times with 10 ml of diethyl ether. The combined mother liquors are dried with sodium sulfate, concentrated in a vacuum, and chromatographed over silica gel (mobile solvent ethyl acetate / petroleum ether 2:8).

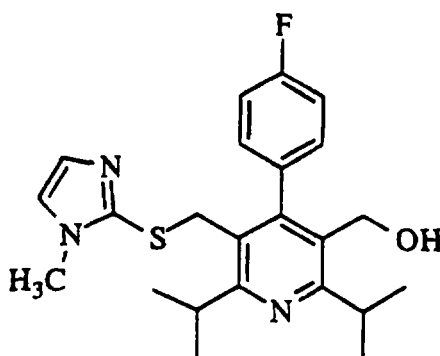
Yield: 149 mg (76.5% of theory)
 R_f value (ethyl acetate / petroleum ether 2:8) = 0.08
 $^1\text{H-NMR}$ (CDCl_3): δ = 1.32 (t, 3H); 1.6-2.1 (m, 8H); 2.95 (q, 4H); 3.41 (m, 1H); 4.16 (s, 2H); 4.38 (s, 2H); 7.0-7.6 (m, 8H) ppm.

15

Example 2

2,6-Diisopropyl-4-(4-fluorophenyl)-5-(1-methylimidazole-2-thiomethyl)-3-hydroxymethylpyridine

20



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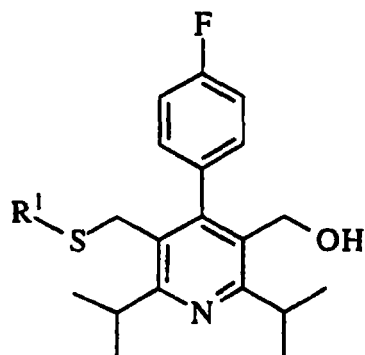
- 0 10 ml of 3 N hydrochloric acid is added to 0.5 g (0.947 mmol) of the compound from Example CXLII dissolved in 10 ml of methanol, and the mixture is stirred for 3 h at room temperature. The mixture is concentrated in a vacuum, covered with a layer of ethyl acetate, and adjusted to a pH of 8.0 with a saturated NaHCO_3 solution, and the organic phase is separated off. The aqueous phase is
- 5 again extracted with ethyl acetate, and the combined organic phases are washed with salt water, dried over Na_2SO_4 , and concentrated.

Yield: 230 mg (58.7% of theory)

$R_f = 0.76$ (toluene / ethyl acetate 1:1)

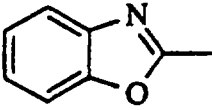
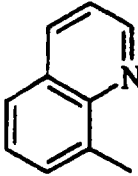
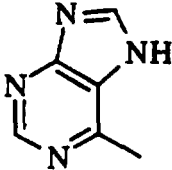
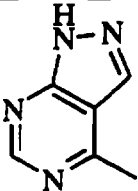
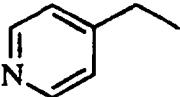
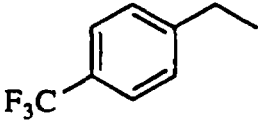
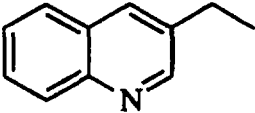
0 The compounds listed in Tables 1(B) through 5(B) are produced analogously to the procedures of Examples 1 and 2:

Table 1(B):



5

Example No.	R ¹	R _f (solvents)
3		0.56 (A12)
4		0.42 (A13)
5		0.12 (A13)
6		0.62 (A13)
7		0.42 (A14)

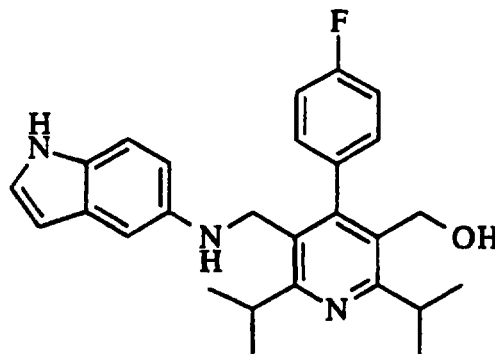
Example No.	R ¹	R _f (solvents)
8		0.54 (A13)
9		0.59 (A13)
10		0.23 (A12)
11		0.54 (A12)
12		0.5 (A12)
13		0.68 (A13)
14		0.71 (A13)

0

5

0 **Example 15**

2,6-Diisopropyl-4-(4-fluorophenyl)-5-(indolyl-5-aminomethyl)-3-hydroxy-methylpyridine

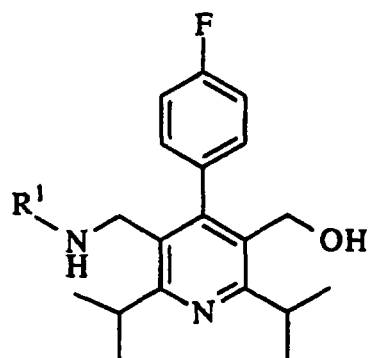


5 Analogously to Example 2, 2.3 g (4.21 mmol) of the compound from Example CXLIII is desilylated in methanol in the presence of 3 N hydrochloric acid.

Yield: 720 mg (39.6% of theory)

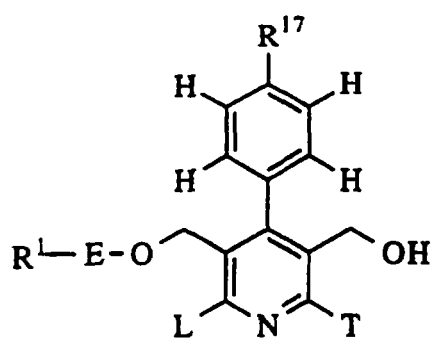
10 $R_f = 0.48$ (A13)

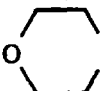
The compounds listed in Table 2(B) are synthesized according to these instructions:

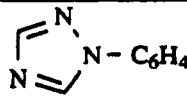
0 Table 2(B):

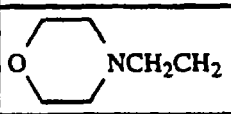
Example No.	R ¹	R _f (solvents)
16		0.46 (A13)
17		0.33 (A13)
18		0.86 (A13)
19		0.48 (A13)
20		0.35 (A13)
21		0.39 (A13)

0 Table 3(B)



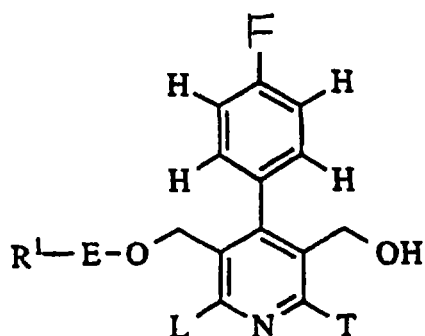
Ex.	R ¹⁷	R ¹ -E	T	L	R _f (solvent)
22	F	4-F-C ₆ H ₄	CH(CH ₃) ₂	CH(CH ₃) ₂	0.43 (A5)
23	F	4-CF ₃ -C ₆ H ₄	CH(CH ₃) ₂	CH(CH ₃) ₂	0.40 (A5)
24	F	3-CF ₃ -C ₆ H ₄	CH(CH ₃) ₂	CH(CH ₃) ₂	0.47 (A5)
25	F	2-CF ₃ -C ₆ H ₄	CH(CH ₃) ₂	CH(CH ₃) ₂	0.41 (A5)
26	F	4-F-C ₆ H ₄ (CH ₂) ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.17 (A3)
27	H	2-CF ₃ -C ₆ H ₄ (CH ₂) ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.38 (A5)
28	F	2-F-C ₆ H ₄ (CH ₂) ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.16 (A3)
29	F	4-CF ₃ -C ₆ H ₄ CHCH ₃	CH(CH ₃) ₂	CH(CH ₃) ₂	0.17 (A3)
30	F	3-CF ₃ -C ₆ H ₄ (CH ₂) ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.49 (A5)
31	F	3-CF ₃ -C ₆ H ₄ CHCH ₃	CH(CH ₃) ₂	CH(CH ₃) ₂	0.47 (A5)
32	F	 NCH ₂ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.20 (A11)
33	F	(4-pyridyl)CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.16 (A9)

Ex.	R ¹⁷	R ¹ -E	T	L	R _f (solvent)
34	F	(3-pyridyl)CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.20 (A9)
35	F	(2-pyridyl)CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.38 (A9)
36	F	4-Ph-C ₆ H ₄	CH(CH ₃) ₂	CH(CH ₃) ₂	0.24 (A4)
37	F	3-Ph-C ₆ H ₄	CH(CH ₃) ₂	CH(CH ₃) ₂	0.27 (A4)
38	F	2-Ph-C ₆ H ₄	CH(CH ₃) ₂	CH(CH ₃) ₂	0.26 (A4)
39	F	4-F-C ₆ H ₄ (CH ₂) ₃	CH(CH ₃) ₂	CH(CH ₃) ₂	0.14 (A3)
40	F		CH(CH ₃) ₂	CH(CH ₃) ₂	0.13 (A9)
41	F	(1-naphthyl)CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.14 (A3)
42	F	2-naphthyl(CH ₂) ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.15 (A3)
43	F	1-naphthyl(CH ₂) ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.15 (A3)
44	F	C ₆ H ₅	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.54 (A5)
45	F	4-F-C ₆ H ₄	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.42 (A5)
46	F	4-CF ₃ -C ₆ H ₄	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.40 (A5)
47	F	3-CF ₃ -C ₆ H ₄ -	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.45 (A5)
48	F	2-CF ₃ -C ₆ H ₄	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.33 (A5)
49	F	4-F-C ₆ H ₄ (CH ₂) ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.15 (A3)
50	H	2-CF ₃ -C ₆ H ₄ (CH ₂) ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.41 (A5)

Ex.	R ¹⁷	R ¹ -E	T	L	R _f (solvent)
51	F	2-F-C ₆ H ₄ (CH ₂) ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.14 (A3)
52	F	4-CF ₃ -C ₆ H ₄ CHCH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.11 (A3)
53	F	3-CF ₃ -C ₆ H ₄ (CH ₂) ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.43 (A5)
54	F	3-CF ₃ -C ₆ H ₄ CHCH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.42 (A5)
55	F		4-F-C ₆ H ₄	CH(CH ₃) ₂	0.48 (A9)
56	F	(2-pyridyl)CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.20 (A9)
57	F	(3-pyridyl)CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.19 (A9)
58	F	4-F-C ₆ H ₄ (CH ₂) ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.33 (A5)
59	F	(4-pyridyl)CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.25 (A11)
60	F	2-Ph-C ₆ H ₄	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.38 (A5)
61	F	3-Ph-C ₆ H ₄	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.32 (A5)
62	F	4-Ph-C ₆ H ₄	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.33 (A5)
63	F	2-naphthyl(CH ₂)	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.33 (A5)
64	F	1-naphthyl(CH ₂)	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.32 (A5)
65	F	2-naphthyl(CH ₂) ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.34 (A5)
66	F	1-naphthyl(CH ₂) ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.34 (A3)
67	F	4-CF ₃ O-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.31 (A5)

Ex.	R ¹⁷	R ¹ -E	T	L	R _f (solvent)
68	F	3-CF ₃ O-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.34 (A5)
69	F	3-CF ₃ -C ₆ H ₄ (CH ₂) ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.16 (A4)
70	F	4-CF ₃ O-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.35 (A5)
71	F	3-CF ₃ O-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.33 (A5)
72	F	3-CF ₃ -C ₆ H ₄ (CH ₂) ₃	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.28 (A4)
73	F	4-F-C ₆ H ₄ O(CH ₂) ₂	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.67 (A7)
74	F	3-CF ₃ -C ₆ H ₄	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.46 (A5)
75	F	4-CF ₃ -C ₆ H ₄	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.42 (A5)
76	F	3-CF ₃ -C ₆ H ₄ (CH ₂) ₂	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.42 (A5)
77	F	3-CF ₃ O-C ₆ H ₄ CH ₂	3-CF ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.33 (A5)
78	F	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	4-F-C ₆ H ₄	0.20 (A7)

0 Table 4(B)

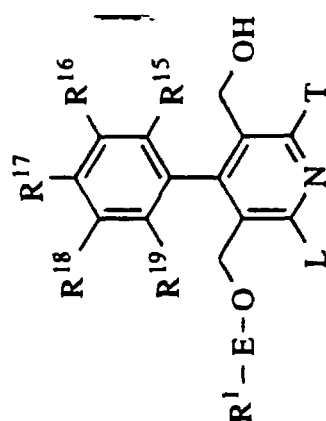


Ex.	R ¹ -E	T	L	R _f (solvent)
79	2-CN-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.16 (A3)
80	3-CN-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.10 (A3)
81	4-CN-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.10 (A3)
82	4-F-C ₆ H ₄ CH ₂	<i>cyclo</i> -C ₃ H ₅	CH(CH ₃) ₂	0.46 (A5)
83	4-F-C ₆ H ₄ CH ₂	C ₂ H ₅	CH(CH ₃) ₂	0.36 (A5)
84	C ₆ H ₅ CH ₂	C ₂ H ₅	CH(CH ₃) ₂	0.36 (A5)
85	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	pyrrolidin-1-yl	0.10 (A3)
86	3-CF ₃ -C ₆ H ₄ CH ₂	CH(CH ₃) ₂	<i>cyclo</i> -C ₆ H ₁₁	0.15 (A3)
87	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	<i>cyclo</i> -C ₆ H ₁₁	0.15 (A3)
88	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	2-CH ₃ -C ₆ H ₄	0.12 (A3)
89	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	4-Cl-C ₆ H ₄	0.19 (A3)
90	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄ (CH ₂) ₂	CH(CH ₃) ₂	0.11 (A3)
91	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CF ₃	0.24 (A5)

Ex.	R ¹ -E	T	L	R _f (solvent)
92	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CF ₃	0.25 (A5)
93	3-CF ₃ -C ₆ H ₄ CH ₂	2,4-F ₂ -C ₆ H ₃	<i>cyclo</i> -C ₅ H ₉	0.18 (A4)
94	4-CF ₃ -C ₆ H ₄ CH ₂	2,4-F ₂ -C ₆ H ₃	<i>cyclo</i> -C ₅ H ₉	0.22 (A4)

0

Table 5(B):



Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ¹ -E	T	L	R _f (solvent)
95	H	H	F	H	H	C ₆ H ₅ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.41 (A3)
96	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.20 (A3)
97	H	H	F	H	H	3-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.17 (A3)
98	H	H	F	H	H	2-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.21 (A3)
99	H	H	F	H	H	4-(benzothiazol-2-yl)-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.09 (A3)
100	H	H	F	H	H	4-CF ₃ O-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.25 (A3)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
101	H	H	F	H	H	2-naphthyl-CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.20 (A3)
102	H	H	F	H	H	4-[(4-tolyl)SO ₂]-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.13 (A4)
103	H	H	F	H	H	4-Cl-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.23 (A4)
104	H	H	F	H	H	4-CH ₃ O-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.17 (A3)
105	H	H	F	H	H	3-CH ₃ O-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.27 (A3)
106	H	H	F	H	H	3,4-F ₂ -C ₆ H ₃ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.15 (A3)
107	H	H	F	H	H	2,4-F ₂ -C ₆ H ₃ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.25 (A3)
108	H	H	F	H	H	2-CH ₃ -C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.30 (A3)
109	H	H	F	H	H	3-CH ₃ -C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.68 (A5)
110	H	H	F	H	H	4-CH ₃ -C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.61 (A5)

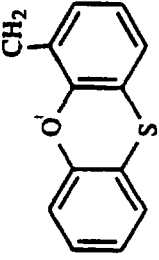
Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
111	H	H	F	H	H	4-F-C ₆ H ₄ CHCH ₃	CH(CH ₃) ₂	CH(CH ₃) ₂	0.21 (A3)
112	H	H	F	H	H	2,6-(CH ₃) ₂ -4-(<i>i</i> -C ₄ H ₉)-C ₆ H ₂ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.25 (A3)
113	H	H	F	H	H	4-(<i>i</i> -C ₃ H ₇)-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.22 (A3)
114	H	H	F	H	H	2,4,6-(<i>i</i> -C ₃ H ₇) ₃ -C ₆ H ₂ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.36 (A3)
115	H	H	F	H	H	3-(C ₆ H ₅ O)-5-CH ₃ -C ₆ H ₃ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.25 (A3)
116	H	H	F	H	H	2,4-Cl ₂ -C ₆ H ₃ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.24 (A3)
117	H	H	F	H	H	3-CF ₃ -4-Cl-C ₆ H ₃ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.19 (A3)
118	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.13 (A3)
119	H	H	F	H	H	C ₆ H ₅ CH ₂	CH(CH ₃) ₂	CH ₃	0.11 (A3)
120	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH ₃	0.29 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
121	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH ₃	0.13 (A11)
122	H	H	F	H	H	C ₆ H ₅ CH ₂	CH ₃	cyclo-C ₃ H ₅	0.14 (A3)
123	H	H	F	H	H	C ₆ H ₅ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.53 (A5)
124	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.47 (A5)
125	H	H	F	H	H	C ₆ H ₅ CH ₂	CH(CH ₃) ₂	cyclo-C ₅ H ₉	0.57 (A5)
126	H	H	F	H	H	C ₆ H ₅ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.23 (A3)
127	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	C ₆ H ₅	CH(CH ₃) ₂	0.43 (A5)
128	H	H	F	H	H	3-F-C ₆ H ₄ CH ₂	C ₆ H ₅	CH(CH ₃) ₂	0.13 (A3)
129	H	H	F	H	H	2-F-C ₆ H ₄ CH ₂	C ₆ H ₅	CH(CH ₃) ₂	0.16 (A3)
130	H	H	F	H	H	4-(benzothiazol-2-yl)-C ₆ H ₄ CH ₂	C ₆ H ₅	CH(CH ₃) ₂	0.33 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
131	H	H	F	H	H	2-naphthyl-CH ₂	C ₆ H ₅	CH(CH ₃) ₂	0.31 (A4)
132	H	H	F	H	H	4-CF ₃ O-C ₆ H ₄ CH ₂	C ₆ H ₅	CH(CH ₃) ₂	0.31 (A4)
133	H	H	F	H	H	4-[(4-tolyl)SO ₂]-C ₆ H ₄ CH ₂	C ₆ H ₅	CH(CH ₃) ₂	0.15 (A5)
134	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	4-F-C ₆ H ₄	0.46 (A5)
135	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.57 (A5)
136	H	H	F	H	H	4-Cl-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.21 (A3)
137	H	H	F	H	H	4-(i-C ₃ H ₇)-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.20 (A3)
138	H	H	F	H	H	3-(2-F-C ₆ H ₄ O)-C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.44 (A5)
139	H	H	F	H	H	3-(4-F-C ₆ H ₄ O)-C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.41 (A5)
140	H	H	F	H	H	3,4-F ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.17 (A3)

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Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
141	H	H	F	H	H	2,4-F ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.18 (A3)
142	H	H	F	H	H	2-CH ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.09 (A2)
143	H	H	F	H	H	3-CH ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.22 (A3)
144	H	H	F	H	H	4-CH ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.23 (A3)
145	H	H	F	H	H	4-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.12 (A3)
146	H	H	F	H	H	4-F-C ₆ H ₄ CHCH ₃	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.28 (A3)
147	H	H	F	H	H	2,4-Cl ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.23 (A3)
148	H	H	F	H	H	3-CF ₃ -4-Cl-C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.16 (A3)
149	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.48 (A5)
150	H	H	F	H	H	2-Cl-4-CF ₃ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.35 (A4)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
151	H	H	F	H	H	3-[4-(C ₆ H ₅)-C ₆ H ₄ O]C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.19 (A5)
152	H	H	F	H	H	2-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.42 (A5)
153	H	H	F	H	H	3-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.46 (A5)
154	H	H	F	H	H	3-(C ₆ H ₅ O)-5-CH ₃ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.46 (A5)
155	H	H	F	H	H		4-F-C ₆ H ₄	CH(CH ₃) ₂	0.42 (A5)
156	H	H	F	H	H	3,5-(CF ₃) ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.28 (A5)
157	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	2-F-C ₆ H ₄	CH(CH ₃) ₂	0.36 (A5)
158	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	pyrrolidin-1-yl	CH(CH ₃) ₂	0.14 (A3)
159	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	cyclo-C ₆ H ₁₁	CH(CH ₃) ₂	0.58 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
160	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	cyclo-C ₆ H ₁₁	CH(CH ₃) ₂	0.53 (A5)
161	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	2-CH ₃ -C ₆ H ₄	CH(CH ₃) ₂	0.15 (A3)
162	H	H	F	H	H	3-CH ₃ -C ₆ H ₄ CH ₂	4-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.19 (A3)
163	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.28 (A3)
164	H	H	F	H	H	3,4-F ₂ -C ₆ H ₃ CH ₂	4-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.18 (A3)
165	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.20 (A3)
166	H	H	F	H	H	4-Cl-C ₆ H ₄ CH ₂	4-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.25 (A3)
167	H	H	F	H	H	2-CH ₃ -C ₆ H ₄ CH ₂	4-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.49 (A5)
168	H	H	F	H	H	4-CH ₃ -C ₆ H ₄ CH ₂	4-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.51 (A5)
169	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.29 (A4)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
170	H	H	F	H	H	2,4-Cl ₂ -C ₆ H ₃ CH ₂	4-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.19 (A3)
171	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	4-F-C ₆ H ₄	0.36 (A5)
172	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.42 (A5)
173	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.30 (A4)
174	H	H	F	H	H	3,4-F ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.09 (A3)
175	H	H	F	H	H	2,4-F ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.13 (A3)
176	H	H	F	H	H	2,4-Cl ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.13 (A3)

Table 5(B): (Continued)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
177	C ₆ H ₅ CH ₂ O	H	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	4-F-C ₆ H ₄	0.08 (A3)
178	C ₆ H ₅ CH ₂ O	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.11 (A3)
179	2-F-C ₆ H ₄ CH ₂ O	H	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.11 (A3)
180	4-F-C ₆ H ₄ CH ₂ O	H	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.17 (A3)
181	4-Cl-C ₆ H ₄ CH ₂ O	H	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.11 (A3)
182	H	2-F-C ₆ H ₄ CH ₂ O	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.17 (A3)

Table 5(B): (Continued)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
183	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH ₃	0.10 (A5)
184	H	H	F	H	H	3,4-F ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	CH ₃	0.31 (A7)
185	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH ₃	0.28 (A7)
186	H	H	F	H	H	3,4-F ₂ -C ₆ H ₃ CH ₂	3-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.73 (A7)
187	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	3-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.62 (A5)
188	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	4-F-C ₆ H ₄ (CH ₂) ₂	0.31 (A5)
189	H	H	F	H	H	3,4-F ₂ -C ₆ H ₃ CH ₂	CH(CH ₃) ₂	4-F-C ₆ H ₄ (CH ₂) ₂	0.37 (A5)
190	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	0.22 (A3)
191	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	4-F-C ₆ H ₄ CH ₂	0.19 (A3)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
192	H	H	OCH ₃	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.45 (A5)
193	H	H	Cl	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.65 (A5)
194	H	H	Cl	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.09 (A3)
195	H	Cl	H	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.15 (A3)
196	H	Cl	H	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.29 (A5)
197	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(C ₂ H ₅) ₂	0.29 (A3)
198	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(C ₂ H ₅) ₂	0.56 (A5)
199	H	Cl	Cl	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.19 (A3)
200	H	CF ₃	H	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.44 (A5)
201	H	CH ₃	H	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.51 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
202	H	CH ₃	H	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.08 (A3)
203	H	H	CH ₃	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.55 (A5)
204	H	Cl	H	Cl	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.37 (A3)
205	H	OCH ₃	H	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.37 (A5)
206	OCH ₃	H	H	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.32 (A5)
207	Cl	Cl	H	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.19 (A5)
208	H	CF ₃	Cl	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.43 (A5)
209	H	CF ₃	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.44 (A5)
210	H	Cl	CF ₃	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.54 (A5)
211	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.31 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
212	H	H	F	H	H	3,5-(CF ₃) ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.37 (A5)
213	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.23 (A4)
214	H	H	F	H	H	2,4-Cl ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.49 (A5)
215	H	H	F	H	H	3-CF ₃ -4-Cl-C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	cyclo-C ₅ H ₉	0.47 (A5)
216	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	cyclo-C ₃ H ₅	0.34 (A5)
217	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	cyclo-C ₃ H ₅	0.14 (A4)
218	H	H	F	H	H	2,4-Cl ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	cyclo-C ₃ H ₅	0.49 (A5)
219	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.38 (A5)
220	H	H	CF ₃	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.42 (A5)
221	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	4-F-C ₆ H ₄	0.33 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
222	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	4-F-C ₆ H ₄	0.24 (A5)
223	Cl	Cl	H	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.42 (A5)
224	Cl	H	H	H	H	4-F-C ₆ H ₄ CH ₂	CH(CH ₃) ₂	CH(CH ₃) ₂	0.33 (A5)
225	Cl	H	H	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	4-F-C ₆ H ₄	0.18 (A5)
226	Cl	H	Cl	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	CH(CH ₃) ₂	0.50 (A5)
227	Cl	H	Cl	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	4-F-C ₆ H ₄	0.34 (A5)
228	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	3-CF ₃ -C ₆ H ₄	CH(CH ₃) ₂	0.46 (A5)
229	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	3-CF ₃ -C ₆ H ₄	CH(CH ₃) ₂	0.47 (A5)
230	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	3-CH ₃ -C ₆ H ₄	CH(CH ₃) ₂	0.25 (A4)
231	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	3-CH ₃ -C ₆ H ₄	CH(CH ₃) ₂	0.22 (A4)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
232	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-CH ₃ -C ₆ H ₄	CH(CH ₃) ₂	0.32 (A4)
233	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-CH ₃ -C ₆ H ₄	CH(CH ₃) ₂	0.25 (A4)
234	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	2-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.20 (A5)
235	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	2-Cl-C ₆ H ₄	CH(CH ₃) ₂	0.21 (A5)
236	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-CH ₃ O-C ₆ H ₄	CH(CH ₃) ₂	0.26 (A5)
237	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-CH ₃ O-C ₆ H ₄	CH(CH ₃) ₂	0.27 (A5)
238	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	2-CH ₃ O-C ₆ H ₄	CH(CH ₃) ₂	0.18 (A5)
239	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	2-CH ₃ O-C ₆ H ₄	CH(CH ₃) ₂	0.21 (A5)
240	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	3-CH ₃ O-C ₆ H ₄	CH(CH ₃) ₂	0.14 (A4)
241	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	3-CH ₃ O-C ₆ H ₄	CH(CH ₃) ₂	0.15 (A4)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
242	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	cyclo-C ₆ H ₁₁	4-F-C ₆ H ₄	0.40 (A5)
243	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	cyclo-C ₆ H ₁₁	4-F-C ₆ H ₄	0.45 (A5)
244	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	cyclo-C ₆ H ₁₁	0.37 (A5)
245	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	cyclo-C ₆ H ₁₁	0.43 (A5)
246	H	H	F	H	H	3-CF ₃ -4-Cl-C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	cyclo-C ₆ H ₁₁	0.29 (A5)
247	H	H	F	H	H	2,4-Cl ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	cyclo-C ₆ H ₁₁	0.35 (A5)
248	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-Cl-C ₆ H ₄	cyclo-C ₅ H ₉	0.56 (A5)
249	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	3-CF ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.44 (A5)
250	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	3-CF ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.41 (A5)
251	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	cyclo-C ₄ H ₇	0.36 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
252	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	cyclo-C ₄ H ₇	0.38 (A5)
253	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	cyclo-C ₇ H ₁₃	4-F-C ₆ H ₄	0.35 (A5)
254	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	cyclo-C ₇ H ₁₃	4-F-C ₆ H ₄	0.33 (A5)
255	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	cyclo-C ₇ H ₁₃	0.39 (A5)
256	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	cyclo-C ₇ H ₁₃	0.44 (A5)
257	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	furan-2-yl	4-F-C ₆ H ₄	0.13 (A5)
258	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	furan-2-yl	0.18 (A5)
259	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	(cyclo-C ₅ H ₉)CH ₂	0.25 (A5)
260	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	(cyclo-C ₅ H ₉)CH ₂	0.23 (A5)
261	H	H	F	H	H	3,5-(CF ₃) ₂ -C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	(cyclo-C ₅ H ₉)CH ₂	0.27 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
262	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	(cyclo-C ₆ H ₁₁)CH ₂	0.24 (A5)
263	H	H	F	H	H	4-F-C ₆ H ₄ CH ₂	4-F-C ₆ H ₄	(cyclo-C ₆ H ₁₁)CH ₂	0.25 (A5)
264	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-CF ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.40 (A5)
265	H	H	F	H	H	4-CF ₃ -C ₆ H ₄ CH ₂	4-CF ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.30 (A4)
266	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	1-naphthyl	cyclo-C ₅ H ₉	0.24 (A5)
267	H	H	F	H	H	4-CF ₃ -C ₆ H ₄ CH ₂	1-naphthyl	cyclo-C ₅ H ₉	0.14 (A4)
268	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	2-naphthyl	cyclo-C ₅ H ₉	0.32 (A5)
269	H	H	F	H	H	4-CF ₃ -C ₆ H ₄ CH ₂	2-naphthyl	cyclo-C ₅ H ₉	0.23 (A4)
270	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	3-CH ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.22 (A4)
271	H	H	F	H	H	4-CF ₃ -C ₆ H ₄ CH ₂	3-CH ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.21 (A4)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1,E}	T	L	R _f (solvent)
272	H	H	F	H	H	4-CF ₃ -C ₆ H ₄ CH ₂	2-CF ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.13 (A5)
273	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	2-CF ₃ -C ₆ H ₄	cyclo-C ₅ H ₉	0.18 (A5)
274	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄ CH ₂	cyclo-C ₅ H ₉	0.24 (A5)
275	H	H	F	H	H	4-CF ₃ -C ₆ H ₄ CH ₂	4-F-C ₆ H ₄ CH ₂	cyclo-C ₅ H ₉	0.26 (A5)
276	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	3,4-F ₂ -C ₆ H ₃	cyclo-C ₅ H ₉	0.29 (A4)
277	H	H	F	H	H	4-CF ₃ -C ₆ H ₄ CH ₂	3,4-F ₂ -C ₆ H ₃	cyclo-C ₅ H ₉	0.30 (A4)
278	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	cyclo-C ₅ H ₉	cyclo-C ₅ H ₉	0.23 (A3)
279	H	H	F	H	H	4-CF ₃ -C ₆ H ₄ CH ₂	cyclo-C ₅ H ₉	cyclo-C ₅ H ₉	0.27 (A3)
280	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	3-CF ₃ -C ₆ H ₄ (CH ₂) ₂	cyclo-C ₅ H ₉	0.35 (A5)
281	H	H	F	H	H	4-CF ₃ -C ₆ H ₄ CH ₂	3-CF ₃ -C ₆ H ₄ (CH ₂) ₂	cyclo-C ₅ H ₉	0.33 (A5)

Ex.	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸	R ¹⁹	R ^{1-E}	T	L	R _f (solvent)
282	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	3-CF ₃ -C ₆ H ₄ (CH ₂) ₂	3-CF ₃ -C ₆ H ₄ (CH ₂) ₂	0.20 (A7)
283	H	H	F	H	H	4-CF ₃ -C ₆ H ₄ CH ₂	3-CF ₃ -C ₆ H ₄ (CH ₂) ₂	3-CF ₃ -C ₆ H ₄ (CH ₂) ₂	0.20 (A7)
284	H	H	F	H	H	3-CF ₃ -C ₆ H ₄ CH ₂	C ₂ H ₅	cyclo-C ₅ H ₉	0.36 (A6)

0 **Detailed description with reference to compounds of general formula (IC)**

In the above structural formula (IC) the following terms have the indicated meanings:

5 The term alkyl means alkyl groups which are straight chain or branched and have the designated number of carbon atoms. Examples of such alkyl groups are methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, and isohexyl.

10 The term cycloalkyl means an alkyl group which is in the form of a ring and contains the designated number of carbon atoms. Examples include the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl groups.

The term alkoxy means a group in which the alkyl portion is straight or branched and has the designated number of carbon atoms. Examples of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, and isohexoxy.

15 The term alkanoyl means groups of formula -C(O)-alkyl in which the alkyl group has the designated number of carbon atoms. Examples include: acetyl, propionyl and butanoyl.

20 The term alkanoyloxy means groups of formula -OC(O)-alkyl in which the alkyl group has the designated number of carbon atoms. Examples include -OC(O)CH₃, -OC(O)C₂H₅, and -OC(O)C₃H₇.

The term alkoxycarbonyl means groups of formula -C(O)O-alkyl in which the alkyl group has the designated number of carbon atoms. Examples include -C(O)OCH₃, -C(O)OC₂H₅, and -C(O)OC₃H₇.

25 The term cycloalkyl-alkyl means groups in which an alkyl group bears a cycloalkyl substituent, and the cycloalkyl and alkyl portions each contain the designated number of carbon atoms. Examples include -C₂H₄-C₅H₉.

The term phenyl-alkyl means groups in which an alkyl group bears a phenyl substituent, and the alkyl portion contains the designated number of carbon atoms. Examples include -C₂H₄-C₆H₅.

30 The term naphthyl-alkyl means groups in which an alkyl group bears a naphthyl substituent, and the alkyl portion contains the designated number of carbon atoms. Examples include -C₂H₄-C₁₀H₇.

35 The term pyridyl-alkyl means groups in which an alkyl group bears a pyridyl substituent, and the alkyl portion contains the designated number of carbon atoms. Examples include -C₂H₄-pyridyl.

0 The term alkenyl means straight chain or branched groups having the designated number of carbon atoms and containing a carbon-carbon double bond. Examples include: ethenyl, propen-1-yl, propen-2-yl and penten-1-yl.

 The term alkynyl means straight chain or branched groups having the designated number of carbon atoms and containing a carbon-carbon triple bond.
5 Examples include ethynyl, propyn-1-yl and butyn-1-yl.

 The term halogen means the halogen atoms fluorine, chlorine, bromine and iodine.

 The term "substituted" is defined implicitly by the exemplary substituents disclosed for the various substituted groups in the above discussion of general
10 formula (IC). These lists of exemplary substituents are not intended to be considered as limiting; those skilled in the art will recognize that other similar substituents can also be employed.

 Certain of the above defined terms may occur more than once in the formulae employed herein, and upon such occurrence each term shall be defined
15 independently of the other.

 Preferred and most preferred groups constituting the compounds of general formula (IC) are as follows:

 X preferably represents CR^8 .

20 When X is CR^8 , R^8 is preferably hydrogen, halogen, trifluoromethyl or (C₁-C₁₀) alkyl. R^8 is most preferably hydrogen.

R^{1a} and R^{1b} preferably are independently trifluoromethyl, (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₂-C₁₀)-alkenyl, substituted (C₂-C₁₀)-alkenyl, (C₃-C₇)-cycloalkyl, or (C₃-C₇)-cycloalkenyl. R^{1a} and R^{1b} most preferably are
25 independently (C₁-C₆)-alkyl or (C₂-C₆)-alkenyl.

R^2 is preferably (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₂-C₁₀)-alkenyl or substituted (C₂-C₁₀)-alkenyl. The substituents on the substituted alkyl and substituted alkenyl R^2 groups preferably are independently from 1 to 3 of halogen, phenyl, substituted phenyl, -C(O)NR⁴R⁵, or -S(O)_mR⁷ wherein m is 0, 1, or 2. Most
30 preferably, the substituents are halogen or -S(O)_mR⁷ wherein m=0.

 The groups R^4 and R^5 are preferably independently hydrogen, (C₁-C₆) alkyl, (C₃-C₆)-alkenyl, (C₃-C₇)-cycloalkyl, phenyl, substituted phenyl, phenyl-(C₁-C₆)-alkyl, substituted phenyl-(C₁-C₆)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C₁-C₆)-alkyl, or substituted naphthyl-(C₁-C₆)-alkyl. R^4 and R^5 are most
35 preferably independently hydrogen, (C₁-C₆)-alkyl, (C₃-C₇)-cycloalkyl, phenyl, substituted phenyl, phenyl (C₁-C₆)-alkyl or substituted phenyl (C₁-C₆)-alkyl.

0 When R^4 and R^5 are joined together to form $-(CH_2)_rA(CH_2)_s-$, in this linkage it is preferable that the subscripts r and s are independently 1 to 3, and A is CHR^6 , NR^6 , O , or $S(O)_n$ wherein n is 0, 1, or 2, and R^6 is hydrogen, (C₁-C₆) alkyl, phenyl, or phenyl (C₁-C₆) alkyl.

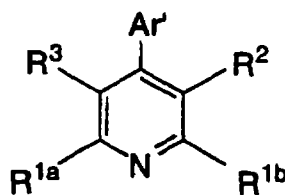
R^7 is preferably (C₁-C₆)-alkyl, phenyl, substituted phenyl, phenyl-(C₁-C₆)-alkyl, substituted phenyl-(C₁-C₆)-alkyl, pyridyl, substituted pyridyl, pyridyl-(C₁-C₆)-alkyl, or substituted pyridyl-(C₁-C₆)-alkyl. R^7 is most preferably (C₁-C₆)-alkyl, phenyl, substituted phenyl, phenyl (C₁-C₆)-alkyl or substituted phenyl (C₁-C₆)-alkyl. The substituents on the substituted R^7 groups are preferably 1-3 of halogen, trifluoromethyl, or (C₁-C₆) alkyl.

10 When R^2 and R^{1b} are joined to form an alkylene bridge, this bridge preferably contains 3 or 4 carbon atoms.

R^3 is preferably (C₁-C₆) alkanoyl, substituted (C₁-C₆)-alkyl, or substituted (C₃-C₆)-alkenyl, wherein the substituents are preferably from 1 to 3 hydroxyl groups. Most preferably, R^3 is substituted (C₁-C₆)-alkyl or substituted (C₃-C₆)-alkenyl where the substituents are from 1 to 2 hydroxyl groups.

Preferences for the aromatic and heteroaromatic groups Ar of structural formula (IC) are presented below. Compounds of general formula (IC) are further classified into four subsets represented by structural formulae 1A, 1B, 1C, and 1D, which relate respectively to 4-heteroaryl-substituted pyridines, 4-aryl-substituted pyridines, heteroaryl-substituted benzenes, and aryl-substituted benzenes.

The 4-heteroaryl pyridine compounds included within formula (IC) have the formula 1A



1A

wherein

R^{1a} and R^{1b} are independently trifluoromethyl, (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₂-C₁₀)-alkenyl, substituted (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, substituted (C₂-C₁₀)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkenyl, or (C₁-C₆)-alkanoyl. The substituents on the substituted alkyl, substituted alkenyl, and substituted alkynyl R^{1a} and R^{1b} groups are independently from 1 to 3 of, for

0 example, $-OR^4$, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^4R^5$, $-NR^4R^5$, or phenyl which is optionally substituted with from 1 to 3 of, for example, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy groups.

The groups R^4 and R^5 are independently hydrogen, (C₁-C₆)-alkyl, (C₃-C₆)-alkenyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₆)-alkyl, phenyl, substituted
5 phenyl, phenyl-(C₁-C₆)-alkyl, substituted phenyl-(C₁-C₆)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C₁-C₆)-alkyl, or substituted naphthyl-(C₁-C₆)-alkyl. The substituents on the substituted phenyl or substituted naphthyl R^4 and R^5 groups are 1 to 3 of, for example, halogen, cyano, trifluoromethyl, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy groups.

10 R^4 and R^5 may be joined together to form $-(CH_2)_rA(CH_2)_s-$ wherein the subscripts r and s are independently 1 to 3 and A is CHR^6 , NR^6 , O , or $S(O)_n$ in which n is 0, 1, or 2; and R^6 is hydrogen, (C₁-C₆)-alkyl, piperidin-1-yl, phenyl, or phenyl-(C₁-C₆)-alkyl.

R^2 is (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₂-C₁₀)-alkenyl, substituted (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, substituted (C₂-C₁₀)-alkynyl, (C₃-C₆)-cycloalkyl-(C₁-C₆)-alkyl, or substituted (C₃-C₆)-cycloalkyl-(C₁-C₆)-alkyl. The substituents on the substituted alkyl, substituted alkenyl, substituted alkynyl, and substituted cycloalkyl R^2 groups are independently from 1 to 3 of halogen, phenyl, substituted phenyl, 1,3-dioxolan-2-yl, $-C(O)NR^4R^5$, or $-S(O)_mR^7$ wherein m is 0, 1,
15 or 2. The substituents on the substituted phenyl R^2 substituent group are from 1 to 3 of, for example, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy.

R^7 is (C₁-C₆)-alkyl, phenyl, substituted phenyl, phenyl-(C₁-C₆)-alkyl, substituted phenyl-(C₁-C₆)-alkyl, pyridyl, substituted pyridyl, pyridyl-(C₁-C₆)-alkyl, substituted pyridyl-(C₁-C₆)-alkyl, naphthyl, substituted naphthyl, naphthyl-
25 (C₁-C₆)-alkyl, or substituted naphthyl-(C₁-C₆)-alkyl. The substituents on the substituted phenyl, substituted pyridyl or substituted naphthyl R^7 groups are from 1 to 5 of, for example, halogen, trifluoromethyl, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, nitro, cyano, or hydroxy.

R^2 and R^{1b} may be joined to form an alkylene bridge containing from 3 to 5
30 carbon atoms, between the ring carbon atoms to which R^2 and R^{1b} are attached.

R^3 is hydroxy, trifluoroacetyl, (C₁-C₆)-alkanoyl, substituted (C₁-C₆)-alkyl, or substituted (C₃-C₆)-alkenyl. The substituents on the substituted alkyl and substituted alkenyl R^3 groups from 1 to 3 hydroxy or trifluoromethyl groups.

Ar' is an optionally substituted heteroaromatic ring. Examples of possible
35 Ar' groups are pyridyls, furanyls, thiophenyls, pyrrolyls, imidazolyls, pyrazolyls, triazolyls, tetrazolyls, oxazolyls, isoxazolyls, thiazolyls and isothiazolyls. The

- 0 optional substituents on the group Ar' are independently 1 to 3 of, for example, halogen, (C₁-C₆)-alkyl, substituted (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, substituted (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, substituted (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, cyano, nitro, trifluoromethyl, -OR⁴, -C(O)R⁴, -OC(O)R⁴, -CO₂R⁴, -NR⁴R⁵, -C(O)NR⁴R⁵, or -S(O)_mR⁷. The substituents on the substituted alkyl, substituted
- 5 alkenyl, and substituted alkynyl substituent groups on Ar' are from 1 to 3 of, for example, halogen, hydroxy, -NR⁴R⁵, phenyl, or substituted phenyl in which the phenyl group may bear, for example, one or more halogen, (C₁-C₄) alkyl, or (C₁-C₄) alkoxy groups.

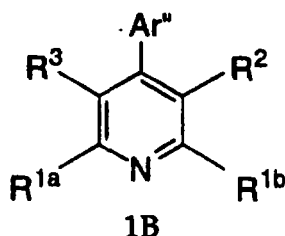
10 Pharmaceutically acceptable salts of these materials are within the scope of the invention.

15 In formula 1A, the preferred and most preferred groups R^{1a}, R^{1b}, R², R³, as well as the additional groups R⁴, R⁵, R⁶, and R⁷ embedded therein, and the various substituent groups thereon, are as defined in connection with general formula (IC) above.

20 In formula 1A, heteroaromatic ring Ar' is preferably selected from the group consisting of pyridyls, furanyls, thiophenyls, pyrazolyls, triazolyls, oxazolyls and thiazolyls, and the optional substituents on Ar' are preferably independently from 1 to 3 of, for example, halogen, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, cyano, -OR⁴, or -OC(O)R⁴ where R⁴ is hydrogen, (C₁-C₆) alkyl, phenyl (C₁-C₆) alkyl or substituted phenyl (C₁-C₆) alkyl where the phenyl substituents are from 1 to 3 of halogen or (C₁-C₄) alkyl. Heteroaromatic ring Ar' is most preferably selected from the group consisting of pyridyls, furanyls and thiophenyls, and the optional substituents thereon are most preferably

25 independently from 1 to 3 of, for example, halogen, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, -OR⁴, or -OC(O)R⁴ where R⁴ is hydrogen or (C₁-C₆) alkyl.

The 4-aryl-substituted pyridines included within formula (IC) have the formula 1B



30 wherein

0 R^{1a} and R^{1b} are independently trifluoromethyl, (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₂-C₁₀)-alkenyl, substituted (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, substituted (C₂-C₁₀)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkenyl, or (C₁-C₆)-alkanoyl. The substituents on the substituted alkyl, substituted alkenyl, and substituted alkynyl R^{1a} and R^{1b} groups are independently from 1 to 3 of, for
5 example, -OR⁴, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁴R⁵, -NR⁴R⁵, or phenyl which is optionally substituted with from 1 to 3 halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy groups.

The groups R⁴ and R⁵ are independently hydrogen, (C₁-C₆)-alkyl, (C₃-C₆)-alkenyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₆)-alkyl, phenyl, substituted
10 phenyl, phenyl-(C₁-C₆)-alkyl, substituted phenyl-(C₁-C₆)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C₁-C₆)-alkyl, or substituted naphthyl-(C₁-C₆)-alkyl. The substituents on the substituted phenyl or substituted naphthyl R⁴ and R⁵ groups are 1 to 3 of, for example, halogen, cyano, trifluoromethyl, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy groups.

15 R⁴ and R⁵ may be joined together to form -(CH₂)_rA(CH₂)_s- wherein the subscripts r and s are independently 1 to 3 and A is CHR⁶, NR⁶, O, or S(O)_n in which n is 0, 1, or 2; and R⁶ is hydrogen, (C₁-C₆)-alkyl, piperidin-1-yl, phenyl, or phenyl-(C₁-C₆)-alkyl.

R² is (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₂-C₁₀)-alkenyl, substituted (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, substituted (C₂-C₁₀)-alkynyl, (C₃-C₆)-cycloalkyl-(C₁-C₆)-alkyl, or substituted (C₃-C₆)-cycloalkyl-(C₁-C₆)-alkyl. The substituents on the substituted alkyl, substituted alkenyl, substituted alkynyl, and substituted cycloalkyl R² groups are independently from 1 to 3 of halogen, phenyl, substituted phenyl, 1,3-dioxolan-2-yl, -C(O)NR⁴R⁵, or -S(O)_mR⁷ wherein m is 0, 1,
20 or 2. The substituents on the substituted phenyl R² substituent group are from 1 to 3 of, for example, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy.

R⁷ is (C₁-C₆)-alkyl, phenyl, substituted phenyl, phenyl-(C₁-C₆)-alkyl, substituted phenyl-(C₁-C₆)-alkyl, pyridyl, substituted pyridyl, pyridyl-(C₁-C₆)-alkyl, substituted pyridyl-(C₁-C₆)-alkyl, naphthyl, substituted naphthyl, naphthyl-
30 (C₁-C₆)-alkyl, or substituted naphthyl-(C₁-C₆)-alkyl. The substituents on the substituted phenyl, substituted pyridyl or substituted naphthyl R⁷ groups are from 1 to 5 of, for example, halogen, trifluoromethyl, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, nitro, cyano, or hydroxy.

R² and R^{1b} may be joined to form an alkylene bridge containing from 3 to 5
35 carbon atoms, between the ring carbon atoms to which R² and R^{1b} are attached.

0 R^3 is hydroxy, trifluoroacetyl, (C_1-C_6) -alkanoyl, substituted (C_1-C_6) -alkyl, or substituted (C_3-C_6) -alkenyl. The substituents on the substituted alkyl and substituted alkenyl R^3 groups are from 1 to 3 hydroxy or trifluoromethyl groups.

5 Ar'' is an optionally substituted aromatic ring. Examples of possible Ar'' groups are phenyls and naphthyls. The optional substituents on the group Ar'' are independently 1 to 3 of, for example, halogen, (C_1-C_6) -alkyl, substituted (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, substituted (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, substituted (C_2-C_6) -alkynyl, (C_3-C_7) -cycloalkyl, cyano, nitro, trifluoromethyl, $-OR^4$, $-C(O)R^4$, $-OC(O)R^4$, $-CO_2R^4$, $-NR^4R^5$, $-C(O)NR^4R^5$, or $-S(O)_mR^7$. The substituents on the substituted alkyl, substituted alkenyl, and substituted alkynyl substituent groups on

10 Ar'' are from 1 to 3 of, for example, halogen, hydroxy, $-NR^4R^5$, phenyl, or substituted phenyl in which the phenyl group may bear, for example, one or more halogen, (C_1-C_4) alkyl, or (C_1-C_4) alkoxy groups.

Pharmaceutically acceptable salts of these materials are within the scope of the invention.

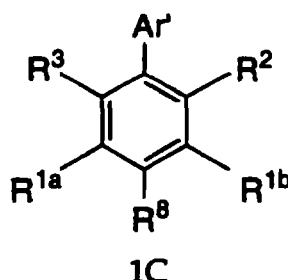
15 In formula 1B, the preferred and most preferred groups R^{1a} , R^{1b} , R^2 , R^3 , as well as the additional groups R^4 , R^5 , R^6 , and R^7 embedded therein, and the various substituent groups thereon, are as defined in connection with general formula (IC) above.

20 In formula 1B, aromatic ring Ar'' preferably is a phenyl ring wherein the optional substituents are preferably independently from 1 to 3 of, for example, halogen, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, (C_3-C_7) -cycloalkyl, cyano, $-OR^4$ or $-OC(O)R^4$, where R^4 is hydrogen, (C_1-C_6) alkyl, phenyl (C_1-C_6) alkyl or substituted phenyl (C_1-C_6) alkyl where the phenyl substituents are from 1

25 to 3 of halogen or (C_1-C_4) alkyl. Most preferably, the optional substituents are from 1 to 3 of, for example, halogen, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, $-OR^4$ or $-OC(O)R^4$, where R^4 is hydrogen or (C_1-C_6) alkyl.

30

0 The heteroaryl-substituted benzenes included within formula (IC) have the formula 1C



wherein

5 R^8 represents hydrogen, halogen, trifluoromethyl, phenyl, substituted phenyl, (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₁-C₆)-alkoxy, (C₃-C₇)-cycloalkyl, phenyl-(C₁-C₃)-alkoxy, (C₁-C₆)-alkanoyloxy, (C₁-C₆)-alkoxycarbonyl, carboxy, formyl, or -NR⁴R⁵. The substituents on the substituted phenyl or substituted alkyl R^8 groups are from 1 to 3 of, for example, hydroxy, fluoro, (C₁-C₆)-alkoxy, (C₃-C₇)-cycloalkyl, phenyl, phenyl-(C₁-C₃)-alkoxy, (C₁-C₆)-alkanoyloxy, (C₁-C₆)-alkoxycarbonyl, carboxy, formyl, or -NR⁴R⁵.

10 The groups R^4 and R^5 are independently hydrogen, (C₁-C₆)-alkyl, (C₃-C₆)-alkenyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₆)-alkyl, phenyl, substituted phenyl, phenyl-(C₁-C₆)-alkyl, substituted phenyl-(C₁-C₆)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C₁-C₆)-alkyl, or substituted naphthyl-(C₁-C₆)-alkyl. The substituents on the substituted phenyl or substituted naphthyl R^4 and R^5 groups are 1 to 3 of, for example, halogen, cyano, trifluoromethyl, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy groups.

20 R^4 and R^5 may be joined together to form -(CH₂)_rA(CH₂)_s- wherein the subscripts r and s are independently 1 to 3 and A is CHR⁶, NR⁶, O, or S(O)_n in which n is 0, 1, or 2; and R^6 is hydrogen, (C₁-C₆)-alkyl, piperidin-1-yl, phenyl, or phenyl-(C₁-C₆)-alkyl.

25 R^{1a} and R^{1b} are independently trifluoromethyl, (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₂-C₁₀)-alkenyl, substituted (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, substituted (C₂-C₁₀)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkenyl, or (C₁-C₆)-alkanoyl. - The substituents on the substituted alkyl, substituted alkenyl, and substituted alkynyl R^{1a} and R^{1b} groups are independently from 1 to 3 of, for example, -OR⁴, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁴R⁵, -NR⁴R⁵, or phenyl which is optionally substituted with from 1 to 3 of, for example, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy groups.

30 R^2 is (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₂-C₁₀)-alkenyl, substituted (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, substituted (C₂-C₁₀)-alkynyl, (C₃-C₆)-cycloalkyl-(C₁-C₆)-alkyl, or substituted (C₃-C₆)-cycloalkyl-(C₁-C₆)-alkyl. The

0 substituents on the substituted alkyl, substituted alkenyl, substituted alkynyl, and substituted cycloalkyl R^2 groups are independently from 1 to 3 of halogen, phenyl, substituted phenyl, 1,3-dioxolan-2-yl, $-C(O)NR^4R^5$, or $-S(O)_mR^7$ wherein m is 0, 1, or 2. The substituents on the substituted phenyl R^2 substituent group are from 1 to 3 of, for example, halogen, (C_1-C_4) -alkyl, or (C_1-C_4) -alkoxy.

5 R^7 is (C_1-C_6) -alkyl, phenyl, substituted phenyl, phenyl- (C_1-C_6) -alkyl, substituted phenyl- (C_1-C_6) -alkyl, pyridyl, substituted pyridyl, pyridyl- (C_1-C_6) -alkyl, substituted pyridyl- (C_1-C_6) -alkyl, naphthyl, substituted naphthyl, naphthyl- (C_1-C_6) -alkyl, or substituted naphthyl- (C_1-C_6) -alkyl. The substituents on the substituted phenyl, substituted pyridyl or substituted naphthyl R^7 groups are from
10 1 to 5 of, for example, halogen, trifluoromethyl, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, nitro, cyano, or hydroxy.

R^2 and R^{1b} may be joined to form an alkylene bridge containing from 3 to 5 carbon atoms, between the ring carbon atoms to which R^2 and R^{1b} are attached.

15 R^3 is hydroxy, trifluoroacetyl, (C_1-C_6) -alkanoyl, substituted (C_1-C_6) -alkyl, or substituted (C_3-C_6) -alkenyl. The substituents on the substituted alkyl and substituted alkenyl R^3 groups are from 1 to 3 hydroxy or trifluoromethyl groups.

Ar' is an optionally substituted heteroaromatic ring. Examples of possible Ar' groups are: pyridyls, furanyls, thiophenyls, pyrrolyls, imidazolyls, pyrazolyls, triazolyls, tetrazolyls, oxazolyls, isoxazolyls, thiazolyls and isothiazolyls. The
20 optional substituents on the group Ar' are independently 1 to 3 of, for example, halogen, (C_1-C_6) -alkyl, substituted (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, substituted (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, substituted (C_2-C_6) -alkynyl, (C_3-C_7) -cycloalkyl, cyano, nitro, trifluoromethyl, $-OR^4$, $-C(O)R^4$, $-OC(O)R^4$, $-CO_2R^4$, $-NR^4R^5$, $-C(O)NR^4R^5$, or $-S(O)_mR^7$. The substituents on the substituted alkyl, substituted
25 alkenyl, and substituted alkynyl substituent groups on Ar' are from 1 to 3 of, for example, halogen, hydroxy, $-NR^4R^5$, phenyl, or substituted phenyl in which the phenyl group may bear, for example, one or more halogen, (C_1-C_4) -alkyl, or (C_1-C_4) -alkoxy groups.

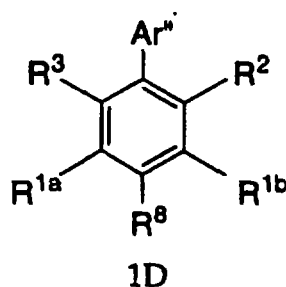
30 Pharmaceutically acceptable salts of these materials are within the scope of the invention.

In formula 1C, the preferred and most preferred groups R^{1a} , R^{1b} , R^2 , R^3 , and R^8 , as well as the additional groups R^4 , R^5 , R^6 , and R^7 embedded therein, and the various substituent groups thereon, are as defined in connection with general
35 formula (IC) above.

In formula 1C, heteroaromatic ring Ar' is preferably selected from the group consisting of pyridyls, furanyls, thiophenyls, pyrazolyls, triazolyls, oxazolyls and

- 0 thiazolylys, and the optional substituents on the group Ar' are preferably independently from 1 to 3 of, for example, halogen, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, cyano, -OR⁴, or -OC(O)R⁴, where R⁴ is hydrogen, (C₁-C₆) alkyl, phenyl (C₁-C₆) alkyl or substituted phenyl (C₁-C₆) alkyl where the phenyl substituents are from 1 to 3 of halogen or (C₁-C₄) alkyl.
- 5 Heteroaromatic ring Ar' is most preferably selected from the group consisting of pyridyls, furanyls and thiophenyls, and the optional substituents thereon are most preferably independently from 1 to 3 of, for example, halogen, (C₁-C₆) alkyl, (C₂-C₆) alkenyl, -OR⁴, or -OC(O)R⁴, where R⁴ is hydrogen or (C₁-C₆) alkyl.

- 10 The aryl-substituted benzenes included within formula (IC) have the formula 1D



wherein

- 15 R⁸ represents hydrogen, halogen, trifluoromethyl, phenyl, substituted phenyl, (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₁-C₆)-alkoxy, (C₃-C₇)-cycloalkyl, phenyl-(C₁-C₃)-alkoxy, (C₁-C₆)-alkanoyloxy, (C₁-C₆)-alkoxycarbonyl, carboxy, formyl, or -NR⁴R⁵. The substituents on the substituted phenyl or substituted alkyl R⁸ groups are from 1 to 3 of, for example, hydroxy, fluoro, (C₁-C₆)-alkoxy, (C₃-C₇)-cycloalkyl, phenyl, phenyl-(C₁-C₃)-alkoxy, (C₁-C₆)-alkanoyloxy, (C₁-C₆)-alkoxycarbonyl, carboxy, formyl, or -NR⁴R⁵.

- 20 The groups R⁴ and R⁵ are independently hydrogen, (C₁-C₆)-alkyl, (C₃-C₆)-alkenyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₆)-alkyl, phenyl, substituted phenyl, phenyl-(C₁-C₆)-alkyl, substituted phenyl-(C₁-C₆)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C₁-C₆)-alkyl, or substituted naphthyl-(C₁-C₆)-alkyl. The substituents on the substituted phenyl or substituted naphthyl R⁴ and R⁵ groups are 1 to 3 of, for example, halogen, cyano, trifluoromethyl, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy groups.

- 25 R⁴ and R⁵ may be joined together to form -(CH₂)_rA(CH₂)_s- wherein the subscripts r and s are independently 1 to 3 and A is CHR⁶, NR⁶, O, or S(O)_n in which n is 0, 1, or 2; and R⁶ is hydrogen, (C₁-C₆)-alkyl, piperidin-1-yl, phenyl, or phenyl-(C₁-C₆)-alkyl.
- 30

0 R^{1a} and R^{1b} are independently trifluoromethyl, (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₂-C₁₀)-alkenyl, substituted (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, substituted (C₂-C₁₀)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkenyl, or (C₁-C₆)-alkanoyl. The substituents on the substituted alkyl, substituted alkenyl, and substituted alkynyl R^{1a} and R^{1b} groups are independently from 1 to 3 of, for
 5 example, -OR⁴, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁴R⁵, -NR⁴R⁵, or phenyl which is optionally substituted with from 1 to 3 of, for example, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy groups.

R^2 is (C₁-C₁₀)-alkyl, substituted (C₁-C₁₀)-alkyl, (C₂-C₁₀)-alkenyl, substituted (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, substituted (C₂-C₁₀)-alkynyl, (C₃-C₆)-cycloalkyl-(C₁-C₆)-alkyl, or substituted (C₃-C₆)-cycloalkyl-(C₁-C₆)-alkyl. The
 10 substituents on the substituted alkyl, substituted alkenyl, substituted alkynyl, and substituted cycloalkyl R^2 groups are independently from 1 to 3 of halogen, phenyl, substituted phenyl, 1,3-dioxolan-2-yl, -C(O)NR⁴R⁵, or -S(O)_mR⁷ wherein m is 0, 1, or 2. The substituents on the substituted phenyl R^2 substituent group are from 1 to
 15 3 of, for example, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy.

R^7 is (C₁-C₆)-alkyl, phenyl, substituted phenyl, phenyl-(C₁-C₆)-alkyl, substituted phenyl-(C₁-C₆)-alkyl, pyridyl, substituted pyridyl, pyridyl-(C₁-C₆)-alkyl, substituted pyridyl-(C₁-C₆)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C₁-C₆)-alkyl, or substituted naphthyl-(C₁-C₆)-alkyl. The substituents on the
 20 substituted phenyl, substituted pyridyl or substituted naphthyl R^7 groups are from 1 to 5 of, for example, halogen, trifluoromethyl, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, nitro, cyano, or hydroxy.

R^2 and R^{1b} may be joined to form an alkylene bridge containing from 3 to 5 carbon atoms, between the ring carbon atoms between the ring carbon atoms to
 25 which R^2 and R^{1b} are attached.

R^3 is hydroxy, trifluoroacetyl, (C₁-C₆)-alkanoyl, substituted (C₁-C₆)-alkyl, or substituted (C₃-C₆)-alkenyl. The substituents on the substituted alkyl and substituted alkenyl R^3 groups are from 1 to 3 hydroxy or trifluoromethyl groups.

Ar" is an optionally substituted aromatic ring. Examples of possible Ar" groups are phenyls and naphthyls. The optional substituents on the group Ar are
 30 independently 1 to 3 of, for example, halogen, (C₁-C₆)-alkyl, substituted (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, substituted (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, substituted (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, cyano, nitro, trifluoromethyl, -OR⁴, -C(O)R⁴, -OC(O)R⁴, -CO₂R⁴, -NR⁴R⁵, -C(O)NR⁴R⁵, or -S(O)_mR⁷. The substituents on the
 35 substituted alkyl, substituted alkenyl, and substituted alkynyl substituent groups on Ar are from 1 to 3 of, for example, halogen, hydroxy, -NR⁴R⁵, phenyl, or

- 0 substituted phenyl in which the phenyl group may bear, for example, one or more halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy groups.

Pharmaceutically acceptable salts of these materials are within the scope of the invention.

- 5 In formula 1D, the preferred and most preferred groups R^{1a}, R^{1b}, R², R³, and R⁸, as well as the additional groups R⁴, R⁵, R⁶, and R⁷ embedded therein, and the various substituent groups thereon, are as defined in connection with general formula (IC) above.

- 10 In formula 1D, aromatic ring Ar" preferably is a phenyl ring wherein the optional substituents are preferably from 1 to 3 of, for example, halogen, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, cyano, -OR⁴ or -OC(O)R⁴, where R⁴ is hydrogen, (C₁-C₆) alkyl, phenyl (C₁-C₆) alkyl or substituted phenyl (C₁-C₆) alkyl where the phenyl substituents are from 1 to 3 of halogen or (C₁-C₄) alkyl. Most preferably, the substituents are from 1 to 3 of, for
15 example, halogen, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, -OR⁴ or -OC(O)R⁴, where R⁴ is hydrogen or (C₁-C₆) alkyl.

- Basic compounds of the invention are generally isolated in the form of their pharmaceutically acceptable acid addition salts derived using inorganic or organic
20 acids. Examples of such materials are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, and malonic acids. Compounds of the invention which contain an acidic functionality such as a carboxyl group can be isolated in the form of pharmaceutically acceptable addition salts derived using inorganic or organic bases. The salt forming ion derived from
25 such bases can be a metal ion such as sodium, potassium, lithium, calcium, magnesium, etc., or an ion of an organic base, such as an ammonium or substituted ammonium ion derived from an amine. Examples of suitable amines for this purpose include ammonia, arylalkylamines such as dibenzylamine and *N,N*-dibenzylethylenediamine, lower alkylamines such as methylamine, *t*-butylamine,
30 procaine, lower alkylpiperidines such as *N*-ethylpiperidine, cycloalkylamines such as cyclohexylamine or dicyclohexylamine, 1-adamantylamine, benzathine, or salts derived from amino acids such as arginine or lysine.

The present invention also encompasses pharmaceutically acceptable "prodrugs" of the compounds of formula (IC) which form such derivatives. These

0 are typically acylated derivatives of alcohol-containing compounds of the invention, though other types of prodrugs are known. Preparation of such derivatives is within the skill of the art.

The inhibitors of the present invention are contemplated for use in veterinary and human applications. For such applications, the active agent(s) are
5 employed in pharmaceutical compositions which comprise the active ingredient(s) plus a pharmaceutically acceptable carrier which contains one or more diluents, fillers, binders, or other excipients, depending on the administration mode and dosage form contemplated. Examples of such agents include carriers such as sucrose, lactose, or starch; lubricating agents such as magnesium stearate;
10 adjuvants, such as wetting agents; excipients such as cocoa butter or suppository wax; emulsifying and suspending agents, and sweetening, flavoring and perfuming agents and buffering agents.

The pharmaceutical compositions of the invention may also include one or more known antidiabetic agents in addition to a compound of structural formula
15 (IC). Examples of such antidiabetic agents are: α -glucosidase inhibitors such as acarbose or voglibose, insulin sensitizers such as bromocriptine, thiazolidinediones such as troglitazone, insulin secretagogues such as glimepride, sulfonylureas such as glyburide, GLP-1 and its derivatives such as insulinotropin, amylin and its derivatives such as AC-137, calcitonin, insulin and its derivatives such as HOE-901,
20 biguanides such as metformin, aldose reductase inhibitors such as tolrestat, β_3 agonists such as BTA-243, and hypocholesterolemic agents such as lovastatin.

The method of treating glucagon-mediated conditions by administering a glucagon receptor antagonist of the present invention may be practiced in mammals, including humans, which exhibit such conditions. A typical application is
25 treatment of diabetes.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

30 Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as
35 magnesium stearate. In the case of capsules, tablets and pills, the dosage forms

0 may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings such as the OROS-CT/Osmet™ and PULSINCAP™ systems from ALZA and Scherer Drug Delivery Systems.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert
5 diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions.
10 Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Alternatively intramuscular, intraarticular or subcutaneous depot injection with or without
15 encapsulation of the drug into degradable microspheres e.g., comprising poly(DL-lactide-co-glycolide) may be used to obtain prolonged sustained drug release. For improved convenience of the dosage form it may be possible to use an i.p. implanted reservoir and septum such as the Percuseal system available from Pharmacia. Improved convenience and patient compliance may also be achieved
20 by the use of either injector pens (e.g. the NovoPen or Q-pen) or needle-free jet injectors (e.g. from Bioject, Mediject or Becton Dickinson). Prolonged zero-order or other precisely controlled release such as pulsatile release can also be achieved as needed using implantable pumps with delivery of the drug through a cannula into the synovial spaces. Examples include the subcutaneously implanted osmotic
25 pumps available from ALZA, such as the ALZET osmotic pump.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients
30 such as cocoa butter or a suppository wax.

The compounds of this invention can be manufactured into the above listed formulations by the addition of various therapeutically inert, inorganic or organic carriers well known to those skilled in the art. Examples of these include, but are not limited to, lactose, corn starch or derivatives thereof, talc, vegetable oils, waxes,
35 fats, polyols such as polyethylene glycol, water, saccharose, alcohols, glycerin and the like. The formulations may be sterilized by, for example, filtration through a

0 bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. Various preservatives, emulsifiers, dispersants, flavorants, wetting agents, 5 antioxidants, sweeteners, colorants, stabilizers, salts, buffers and the like are also added, as required to assist in the stabilization of the formulation or to assist in increasing bioavailability of the active ingredient(s) or to yield a formulation of acceptable flavor or odor in the case of oral dosing.

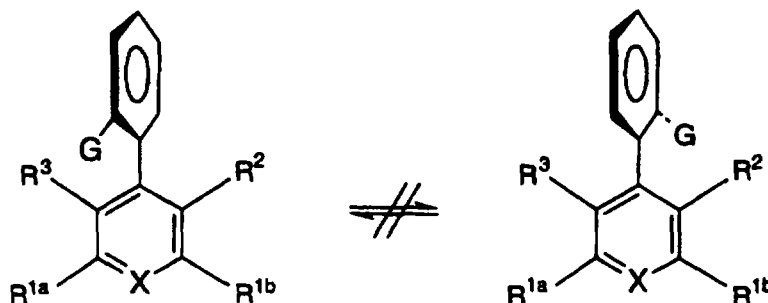
10 The amount of the pharmaceutical composition to be employed will depend on the recipient and the condition being treated. The requisite amount may be determined without undue experimentation by protocols known to those skilled in the art. Alternatively, the requisite amount may be calculated, based on a determination of the amount of target receptor which must be inhibited to treat the condition. An effective amount of active ingredient is generally in the range 0.0001 15 mg/kg to 100 mg/kg of body weight.

The treatment method of the invention is not limited to administration of the above-described pharmaceutical composition. Rather, this treatment regimen may be employed in combination with conventional treatments of diabetes (both Type I 20 and Type II) or of other conditions which are sometimes found in diabetic subjects. Thus, for example, treatment may be administered in conjunction with (a) diet restrictions and exercise; (b) insulin, or other drugs used to treat ketoacidosis; (c) any drug used for the treatment of hyperlipidemia, such as lovastatin, or cardiovascular disease, such as enalapril; (d) drugs used to treat diabetic 25 complications, such as epalrestat and (e) drugs that lower body weight, such as dexfenfluramine.

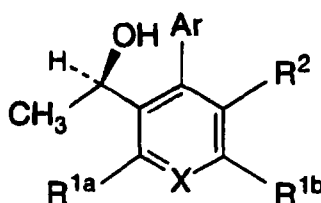
The glucagon receptor antagonists of the invention are useful not only for treatment of the pathophysiological conditions discussed above, but are also useful in other applications such as a diagnostic agent. For example, these compounds 30 can be administered to humans *in vivo* in the fasting state as a diagnostic tool to directly determine whether the glucagon receptor is functional. Serum samples taken before and after such administration can be assayed for glucose levels; comparison of the amounts of blood glucose in each of these samples would be a means for directly determining the ability of the patient's glucagon receptor to

- 0 modulate hepatic glucose output. Alternatively, compounds of the present invention may be useful for finding new glucagon antagonists. For example, a binding assay employing a radiolabeled derivative (such as ^3H) of a compound of formula (IC) would be useful in identifying new compounds that competitively bind to the glucagon receptor. Such an assay is useful in identifying structurally
- 5 novel antagonists that may offer advantages in ease of chemical modification, selectivity and oral bioavailability.

- 0 The compounds of the present invention may contain asymmetric centers on the molecule, depending upon the nature of the various substituents. Each such asymmetric center will produce two optical isomers. In certain instances, asymmetry may also be present due to restricted rotation about the central bond adjoining the two aromatic rings of the specified compounds. For example, for
- 5 certain compounds of Formula (IC) wherein Ar is taken as substituted phenyl, there exist additional isomers due to restricted rotation about the central aryl-aryl bond, depending on the substitution pattern.



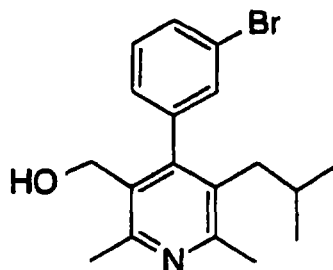
- 10 It is intended that all isomers, either by nature of asymmetric centers or by restricted rotation as described above, as separated, pure or partially purified isomers or racemic mixtures thereof, be included within the ambit of the instant invention. In the case of compounds of Formula (IC) wherein R³ is taken as 1-hydroxyethyl, it has been found that the isomer in which the hydroxy substituent is
- 15 above the plane of the structure, as seen in Formula Ic, is more active and thus more preferred over the compound in which the hydroxy substituent is below the plane of the structure.



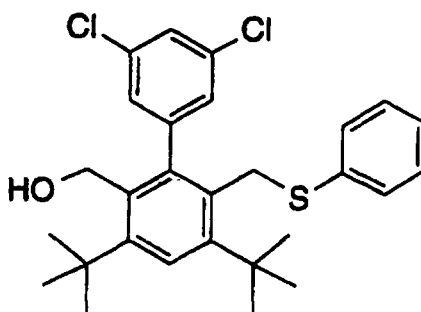
Ic

0 Representative examples of the nomenclature employed herein are given below:

2,6-Dimethyl-3-hydroxymethyl-4-(3-bromophenyl)-5-isobutylpyridine



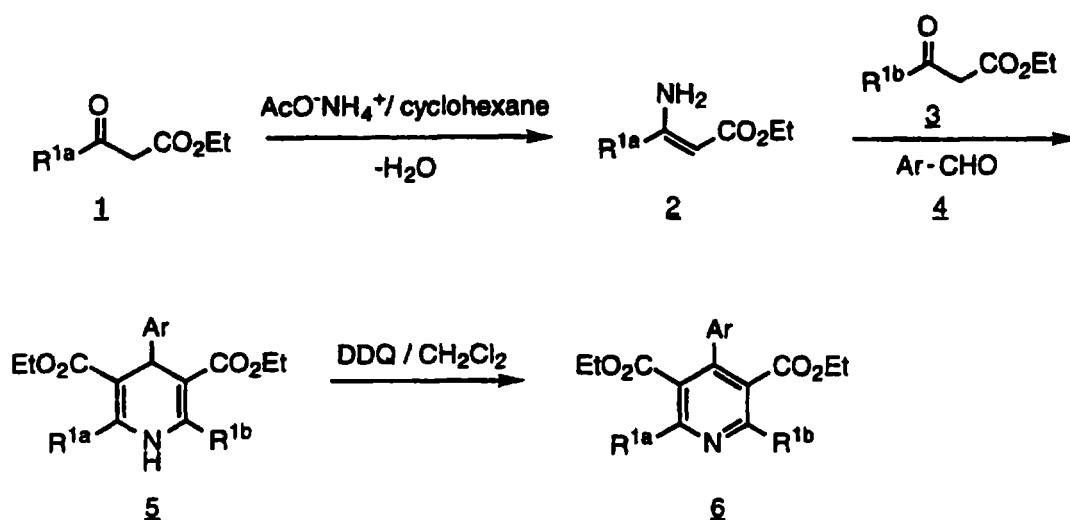
3,5-Di-*t*-butyl-2-(phenylthio)methyl-6-hydroxymethyl-3',5'-dichloro-1,1'-biphenyl



The compounds of general formula (IC) of the present invention are prepared as indicated in the following reaction Schemes.

15 The phenylpyridine compounds of formula (IC) (X= N) are prepared from a common intermediate 6 using the well-known Hantzsch pyridine synthesis, as shown in Scheme 1 (Stout, D. M.; Myers, A. I. *Chem. Rev.* 1982, 223).

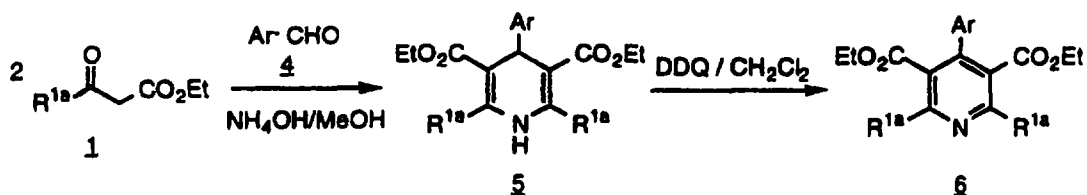
SCHEME 1



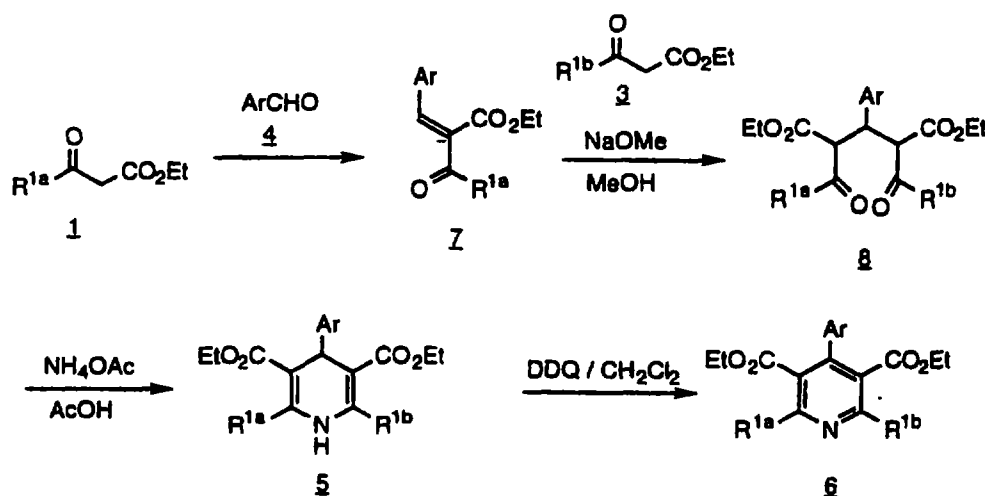
The ketoester 1, (commercially available or prepared according to the procedure of Deslongchamps, *Synth. Comm.*, 1976, 6, 169) is treated with an ammonium salt such as ammonium acetate, in an inert solvent such as cyclohexane capable of forming an azeotrope with water, to give the enamine 2. Compound 2 is then treated with the ketoester 3, which may or may not be identical to the ketoester 1, and an aromatic aldehyde, in a polar solvent such as ethanol, to produce the dihydropyridine 5. Certain substituents on aldehyde 4 may need to be protected during the Hantzsch pyridine synthesis. A description of suitable protecting groups may be found in: Protective Groups in Organic Synthesis, Second Edition, T. W. Greene, John Wiley and Sons, New York, 1991. Oxidation of 5 is achieved by any of several known methods. For example, treatment of 5 with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in a solvent such as methylene chloride (CH_2Cl_2), or with ceric ammonium nitrate (CAN) in a mixture of solvents such as aqueous acetone, affords the intermediate 6. Separation of unwanted side products and purification of intermediates is achieved by chromatography on silica gel, employing flash chromatography (Still, W.C.; Khan, M.; Mitra, A. *J. Org. Chem.*, 1978, 43, 2923)

An alternative Hantzsch pyridine synthesis of the intermediate 6, where R^{1a} and R^{1b} of formula (IC) are identical, can be accomplished following the procedure of Chucholowski (U.S. Patent 4,950,675), Scheme 2. By heating two equivalents of ketoester 1 with ammonium hydroxide and the aldehyde 4 in a polar solvent such as methanol, the dihydropyridine 5 is obtained directly. Compound 5 is oxidized to pyridine 6, according to the procedure described in Scheme 1.

0

SCHEME 2

In Scheme 3, another alternative Hantzsch pyridine synthesis of intermediate **6** is described. Ketoester **1** is condensed with aldehyde **4** by treatment with catalysts such as acetic acid and piperidine without solvent to afford intermediate **7**. Treatment of **7** with ketoester **3** in the presence of a base such as sodium methoxyde, in a polar solvent such as methanol produces the diketone **8**. Cyclization of **8** is achieved by treatment with an ammonium salt such as ammonium acetate in a polar solvent such as acetic acid to afford the previously described dihydropyridine **5** (Scheme 1), which is oxidized to the pyridine **6** according to the procedure as indicated in Scheme 1.

SCHEME 3

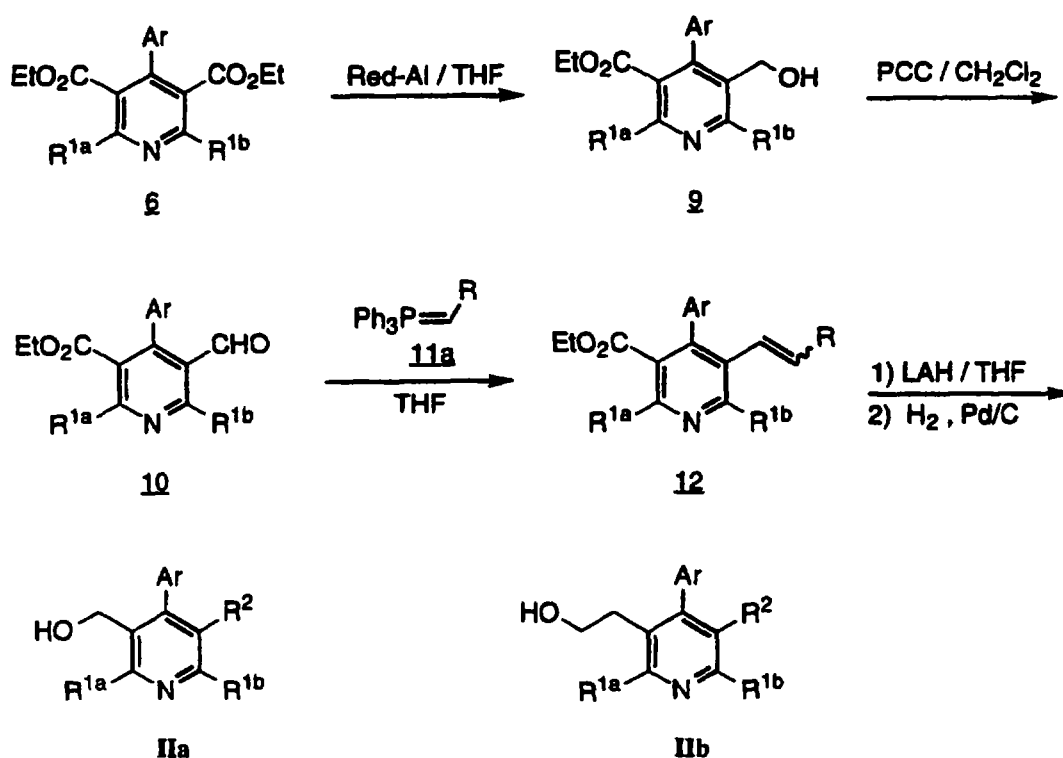
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The synthesis of aryl pyridine derivatives of formula (IC) wherein R² is alkyl and R³ is hydroxymethyl (IIa) is described in Scheme 4.

20

0

SCHEME 4



- Chemical reducing agents such as sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in an inert solvent, such as tetrahydrofuran (THF) or diethyl ether (Et_2O), can result in a monoreduction of the pyridinediester **6** to give the alcohol **9**. Oxidants such as pyridinium chlorochromate (PCC), in a solvent such as CH_2Cl_2 , convert compound **9** to the aldehyde **10**. Wittig reaction with compound **10** and an ylide **11a**, in an inert solvent such as THF or Et_2O , affords olefin **12** obtained usually, but not always, as a mixture of *E* and *Z* isomers. The reagent **11a** is prepared from an alkyl triphenyl phosphonium salt, wherein the alkyl group may contain a heteroatom, and a suitable base such as butyllithium or sodium amide, according to known methods (Maercker, A. in *Organic Reactions*, Vol. 14, Ed.; Wiley, New York, 1965, Chapter 3). Olefin **12** is successively treated with a reducing agent such as lithium aluminum hydride (LAH), in an inert solvent such as THF or Et_2O , and hydrogen in the presence of a metal catalyst, such as palladium on carbon, in a polar solvent such as ethanol, to afford compounds of formula IIa. In some of these compounds, R^2 may contain substituents such as alcohol, acetate, ester, carboxylic acid, and amide. These products can be obtained directly by the procedures of Scheme 4, with or without the use of appropriate protecting groups, or by additional steps familiar to those skilled in the art. For example, a primary alcohol can be converted to a carboxylic acid by standard methods of oxidation,

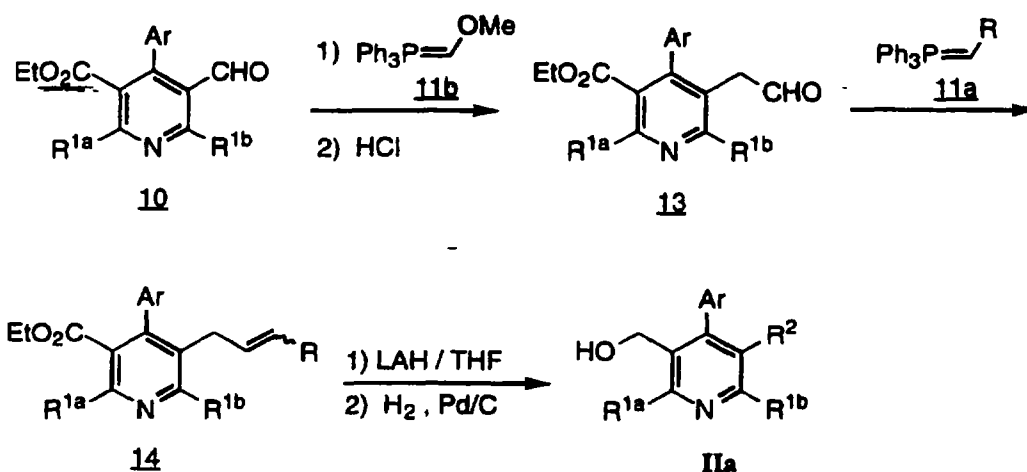
such as those described by Eisenbraun (Eisenbraun, E. J. *Org. Syn. Coll.*, 1973, 5, 310).

If the Wittig reaction is performed with methoxymethyl triphenylphosphonium as ylide (11b), followed by treatment with an acid such as hydrochloric acid, the homologous aldehyde 13 is obtained. This can undergo another Wittig reaction to afford olefin 14, (Scheme 5). This known procedure (Wittig, G.; Walter, B.; Kruck, K.-H. *Chem. Ber.* 1962, 2514) allows one to synthesize extended alkyl chain (R^2) analogs of formula IIa, which may not be directly prepared by usual Wittig reaction due to limited availability of the requisite alkyl triphenylphosphonium salt.

Oxidation of the compounds of formula IIa by the method described in Scheme 4 affords intermediates that can be converted to homologues of compounds of formula IIa, containing the $-CH_2-CH_2-$ linkage between the pyridine nucleus and the hydroxy group (IIb).

15

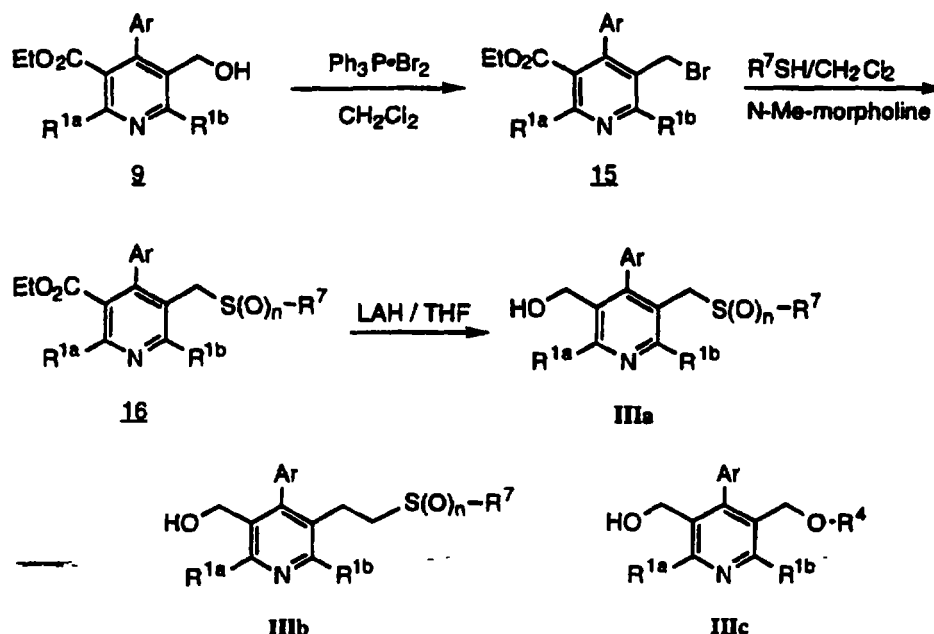
SCHEME 5



Synthesis of aryl pyridine derivatives of formula (IC) wherein R^2 is alkyl containing a heteroatom such as sulfur and R^3 is hydroxymethyl (IIIa and IIIb), is outlined in Scheme 6. Alcohol 9 is converted to an alkyl halide 15 by treatment with a suitable reagent such as dibromotriphenylphosphorane in an inert solvent. Treatment of 15 with a thiol and a base such as N-methyl morpholine in an inert solvent produces intermediate 16. The sulfur atom of compounds 16 can be oxidized ($n = 1$ or 2) by any of several known methods. For example, it can be accomplished by treatment of 16 wherein $n=0$, with an oxidant such as m-chloroperbenzoic acid in a solvent such as CH_2Cl_2 . Chemical reducing agents such

- 0 as lithium aluminum hydride (LAH) in an inert solvent such as tetrahydrofuran or diethyl ether, can reduce the ester 16 to a compound of formula IIIa. Intermediate 15 can also react with alcohols following the methods outlined in Scheme 6, to afford compounds of formula IIIc.

5

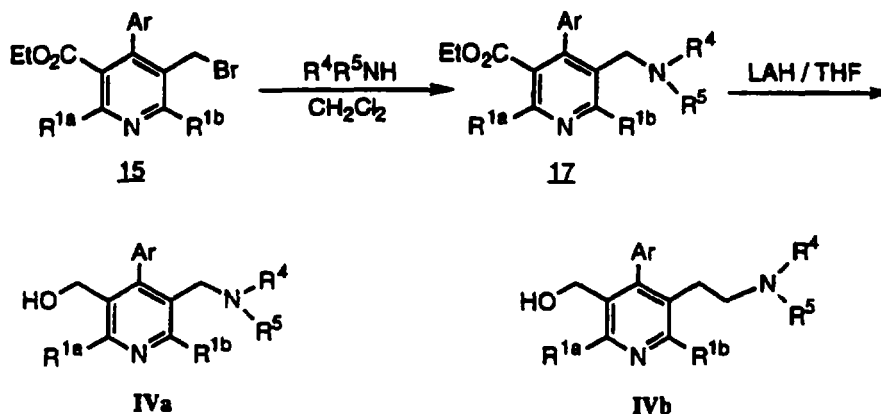
SCHEME 6

- The synthesis of aryl pyridine derivatives of formula (IC) wherein R^2 is alkyl containing a heteroatom such as nitrogen and R^3 is hydroxymethyl (IVa), is outlined in Scheme 7. Treatment of **15** with a primary or secondary amine in an inert solvent results in the intermediate **17**. Chemical reducing agents such as lithium aluminum hydride in an inert solvent, such as tetrahydrofuran or diethyl ether, can reduce ester **17** to a compound of formula IVa. Reduction of aldehyde **13** by the method outlined in Scheme 4 affords an intermediate that can be converted to homologues of compounds of formula IIIa and IVa, containing the $-CH_2-CH_2-$ linkage between the pyridine nucleus and the sulfur or nitrogen substituent (IIIb and IVb).

20

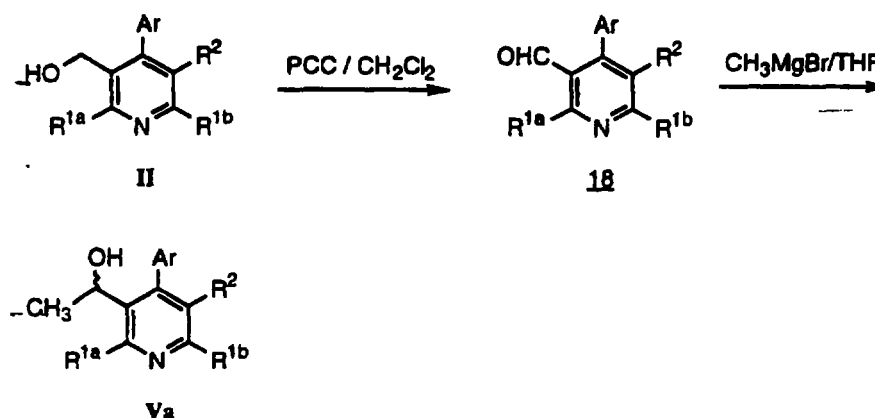
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SCHEME 7



Synthesis of aryl pyridine derivatives of formula (IC) wherein R^2 is alkyl and R^3 is 1-hydroxyethyl (Va), is outlined in Scheme 8. Oxidants such as pyridinium chlorochromate (PCC), are used to convert compounds of formula II to the aldehyde 18. Treatment of 18 with an organometallic reagent such as methyl magnesium bromide or methyl lithium in an inert solvent such as THF or Et₂O affords racemic compounds of formula Va. Chiral 1-hydroxyethyl aryl pyridine derivatives of formula Vb are obtained by resolution of the racemates Va by classical methods. For example, resolution can be achieved by formation of diastereomeric adducts of the racemic compounds with optically active reagents such as α -methoxy- α -(trifluoromethyl)phenylacetic acid (Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* 1969, 34, 2543). Alternatively, separation of enantiomers is achieved by HPLC on chiral solid phase. Determination of absolute stereochemistry can be achieved in a number of ways familiar to those skilled in the art, including X-ray analysis of a suitable crystalline derivative, such as a Mosher ester.

SCHEME 8

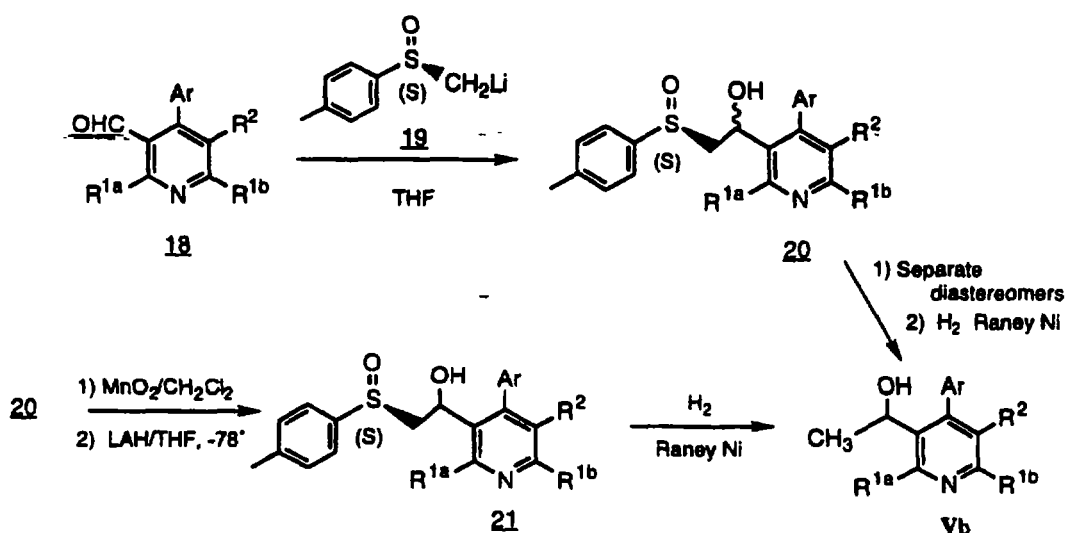


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An alternative synthesis of aryl pyridine derivatives of formula Vb is achieved by treating aldehyde 18 with the anion of methyl toluylsulfoxide 19 to give a diastereomeric mixture of alcohols 20 as shown in Scheme 9 (Blase, F. R.; Le H. *Tet. Lett.* 1995, 36, 4559). The diastereomers are separated by flash chromatography and treated separately with Raney nickel and hydrogen in ethanol to provide pure enantiomers (>99% enantiomeric excess, e.e.) of the compounds of formula Vb. Alternatively, the chromatographic step is avoided by a two step sequence consisting of (1) oxidation of the mixture 20 with manganese dioxide in an inert solvent, followed by (2) reduction of the ketone with a chemical reductant such as LAH, to provide the enantiomerically pure alcohol 21. Treatment of 21 with Raney nickel and hydrogen in a polar solvent provides pure enantiomer (>99% e.e.) of the compounds of formula Vb.

SCHEME 9



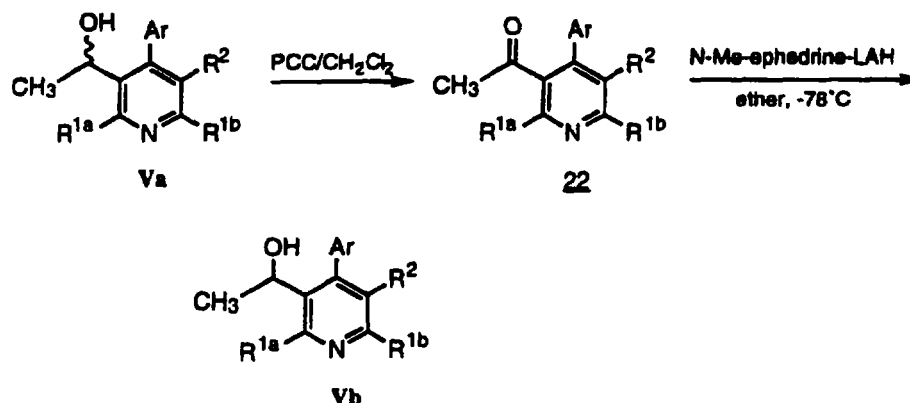
15

A preferred alternative enantioselective synthesis of aryl pyridine derivatives of formula Vb is shown in Scheme 10. Treatment of the racemic mixture of compounds of formula Va with an oxidant such as pyridinium chlorochromate (PCC), gives the ketone 22. Reduction of 22 with a complex of LAH and N-methylephedrine (Kawasaki, M.; Susuki, Y.; Terashima, S. *Chem. Lett.* 1984, 239) in an inert solvent, provides the alcohol of formula Vb with an enantiomeric excess of 95%.

25

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SCHEME 10

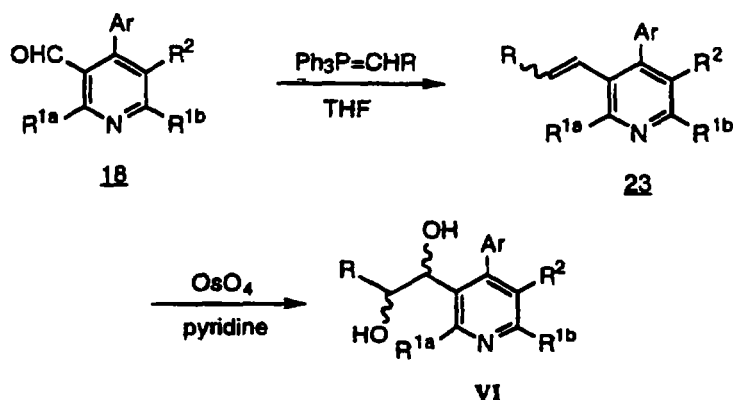


5

The synthesis of aryl pyridine derivatives of formula (IC) wherein R^2 is alkyl and R^3 is 1,2-dihydroxyalkyl (VI), is described in Scheme 11. A methyl triphenylphosphonium salt is treated with a suitable base such as butyllithium in an inert solvent and reacted with intermediate 18 to afford olefin 23. Treatment of compound 23 with a suitable oxidant such as osmium tetroxide in a polar solvent such as pyridine gives the compounds of formula VI.

10

SCHEME 11



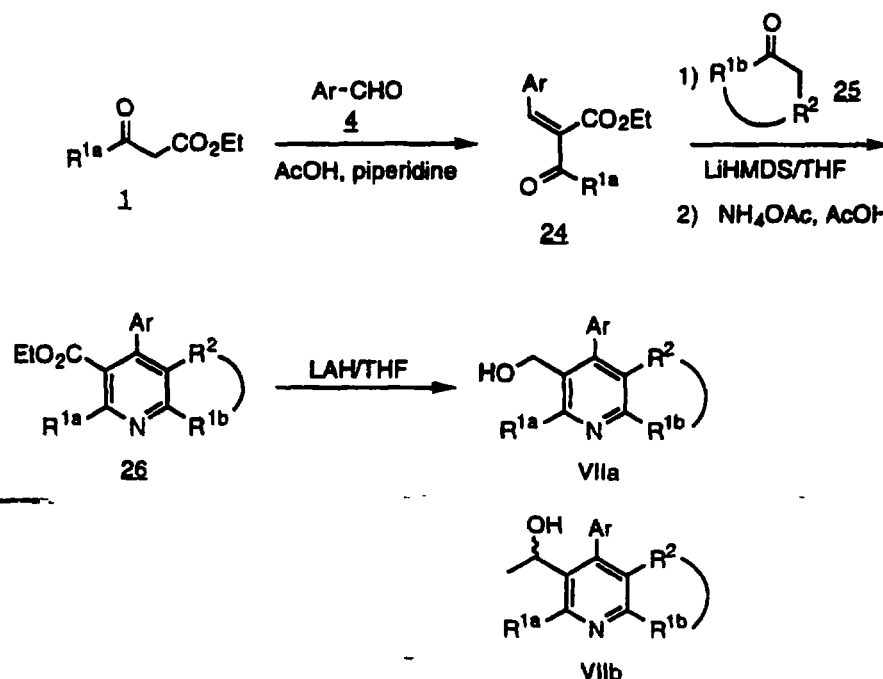
15

The synthesis of aryl pyridine derivatives of formula (IC) wherein R^2 and R^{1b} are taken together to form an alkylene bridge and R^3 is hydroxymethyl (VIIa), is described in Scheme 12. The ketoester 1, is treated with an aromatic aldehyde and catalysts such as acetic acid and piperidine, in ethanol, to afford the α,β -unsaturated ketoester 24. Treatment of 24 with the cyclic ketone 25 and a base such as lithium-bis(trimethylsilyl)amide in an inert solvent such as THF affords an intermediate which is treated with ammonium acetate and copper acetate in acetic

acid to give the pyridine 26. Chemical reducing agents reduce the ester 26 to analogs of formula VIIa. It may be appreciated that these analogs can be used as intermediates to generate new derivatives of formula (IC) wherein R² and R^{1b} are taken together and R³ is 1-hydroxyethyl (VIIb) according to the procedures described in Scheme 8.

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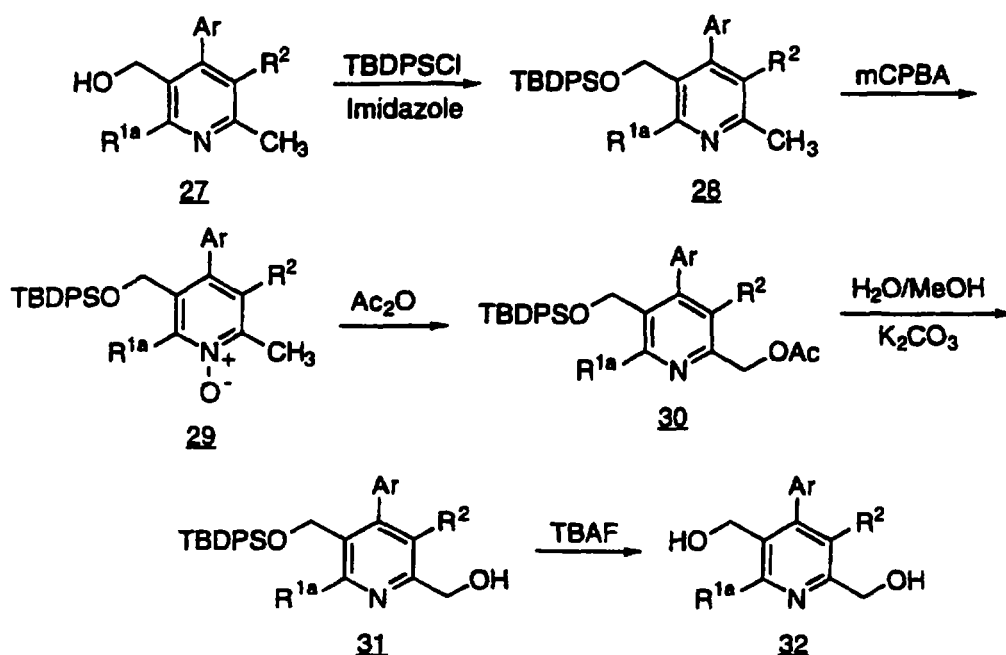
SCHEME 12



The synthesis of the aryl pyridine derivative IIa wherein R^{1b} is CH₂OH is described in Scheme 13. Alcohol 27 (aryl pyridine IIa in which R^{1b} is CH₃) is treated with a trialkylsilyl chloride, such as *tert*-butyldiphenylsilyl chloride, and a base to yield silyl ether 28. Treatment of 28 with *meta*-chloroperbenzoic acid in an inert solvent, such as chloroform, provides the N-oxide 29. The N-oxide is treated with acetic anhydride to afford pyridine acetate 30. Treatment of 30 with aqueous methanol in the presence of potassium carbonate, yields alcohol 31. The silyl ether is cleaved with tetrabutylammonium fluoride in THF to provide aryl pyridine derivative 32.

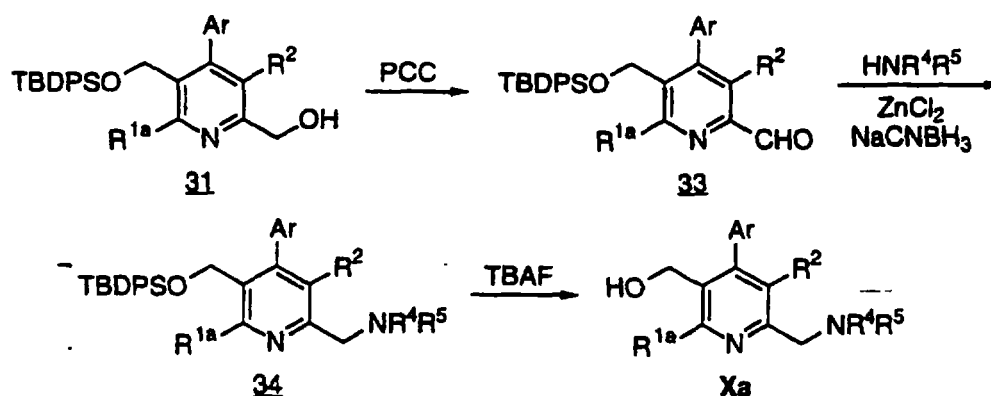
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SCHEME 13

The synthesis of aryl pyridine derivatives Xa wherein R^{1b} is $-\text{CH}_2\text{NR}^4\text{R}^5$ is described in Scheme 14. Oxidation of alcohol 31 as described in Scheme 4 yields aldehyde 33. Treatment of the aldehyde with an amine in the presence of a Lewis acid, such as zinc chloride, and a reducing agent, such as sodium cyanoborohydride, provides the amine 34. Deprotection of the alcohol as described in Scheme 13 affords aryl pyridine derivative Xa.

10

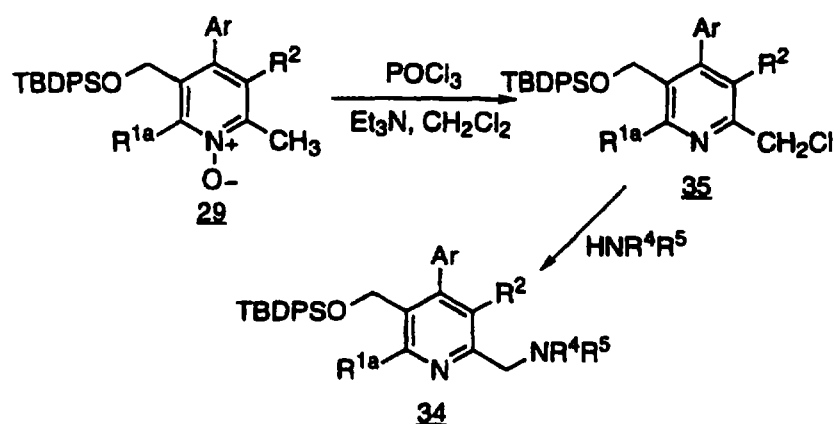
SCHEME 14

15

An alternative synthesis of amine 34 is shown in Scheme 15. Treatment of pyridine N-oxide 29 with phosphorus oxychloride and a base, such as triethylamine, in CH_2Cl_2 , yields chloromethylpyridine 35. The chloride is treated

0 with an amine providing amine 34.

SCHEME 15

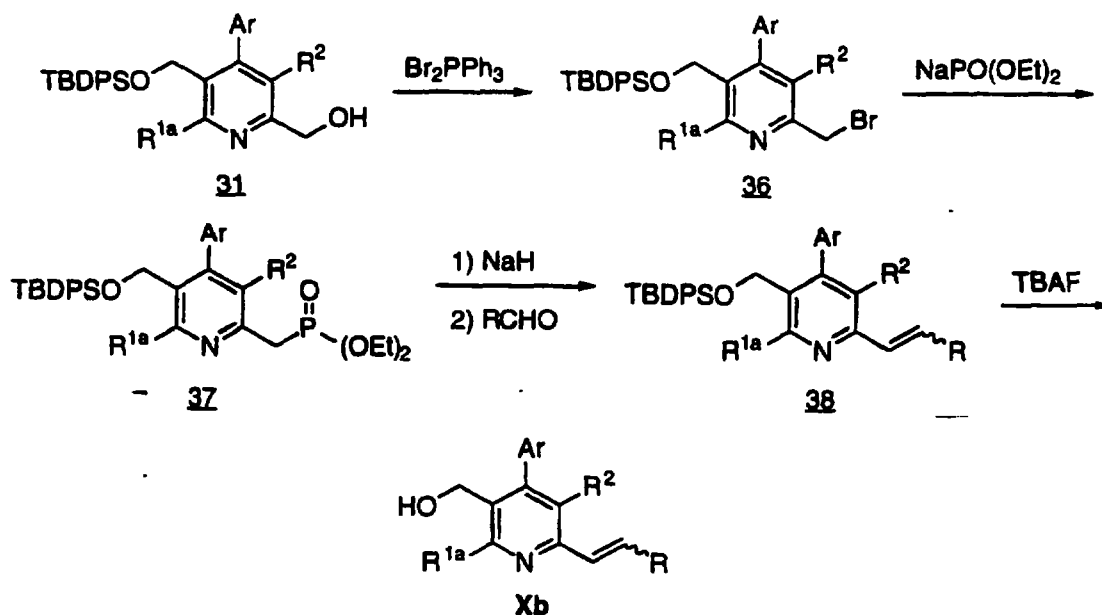


5

The synthesis of aryl pyridine derivatives Xb wherein R^{1b} is $-\text{CH}=\text{CHR}$ is described in Scheme 16. Alcohol 31 is converted to the corresponding bromide as described in Scheme 6. Treatment of 36 with sodium phosphite in benzene yields phosphonate 37. The phosphonate is treated with a base, such as sodium hydride, and subsequently with an aldehyde affording olefin 38. Deprotection of the alcohol as described affords aryl pyridine Xb.

10

SCHEME 16

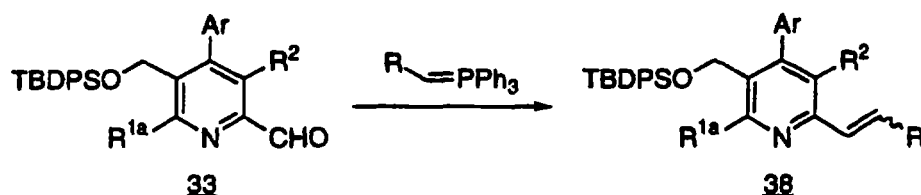


15

An alternative synthesis of olefin 38 is shown in Scheme 17. Aldehyde 33 is

0 treated with an ylide as described in Scheme 4 to yield olefin 38.

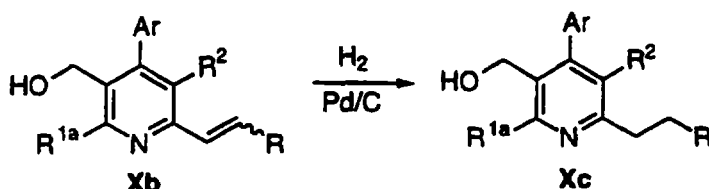
SCHEME 17



5

The synthesis of aryl pyridine derivative Xc wherein R^{1b} is $-CH_2CH_2R$ is described in Scheme 18. Hydrogenation of olefin Xb as described in Scheme 4 yields the alkane Xc.

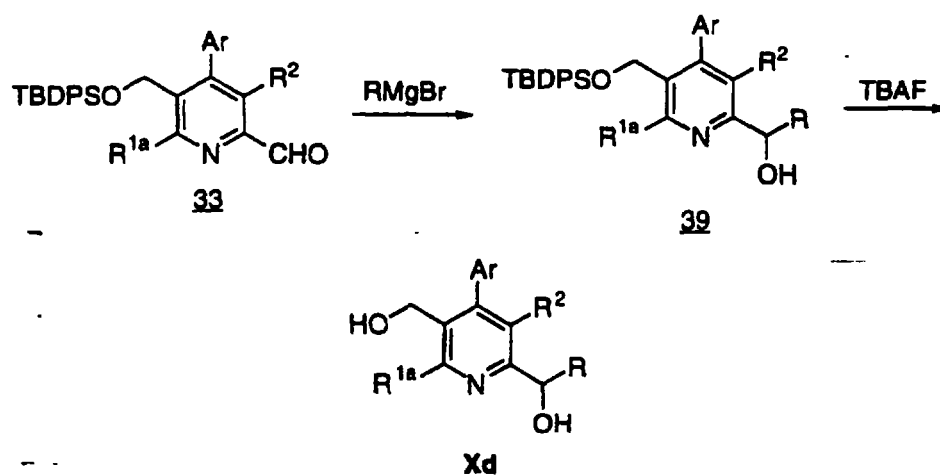
SCHEME 18



10

15 The synthesis of aryl pyridine derivative Xd wherein R^{1b} is $-CH(OH)R$ is described in Scheme 19. Treatment of aldehyde **33** with a Grignard reagent in an inert solvent, such as THF, yields alcohol **39**. Deprotection of the alcohol as described affords aryl pyridine derivative Xd.

SCHEME 19

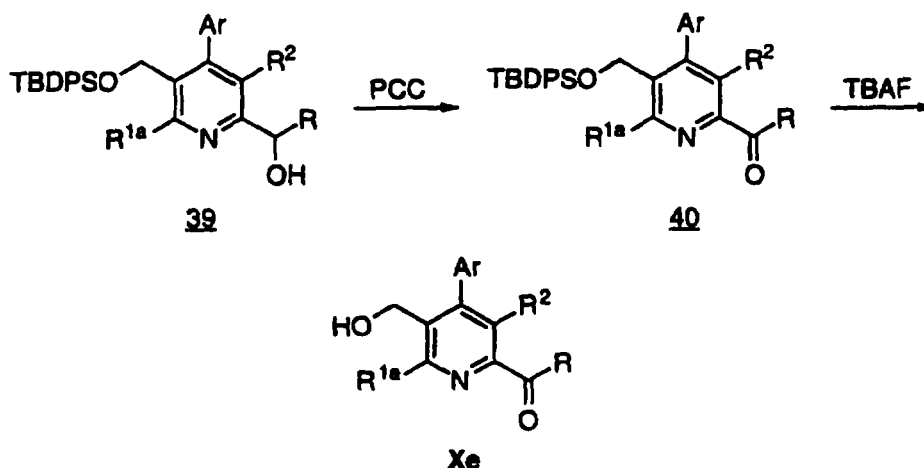


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The synthesis of aryl pyridine derivatives Xe wherein R^{1b} is $-COR$ is

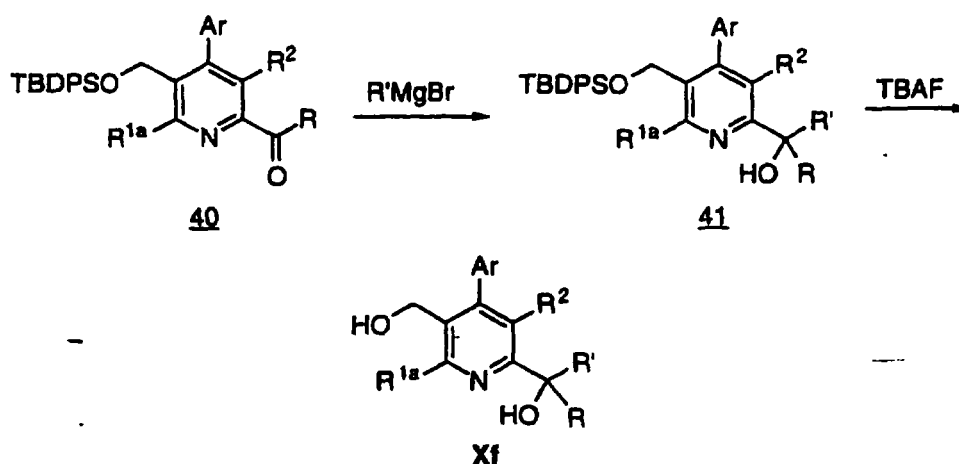
- 0 described in Scheme 20. Oxidation of alcohol 39 as described in Scheme 4 yields ketone 40. Deprotection of the alcohol as described affords the aryl pyridine derivative Xe.

SCHEME 20



- 10 The synthesis of aryl pyridine derivatives Xf wherein R^{1b} is $-\text{C}(\text{OH})\text{RR}'$ is described in Scheme 21. Grignard addition to ketone 40 as described in Scheme 19 yields alcohol 41. Deprotection of the alcohol as described affords the aryl pyridine derivative Xf.

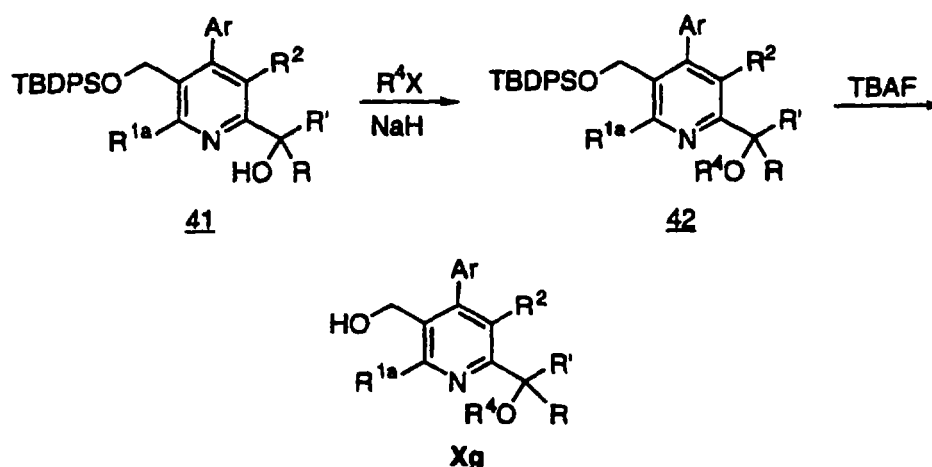
SCHEME 21



The synthesis of aryl pyridine derivatives Xg wherein R^{1b} is $-\text{C}(\text{OR}^4)\text{RR}'$ is described in Scheme 22. Treatment of alcohol 41 with a base, such as sodium hydride, and an alkylating agent in THF, yields ether 42. Deprotection of the

0 alcohol as described affords the aryl pyridine derivative Xg.

SCHEME 22

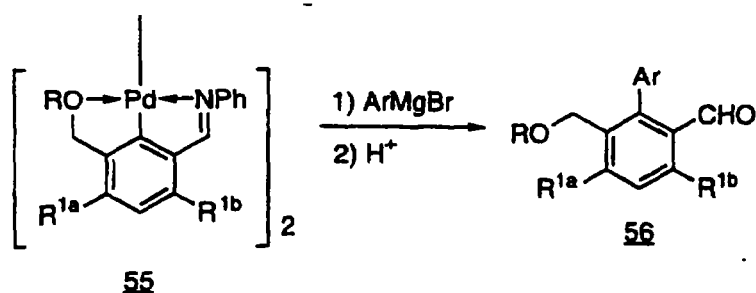


5

The biphenyl analogs described in formula (IC) ($X = \text{C-R}^8$, wherein R^8 is H), are prepared by the methods described by Fey, *et al.* US Patent 5,138,090. The key step of the synthesis is the coupling of an arylpalladium dimer with an aryl Grignard reagent (Scheme 23).

10

SCHEME 23



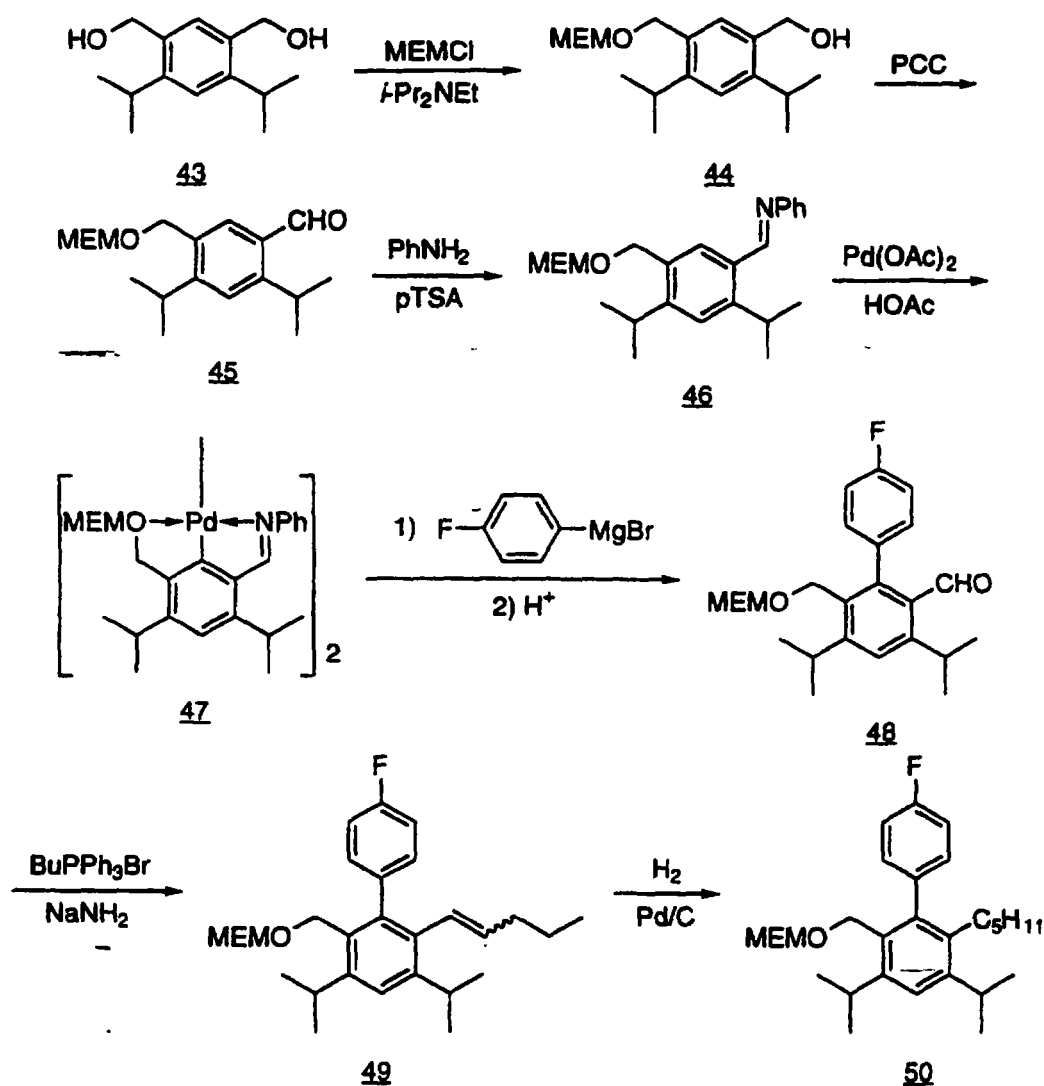
15 A specific example of this method is shown in Scheme 24. Treatment of diol 43 (prepared according to the procedure of Fey, *et al.* US Patent 5,138,090) with (2-methoxy)ethoxymethyl chloride and diisopropylethylamine in CH_2Cl_2 solvent gives MEM ether 44. Oxidation of the remaining alcohol of 44 as described in Scheme 4 provides aldehyde 45. Treatment of the aldehyde with aniline in the presence of a catalytic amount of p-toluenesulfonic acid (pTSA) and molecular sieves in toluene solvent gives imine 46. The imine is converted to the palladium dimer 47 upon treatment with palladium acetate in acetic acid solvent. Treatment of 47 with triphenylphosphine, then with 4-fluorophenylmagnesium bromide

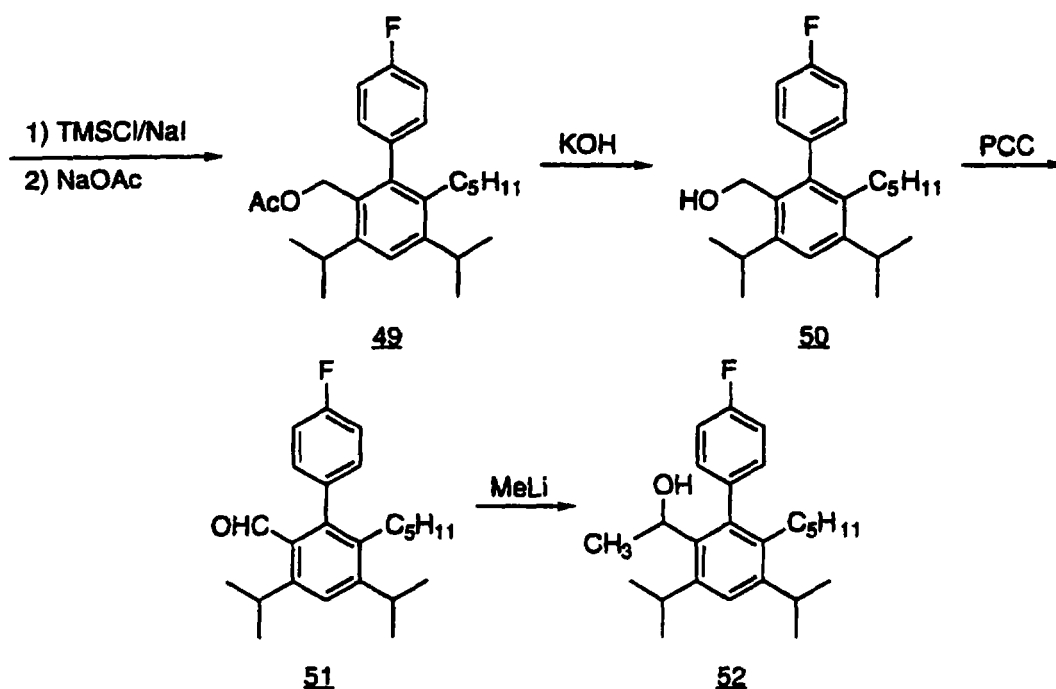
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- 0 (prepared from 1-bromo-4-fluorobenzene and magnesium metal), and finally with aqueous hydrochloric acid in benzene solvent yields biphenyl 48. The aldehyde moiety of biphenyl 48 is converted to a pentyl group by the methods described in Scheme 4. MEM ether 50 is treated with trimethylsilyl chloride and sodium iodide in acetonitrile solvent, and subsequently with sodium acetate in DMF solvent to
- 5 provide acetate 51. Saponification of the acetate using potassium hydroxide in methanol solvent provides alcohol 52. Hydroxymethyl biphenyl 52 is transformed to racemic hydroxyethyl biphenyl 54 as described in Scheme 8.

SCHEME 24

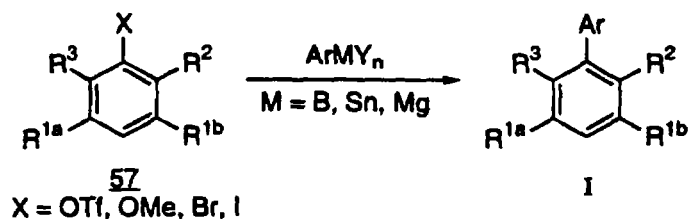
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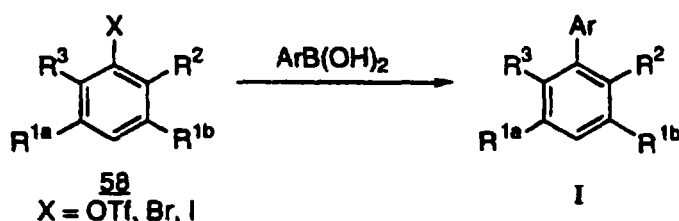
An alternative synthesis of biphenyls of formula (IC) is the coupling of a suitably functionalized benzene derivative 57 (where X can be trifluoromethanesulfonate, methoxy, bromide, or iodide) with an arylmetal reagent ArMY_n (where M may be B, Sn, or Mg, and Y is a ligand).

SCHEME 25

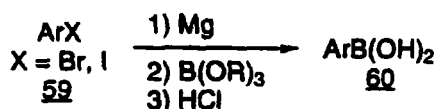


An example of such a biaryl coupling is the Suzuki reaction (Miyaura, N., Yanagi, T., Suzuki, A. *Synth. Comm.* 1981, 11, 513-519; Oh-e, T., Miyaura, N., Suzuki, A. *J. Org. Chem.* 1993, 58, 2201-2208) in which a benzene derivative 58 (in which X can be trifluoromethanesulfonate, bromide, or iodide) is coupled with an arylboronic acid (Scheme 26).

0

SCHEME 26

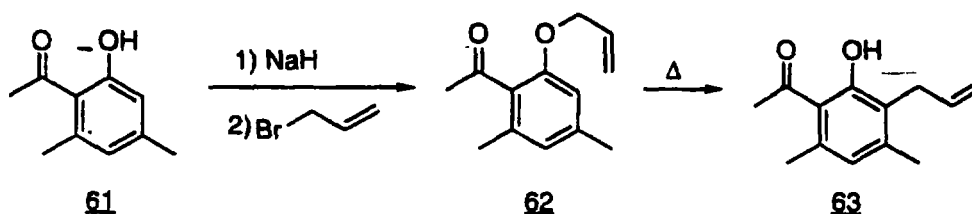
5 The requisite arylboronic acid 60 may be prepared by sequential reaction of an aryl halide 59 (X = Br or I) with magnesium metal, a boronic ester, and hydrochloric acid.

SCHEME 27

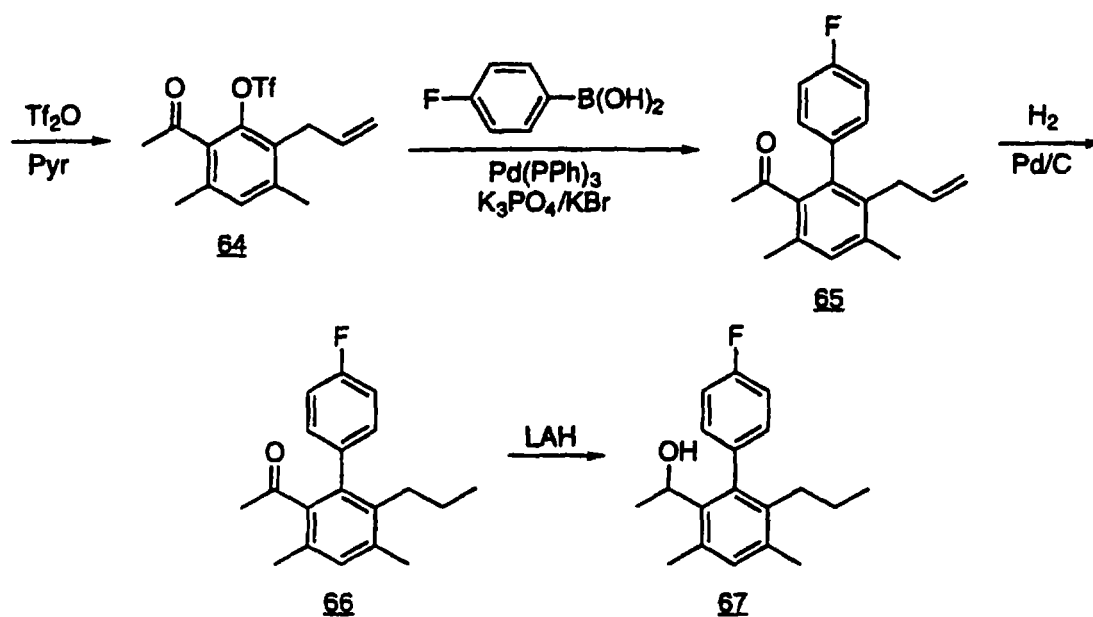
10

15 A specific example of the use of the Suzuki reaction to synthesize a biphenyl analog is depicted in Scheme 28. Phenol 61 is treated sequentially with sodium hydride and allyl bromide in dimethylformamide solvent to afford allyl ether 62. Claisen rearrangement of the ether provides phenol 63. The phenol is treated with trifluoromethanesulfonic anhydride (triflic anhydride) and pyridine in CH_2Cl_2 solvent to give triflate 64. Treatment with 4-fluorophenylboronic acid, tetrakis(triphenylphosphine) palladium (0), potassium phosphate (tribasic), and potassium bromide in 1,4-dioxane solvent affords biphenyl 65. Catalytic hydrogenation as described in Scheme 4, and reduction of the ketone with lithium aluminum hydride in THF solvent provides the desired biphenyl analog 67.

20

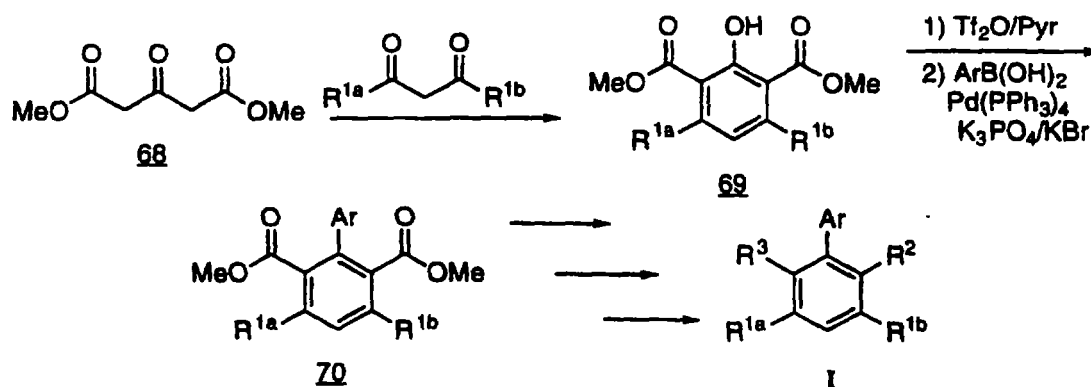
SCHEME 28

25



An alternative synthesis of biphenyls of type I uses a cycloaromatization of a ketodiester 68 with a diketone in the presence of a catalytic amount of sodium methoxide in methanol solvent to give a phenol 69. The phenol is then coupled with an arylboronic acid as described in Scheme 28 to afford biphenyl diester 70. The diester is then transformed as described in Schemes 4, 8, and 10 to give the analog with the desired R^2 and R^3 groups.

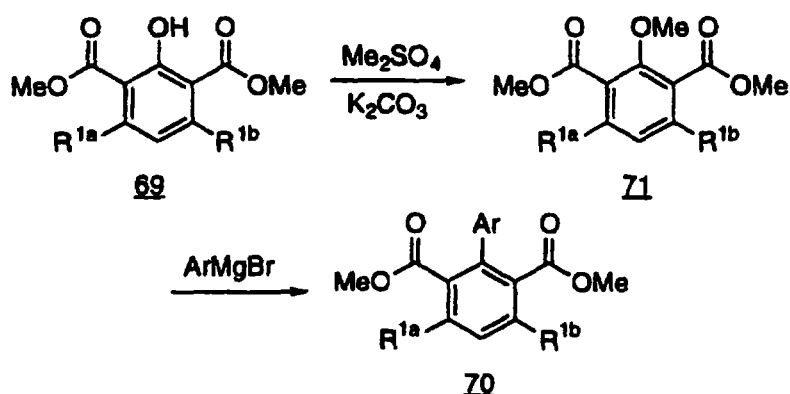
SCHEME 29



An alternative method of transforming phenol 69 to biphenyl 70 is shown in Scheme 30. Treatment of the phenol with dimethylsulfate and a base such as potassium carbonate yields the methyl ether 71. The ether is treated with an aryl Grignard reagent to afford biphenyl 70.

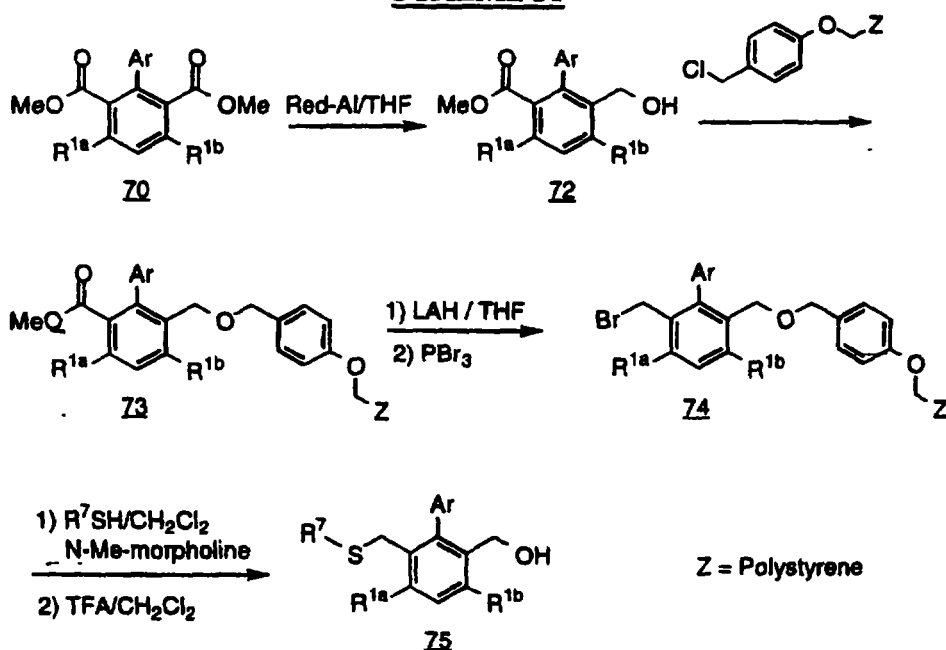
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SCHEME 30



- 5 The diester **70** can be further transformed by an alternative method shown in Scheme 31, to give the analogs with the desired R² and R³ groups. Chemical reducing agents such as sodium bis-(2-methoxyethoxy)-aluminum hydride (Red-Al), can result in a mono reduction of the diester **70** to give the alcohol **72**. Alcohol **72** can be attached to a polymeric support such as Wang resin, by treatment with a base such as sodium hydride in DMF, to give the intermediate **73**. The ester group of intermediate **73** can be transformed to an alkyl halide in a two step process; **73** is treated with a reducing agent such as LAH, then Phosphorous tribromide to afford compound **74**. The alkyl halide **74** is treated with an alkyl thiol and a base such as N-methyl morpholine, then by TFA to cleave the ether linkage with the polymeric resin, to afford the alcohol **75**.
- 10
- 15

SCHEME 31



0

It will be appreciated that synthesis of some compounds of formula (IC) may require use of protecting groups at various stages of the procedures. These are removed in subsequent steps. For example, the removal of O-benzyl ether protecting groups is carried out by treatment with hydrogen in the presence of a metal catalyst, such as palladium on carbon, in a polar solvent such as ethanol. The removal of silyl ether protecting groups is carried out by treatment with fluoride salts, such as tetrabutylammonium fluoride in a solvent such as THF. Conditions required to remove other protecting groups which may be present can be found in: Protective Groups in Organic Synthesis, Second Edition, T. W. Greene, John Wiley and Sons, New York, 1991.

10

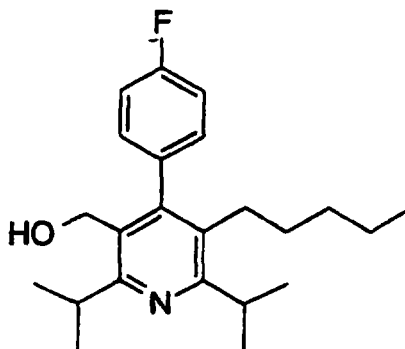
The order of carrying out the steps of the foregoing reaction schemes is not always significant, and it is within the skill of the art to vary the order of reactions to facilitate the reaction or to avoid unwanted reaction products.

15

The following examples are provided for the purpose of further illustration only and are not intended to limit the disclosed invention.

EXAMPLE 1

20



2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentylpyridine

25

Step A: 3-Amino-4-methyl-2-pentenoic acid, ethyl ester

To 100 g (0.63 mol) of ethyl isobutyryl acetate was added ammonium acetate (68.2 g, 0.89 mol), cyclohexane (230 mL) and isopropanol (74 mL). The mixture was heated at reflux under argon atmosphere with a Dean-Stark trap. After 2 hours, a second portion of ammonium acetate (14.6 g, 0.19 mol) was added to the reaction.

30

The reaction was heated at reflux for 12 hours and then allowed to cool to room

0 temperature. A total of ~30 mL of water was collected in the Dean-Stark trap. An ice bath was used to cool the reaction to 10°C and then ammonium hydroxide (63 mL) was added dropwise. The organic layer was separated, dried with sodium sulfate, filtered, and concentrated to yield a yellow oil. The crude product (90.9 g, 0.58 mol, 92%) was taken directly to the next step without any further purification.

5

Step B: Diethyl 1,4-dihydro-2,6-diisopropyl-4-(4-fluorophenyl)-3,5-pyridinedicarboxylate

To ethyl 3-amino-4-methylpent-2-enoate (Step A) (90 g, 57 mmol) was added ethyl isobutyryl acetate (90g, 57 mmol) and 4-fluorobenzaldehyde (61.4 mL, 0.57
10 mmol). The mixture was heated under argon at 130°C for 26 hours (Precaution: Check the reflux condenser after a few hours as excess ammonium acetate will clog the condenser). The reaction was allowed to cool to room temperature and left to crystallize for 4 days. The solid was collected by filtration with vacuum (46.9 g, 116 mmol, 20%) and taken directly to the next step without further purification.

15

Step C: Diethyl 2,6-diisopropyl-4-(4-fluorophenyl)-3,5-pyridinedicarboxylate

To the intermediate obtained in Step B (33 g, 82 mmol) in dichloromethane (400 ml) was added 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 20.5 g, 90 mmol)
20 under argon and the mixture was stirred for 2 hours. The stirring was stopped to allow the precipitate to settle. The precipitate was filtered, washed with dichloromethane (3 x 30 mL), and discarded. The filtrate was concentrated to afford a brown solid, which was subjected to flash chromatography (6/4 mixture of dichloromethane/hexanes) resulting in a pure white solid (25.8 g, 64.3 mmol, 78%).
25 ¹H NMR (300 MHz, CDCl₃): δ 7.28 (m, 2 H), 7.06 (m, 2 H), 4.03 (q, J = 7.0 Hz, 4 H), 3.11 (septet, J = 6.6 Hz, 2 H), 1.32 (d, J = 6.5 Hz, 12 H), 0.979 (t, J = 3.3 Hz, 6 H). FAB-MS: calculated for (C₂₃H₂₈NO₄F) 401, found 402 (M+H). Anal. calc for C₂₃H₂₈NO₄F: C, 68.64; H, 7.24; N, 3.48; F, 4.72. Found: C, 69.12; H, 6.98; N, 3.42; F, 4.96. mp 72-74°C. R_f=0.4 (10% ethyl acetate/hexane).

30

Step D: Ethyl 2,6-diisopropyl-4-(4-fluorophenyl)-5-hydroxymethyl-3-pyridinecarboxylate

To a solution of the intermediate obtained in Step C (23.4 g, 58.3 mmol) in anhydrous tetrahydrofuran (300 mL) stirred under argon at 0°C was added a
35 solution of 3.4M of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (Red-Al) (61 mL, 204 mmol, 65 wt% in toluene) via syringe over 20 min. The reaction mixture was allowed to stir at room temperature for 7 hr, then cooled

0 again to 0°C and carefully quenched by the dropwise addition of water. The solution was decanted from the solid which forms and the solvent removed *in vacuo*. The residue was purified by flash chromatography (300 g silica) via step gradient. Elution with 5% diethyl ether/hexane afforded 6.6 g (16.4 mmol, 28%) of recovered starting material and elution with 40% diethyl ether(Et₂O)/hexane
5 yielded the desired product as a yellow waxy solid (14 g, 39 mmol, 67%). ¹H NMR (300 MHz, CDCl₃): δ 7.27 (m, 2 H), 7.10 (m, 2 H), 4.46 (d, *J* = 5.2 Hz, 2 H), 3.98 (q, *J* = 7 Hz, 2 H), 3.48 (sept, *J* = 6.6 Hz, 1 H), 3.05 (sept, *J* = 6.6 Hz, 1 H), 1.32 (t, *J* = 6.6 Hz, 12 H), 0.97 (t, *J* = 7 Hz, 3 H). FAB-MS: calculated for (C₂₁H₂₆FNO₃) 359, found 360 (M+H). *R*_f = 0.2 (20% ethyl acetate/hexane).

10

Step E: 5-Carboethoxy-2,6-diisopropyl-4-(4-fluorophenyl)-3-pyridinecarboxaldehyde

To a solution of the intermediate obtained in Step D (13 g, 36 mmol) in dichloromethane (1 L) was added Brockman I neutral alumina (7.4 g, 72 mmol).
15 The suspension was stirred at room temperature and treated with pyridinium chlorochromate (PCC) (16 g, 72 mmol) in three portions. The suspension was stirred at room temperature for 1 hr, then poured into 1:1 diethyl ether/hex (1 L), filtered through a pad of silica, the pad washed with diethyl ether (500 mL) and the combined eluent concentrated to afford a viscous oil which slowly solidified (12.8 g,
20 35.9 mmol, 99%); *R*_f = 0.31 (10% ethyl acetate/hexane). ¹H NMR (300 MHz, CDCl₃): δ 9.85 (s, 1 H), 7.27 (m, 2 H), 7.13 (m, 2 H), 4.04 (q, *J* = 7 Hz, 2 H), 3.88 (sept, *J* = 6.6 Hz, 1 H), 3.12 (sept, *J* = 6.6 Hz, 1 H), 1.33 (t, *J* = 6.6 Hz, 12 H), 1.00 (t, *J* = 7 Hz, 3 H). EI-MS calcd for (C₂₁H₂₄FNO₃) 357, found 358 (M+H). Anal. Calcd for C₂₁H₂₄FNO₃: C, 70.57; H, 6.77; N, 3.92. Found: C, 70.62; H, 6.78; N, 3.84.

25

Step F: Ethyl 2,6-diisopropyl-4-(4-fluorophenyl)-5-(1-pentenyl)-3-pyridinecarboxylate

Butyltriphenylphosphonium bromide (2.7 g, 6.76 mmol) was suspended in anhydrous THF (75 mL) under argon and stirred at -78°C. A 1.6 M solution of *n*-butyllithium in hexanes (4.2 mL, 6.76 mmol) was added dropwise. The reaction
30 mixture was allowed to come to 0°C and was stirred at that temperature for 1.5 hr. The resulting brightly colored solution was cooled again to -78°C and treated dropwise with a solution of the intermediate obtained in Step E (2 g, 5.60 mmol) in THF (20 mL). The reaction mixture was allowed to stir at 0°C for 1 hr, then
35 quenched by the addition of water (5 mL). The THF was removed *in vacuo*, the residue partitioned between ethyl ether (200 mL) and water (50 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated. Flash

0 chromatography through silica (5% diethyl ether/hexane) affords a viscous oil (2 g,
5 mmol, 90%) (E,Z mixture). ^1H NMR (300 MHz, CDCl_3): δ 7.14 (m, 2 H), 7.02 (m,
2 h), 6.10 (dt, $J = 1.8$, 11.4 Hz, 0.4 H), 6.04 (dt, $J = 1.5$, 16.2 Hz, 0.6 H), 5.48 (dt, $J = 7$,
11.4 Hz, 0.4 H), 5.33 (dt, $J = 7$, 16.2 Hz, 0.6 H), 4.00 (q, $J = 7$ Hz, 0.8 H), 3.98 (q, $J = 7$
5 Hz, 1.2 H), 3.39 (sept, $J = 6.6$ Hz, 0.6 H), 3.27 (sept, $J = 6.6$ Hz, 0.4 H), 3.06 (m, 1 H),
1.95 (dq, $J = 1.5$, 7 Hz, 1 H), 1.26 (m, 13 H), 1.19 (m, 2 H), 0.97 (t, $J = 7$ Hz, 3 H), 0.77
(t, $J = 7$ Hz, 1.2 H), 0.76 (t, $J = 7$ Hz, 1.8 H). EI-MS calculated for $(\text{C}_{25}\text{H}_{32}\text{FNO}_2)$ 397,
found 397 (M^+). $R_f = 0.5$ (10% ethyl acetate/hexane).

10 Step G: 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-
pentenyl)pyridine

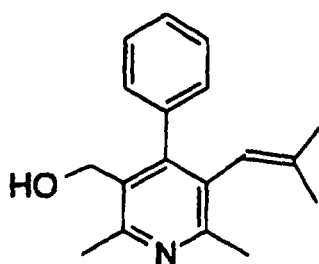
The intermediate obtained in Step F (2 g, 5.03 mmol) was dissolved in anhydrous THF (100 mL) under argon and treated dropwise at room temperature with lithium aluminum hydride (1.0 M in THF, 10 mL, 10 mmol). The reaction mixture was stirred at reflux for 1 hr, cooled to room temperature and quenched by the addition of 0.38 mL H_2O , 0.38 mL 20% aqueous NaOH and 1.1 mL H_2O . The resulting suspension was filtered through a cake of Celite and the filtrate concentrated and purified by chromatography through silica (5% ethyl acetate/hexane) to afford the product as a white foam (1.42 g, 4.0 mmol, 80%). $R_f = 0.2$ (10% ethyl acetate/hexane).

20 Step H: 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-
pentylpyridine

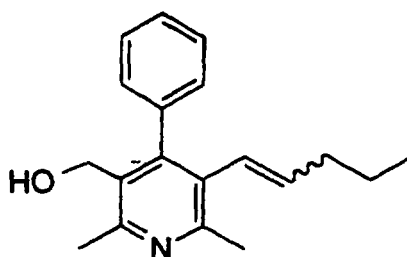
The intermediate obtained in Step G was dissolved in absolute ethanol (50 mL) under argon, treated with 10% palladium on carbon (140 mg, 0.1 eq), then stirred under a hydrogen atmosphere for 2 hr. After purging the system with argon, the catalyst was removed by filtration through a pad of Celite. The solvent was removed and the product dried *in vacuo* to afford the title compound as a white solid (1.4 g, 3.9 mmol, 98%). ^1H NMR (300 MHz, CDCl_3): δ 7.15 (m, 4 H), 4.33 (d, $J = 4.4$ Hz, 2 H), 3.41 (sept, $J = 6.6$ Hz, 1 H), 3.23 (sept, $J = 6.6$ Hz, 1 H), 2.26 (m, 2 H), 1.33 (d, $J = 6.6$ Hz, 6 H), 1.30 (d, $J = 6.6$ Hz, 6 H), 1.27 (m, 2 H), 1.13 (m, 5 H), 0.79 (t, $J = 6.6$ Hz, 3 H). FAB-MS: calculated for $(\text{C}_{23}\text{H}_{32}\text{FNO})$ 357, found 358 ($\text{M}+\text{H}$). Anal. calcd for $\text{C}_{23}\text{H}_{32}\text{FNO}$: C, 77.27; H, 9.02; N, 3.92. Found: C, 77.46; H, 8.95; N, 3.78. $R_f = 0.3$ (20% ethyl acetate/hexane). mp 100-101°C.

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EXAMPLE 22,6-Dimethyl-3-hydroxymethyl-4-phenyl-5-(2-methyl-1-propenyl)-pyridine

5 The title compound was prepared from ethyl acetoacetate, benzaldehyde and isopropyl triphenylphosphonium iodide according to the procedures described in Example 1, Steps A-G. ¹H NMR (300 MHz, CDCl₃): δ 7.34 (m, 3 H), 7.10 (m, 2 H), 5.70 (s, 1 H), 4.42 (s, 2 H), 2.69 (s, 3 H), 2.43 (s, 3 H), 1.60 (s, 3 H), 1.35 (s, 3 H). EI-MS calculated for (C₁₈H₂₁NO) 267, found 267 (M⁺). mp 48-50°C. R_f = 0.3 (90%
10 ethyl acetate/hexane).

EXAMPLE 3

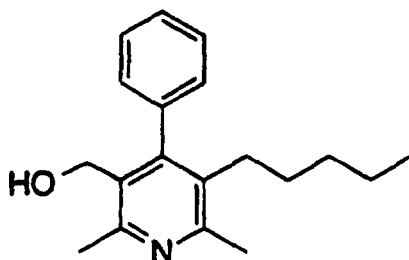
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2,6-Dimethyl-3-hydroxymethyl-4-phenyl-5-(1-pentenyl)pyridine

The title compound was prepared from ethyl acetoacetate, benzaldehyde and butyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. The product was obtained as a mixture 3:1 trans:cis
20 isomers; gummy oil. ¹H NMR (300 MHz, CDCl₃): δ 7.37 (m, 3 H), 7.12 (m, 2 H), 5.94 (m, 1 H), 5.40 (m, 1 H), 4.41 (bs, 2 H), 2.71 & 2.68 (2s, 3 H), 2.57 & 2.46 (2s, 3 H), 1.91 & 1.69 (2q, J = 7 Hz, 2 H), 1.52 (bs, 1 H), 1.19 (m, 2 H), 0.77 (m, 3 H). EI-MS: calculated for (C₁₉H₂₃NO) 281, found 281. R_f = 0.4 (90% ethyl acetate/hexane).

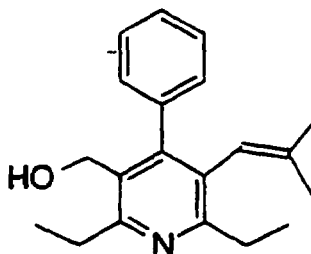
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EXAMPLE 45 2,6-Dimethyl-3-hydroxymethyl-4-phenyl-5-pentylpyridine

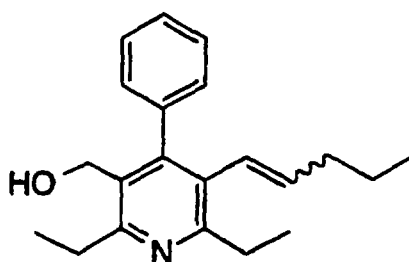
The title compound was prepared from 2,6-dimethyl-3-hydroxymethyl-4-phenyl-5-(1-pentenyl)pyridine (Example 3) according to the procedure described in Example 1, Step H. ¹H NMR (300 MHz, CDCl₃): δ 7.42 (m, 3 H), 7.15 (m, 2 H), 4.33 (s, 2 H), 2.65 (s, 3 H), 2.56 (s, 3 H), 2.27 (m, 2 H), 1.29 (m, 2 H), 1.11 (m, 4 H), 0.76 (t, J = 7 Hz, 3 H). EI-MS: calculated for (C₁₉H₂₅NO) 283, found 283 (M⁺). Anal. calculated for C₁₉H₂₅NO: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.39; H, 8.85; N, 4.85. mp 99-100°C. R_f = 0.3 (90% ethyl acetate/hexane).

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EXAMPLE 5

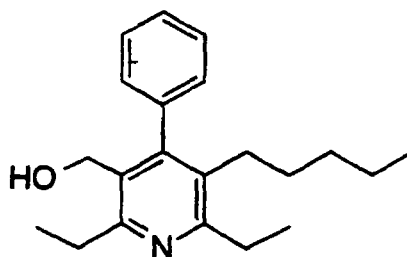
2,6-Diethyl-3-hydroxymethyl-4-phenyl-5-(2-methyl-1-propenyl)pyridine The title compound was prepared from ethyl propionylacetate, benzaldehyde and isopropyl triphenylphosphonium iodide according to the procedures described in Example 1, Steps A-G. ¹H NMR (300 MHz, CDCl₃): δ 7.34 (m, 3 H), 7.11 (m, 2 H), 5.76 (s, 1 H), 4.44 (d, J = 5.5 Hz, 2 H), 3.01 (q, J = 7.4 Hz, 2 H), 2.75 (q, J = 7.4 Hz, 2 H), 1.58 (s, 3 H), 1.35 (m, 7 H), 1.21 (t, J = 7.4 Hz, 3 H). FAB-MS: calculated for (C₂₀H₂₅NO) 295, found 296 (M+H). Anal. Calcd for C₂₀H₂₅NO: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.03; H, 8.55; N, 4.65. mp 103-104°C. R_f = 0.4 (50% ethyl acetate/hexane).

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EXAMPLE 62,6-Diethyl-3-hydroxymethyl-4-phenyl-5-(1-pentenyl)pyridine

5 The title compound was prepared from ethyl propionylacetate, benzaldehyde and butyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. The product was obtained as a mixture 6:4 trans:cis isomers. ¹H NMR (300 MHz, CDCl₃): δ 7.36 (m, 3 H), 7.14 (m, 2 H), 6.00 (m, 1 H), 5.37 (m, 1 H), 4.42 (m, 2 H), 2.90 (m, 4 H), 1.89 & 1.67 (2q, J = 7 Hz, 2 H), 1.25 (m, 9 H), 0.76 (m, 3 H). FAB-MS: calculated for (C₂₁H₂₇NO) 309, 10 found 310 (M+H); Anal. Calcd for C₂₁H₂₇NO: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.95; H, 8.90; N, 4.45. mp 74-76°C. R_f = 0.5 (50% ethyl acetate/hexane)

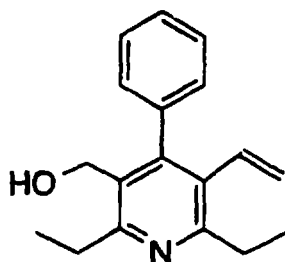
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EXAMPLE 72,6-Diethyl-3-hydroxymethyl-4-phenyl-5-pentylpyridine

20 The title compound was prepared from 2,6-diethyl-3-hydroxymethyl-4-phenyl-5-(1-pentenyl)pyridine (Example 6) according to the procedure described in Example 1, Step H. ¹H NMR (300 MHz, CDCl₃): δ 7.42 (m, 3 H), 7.18 (m, 2 H), 4.34 (d, J = 6 Hz, 2 H), 2.96 (q, J = 7.7 Hz, 2 H), 2.84 (q, J = 7.7 Hz, 2 H), 2.28 (m, 2 H), 1.34 (m, 9 H), 1.09 (m, 4 H), 0.76 (t, J = 7 Hz, 3 H). FAB-MS: calculated for (C₂₁H₂₉NO) 311, found 312 (M+H). mp 76-77°C. R_f = 0.5 (50% ethyl acetate/hexane).

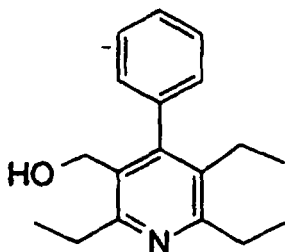
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EXAMPLE 82,6-Diethyl-3-hydroxymethyl-4-phenyl-5-(1-ethenyl)pyridine

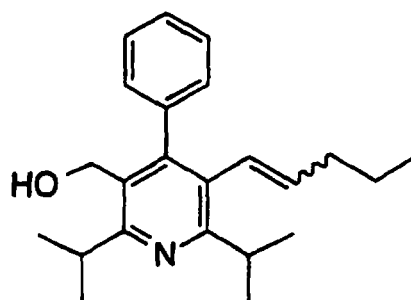
5 The title compound was prepared from ethyl propionylacetate, benzaldehyde and methyl triphenylphosphonium bromide/sodium amide according to the procedures described in Example 1, Steps A-G. ¹H NMR (300 MHz, CDCl₃): δ 7.40 (m, 3 H), 7.20 (m, 2 H), 6.36 (dd, *J* = 11, 18 Hz, 1 H), 5.22 (dd, *J* = 11, 2 Hz, 1 H), 5.00 (dd, *J* = 18, 2 Hz, 1 H), 4.41 (d, *J* = 6 Hz, 2 H), 2.96 (m, 4 H),
 10 1.35 (m, 7 H). FAB-MS: calculated for (C₁₈H₂₁NO) 267, found 268 (M+H). Anal. Calcd for C₁₈H₂₁NO: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.65; H, 8.06; N, 5.09. mp 84-85°C. R_f = 0.4 (50% ethyl acetate/hexane).

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EXAMPLE 92,5,6-Triethyl-3-hydroxymethyl-4-phenylpyridine

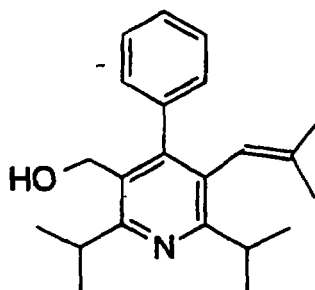
20 The title compound was prepared from 2,6-diethyl-3-hydroxymethyl-4-phenyl-5-(1-ethenyl)pyridine (Example 8) according to the procedure described in Example 1, Step H. ¹H NMR (300 MHz, CDCl₃): δ 7.44 (m, 3 H), 7.18 (m, 2 H), 4.33 (d, *J* = 6 Hz, 2 H), 2.97 (q, *J* = 8 Hz, 2 H), 2.86 (q, *J* = 8 Hz, 2 H), 2.36 (q, *J* = 8 Hz, 2 H), 1.34 (m, 7 H), 0.93 (t, *J* = 8 Hz, 3 H). FAB-MS: calculated for (C₁₈H₂₃NO) 269, found 270 (M+H). Anal. Calcd for C₁₈H₂₃NO: C, 80.26; H, 8.61; N, 5.20. Found:
 25 C, 79.70; H, 8.54; N, 5.08. mp 100°C. R_f = 0.4 (50% ethyl acetate/hexane).

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EXAMPLE 102,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-(1-pentenyl)pyridine

5 The title compound was prepared from ethyl isobutyrylacetate, benzaldehyde and butyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. ^1H NMR (300 MHz, CDCl_3): δ 7.35 (m, 3 H), 7.14 (m, 2 H), 5.99 (m, 1 H), 5.35 (m, 1 H), 4.41 (m, 2 H), 3.36 (m, 2 H), 1.89 & 1.70 (2q, J = 7 Hz, 2 H), 1.24 (m, 15 H), 0.80 & 0.72 (2t, J = 7 Hz, 3 H). FAB-MS: calculated for $(\text{C}_{23}\text{H}_{31}\text{NO})$ 337, found 338 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{23}\text{H}_{31}\text{NO}$: C, 81.85; H, 9.26; N, 4.15. Found: C, 81.88; H, 9.22; N, 3.93. mp 67-73°C. R_f = 0.1 (10% ethyl acetate/hexane).

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EXAMPLE 11

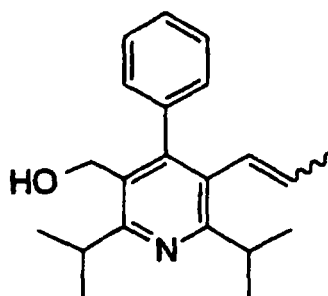
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2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-(2-methyl-1-propenyl)-pyridine

20 The title compound was prepared from ethyl isobutyrylacetate, benzaldehyde and isopropyl triphenylphosphonium iodide according to the procedures described in Example 1, Steps A-G. ^1H NMR (300 MHz, CDCl_3): δ 7.32 (m, 3 H), 7.11 (m, 2 H), 5.75 (s, 1 H), 4.43 (bs, 2 H), 3.46 (sept, J = 6.6 Hz, 1 H), 3.18 (sept, J = 6.6 Hz, 1 H), 1.57 (s, 3 H), 1.31 (m, 15 H). FAB-MS: calculated for $(\text{C}_{22}\text{H}_{29}\text{NO})$ 323, found 324 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{22}\text{H}_{29}\text{NO}$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.59; H, 8.94; N, 4.29. mp 93-95°C. R_f = 0.1 (10% ethyl acetate/hexane).

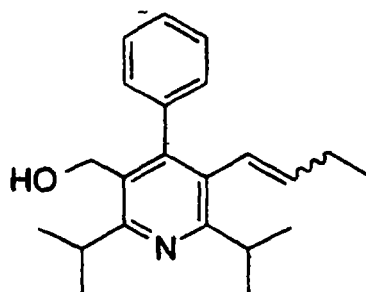
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EXAMPLE 122,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-(1-propenyl)pyridine

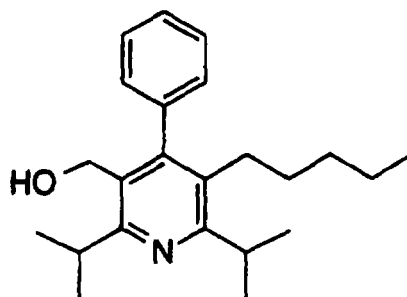
5 The title compound was prepared from ethyl isobutyrylacetate, benzaldehyde and ethyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. The product was obtained as a mixture 1:1 trans:cis isomers; gummy oil. ¹H NMR (300 MHz, CDCl₃): δ 7.4 (m, 3 H), 7.2 (m, 2 H), 6.0 (m, 1 H), 5.5 & 5.4 (2m, 1 H), 4.4 (m, 2 H), 3.4 & 3.2 (2m, 2 H),
 10 1.6 (m, 2 H), 1.4 (m, 7 H), 1.3 (m, 7 H). FAB-MS: calculated for (C₂₁H₂₇NO) 309, found 310 (M+H). Anal. Calcd for C₂₁H₂₇NO: C, 81.53; H, 9.98; N, 3.96. Found: C, 79.06; H, 9.65; N, 3.61. R_f = 0.4 (20% ethyl acetate/hexane).

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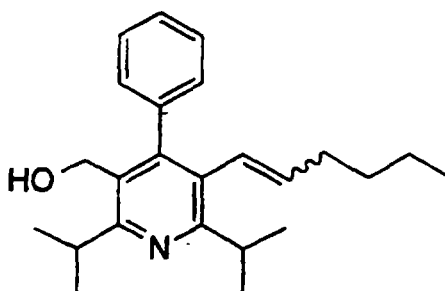
EXAMPLE 132,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-(1-butenyl)pyridine

20 The title compound was prepared from ethyl isobutyrylacetate, benzaldehyde and propyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. The product was obtained as a mixture 1:1 trans:cis isomers; gummy oil. ¹H NMR (300 MHz, CDCl₃): δ 7.4 (m, 3 H), 7.2 (m, 2 H), 6.0 (m, 1 H), 5.4 (m, 1 H), 4.4 (m, 2 H), 3.3 (m, 3 H), 1.9 & 1.7 (2m, 2 H), 1.3 (m, 12 H), 0.7 (m, 3 H). FAB-MS: calculated for (C₂₂H₂₉NO) 323, found 324
 25 (M+H). R_f = 0.4 (20% ethyl acetate/hexane).

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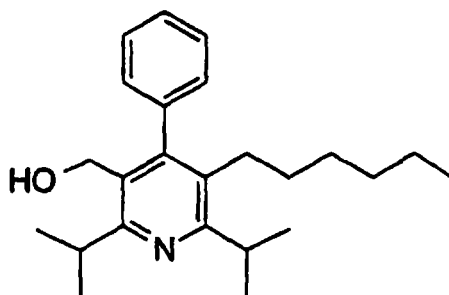
EXAMPLE 142,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-pentylpyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-phenyl-5-(1-pentenyl)pyridine (Example 10) according to the procedure described in Example 1, Step H. ^1H NMR (300 MHz, CDCl_3) δ 7.41 (m, 3 H), 7.18 (m, 2 H), 4.33 (s, 2 H), 3.42 (sept, $J = 6.6$ Hz, 1 H), 3.23 (sept, $J = 6.6$ Hz, 1 H), 2.26 (m, 2 H), 1.32 (m, 13 H), 1.11 (m, 5 H), 0.76 (t, $J = 7$ Hz, 3 H). FAB(HR)-MS calcd for $\text{C}_{23}\text{H}_{33}\text{NO}$ 339.2640; found 340.2640 ($\text{M}+\text{H}$). mp 81-82°C. $R_f = 0.1$ (10% ethyl acetate/hexane).

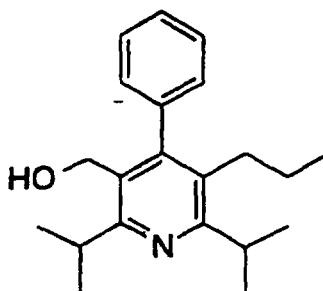
EXAMPLE 152,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-(1-hexenyl)pyridine

The title compound was prepared from ethyl isobutyrylacetate, benzaldehyde and pentyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. The product was obtained as a mixture 1:1 trans:cis isomers; gummy oil. ^1H NMR (300 MHz, CDCl_3): δ 7.35 (m, 3 H), 7.14 (m, 2 H), 5.99 (m, 1 H), 5.35 (m, 1 H), 4.40 (m, 2 H), 3.36 (m, 2 H), 1.92 & 1.70 (2m, 2 H), 1.20 (m, 17 H), 0.80 (m, 3 H). FAB-MS: calculated for $(\text{C}_{24}\text{H}_{33}\text{NO})$ 351, found 352 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{24}\text{H}_{33}\text{NO}$: C, 82.00; H, 9.46; N, 3.98. Found: C, 81.58; H, 9.50; N, 4.62. $R_f = 0.1$ (10% ethyl acetate/hexane);

0

EXAMPLE 162,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-hexylpyridine

5 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-phenyl-5-(1-hexenyl)pyridine (Example 15) according to the procedure described in Example 1, Step H. ^1H NMR (300 MHz, CDCl_3): δ 7.40 (m, 3 H), 7.18 (m, 2 H), 4.33 (d, J = 5 Hz, 2 H), 3.42 (septet, J = 7 Hz, 1 H), 3.23 (septet, J = 7 Hz, 1 H), 2.26 (m, 2 H), 1.31 (m, 13 H), 1.12 (m, 8 H), 0.80 (t, J = 7 Hz, 3 H). FAB-MS: calculated for ($\text{C}_{24}\text{H}_{35}\text{NO}$) 353, found 354 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{24}\text{H}_{35}\text{NO}$: C, 81.53; H, 9.98; N, 3.96. Found: C, 79.06; H, 9.65; N, 3.61. mp 71-72°C. R_f = 0.1 (10% ethyl acetate/hexane).

EXAMPLE 17

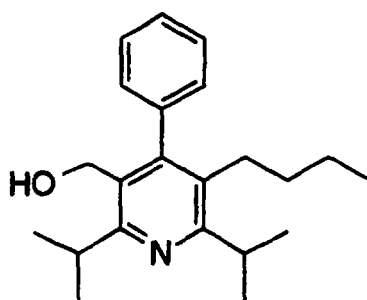
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2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-propylpyridine

20 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-phenyl-5-(1-propenyl)pyridine (Example 12) according to the procedure described in Example 1, Step H. ^1H NMR (300 MHz, CDCl_3): δ 7.41 (m, 3 H), 7.17 (m, 2 H), 4.33 (s, 2 H), 3.42 (sept, J = 6.6 Hz, 1 H), 3.23 (sept, J = 6.6 Hz, 1 H), 2.25 (m, 2 H), 1.33 (d, J = 6.6 Hz, 6 H), 1.30 (d, J = 6.6 Hz, 6 H), 1.27 (m, 2 H), 1.20 (m, 1 H), 0.74 (t, J = 7 Hz, 3 H). FAB-MS: calculated for ($\text{C}_{21}\text{H}_{29}\text{NO}$) 311, found 312 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{21}\text{H}_{29}\text{NO}$: C, 80.98; H, 9.38; N, 4.50. Found: C, 80.72; H, 9.47; N, 4.38. mp 89-90°C. R_f = 0.4 (20% ethyl acetate/hexane).

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EXAMPLE 18**2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-butylpyridine**

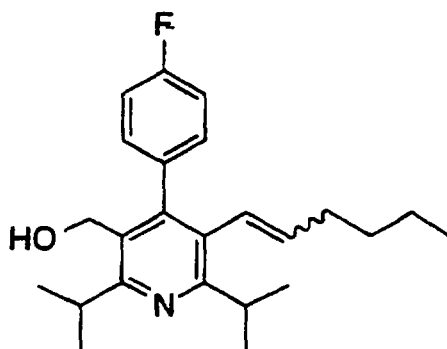
5

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-phenyl-5-(1-butenyl)pyridine (Example 13) according to the procedure described in Example 1, Step H. ^1H NMR (300 MHz, CDCl_3): δ 7.41 (m, 3 H), 7.17 (m, 2 H), 4.33 (s, 2 H), 3.42 (sept, $J = 6.6$ Hz, 1 H), 3.24 (sept, $J = 6.6$ Hz, 1 H), 2.28 (m, 2 H), 1.33 (d, $J = 6.6$ Hz, 6 H), 1.31 (d, $J = 6.6$ Hz, 6 H), 1.28 (m, 2 H), 1.14 (m, 3 H), 0.71 (t, $J = 7$ Hz, 3 H). FAB-MS: calculated for $(\text{C}_{22}\text{H}_{31}\text{NO})$ 325, found 326 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{22}\text{H}_{31}\text{NO}$: C, 81.18; H, 9.60; N, 4.30. Found: C, 81.28; H, 9.87; N, 4.07. mp 83-84°C. $R_f = 0.4$ (20% ethyl acetate/hexane).

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EXAMPLE 19

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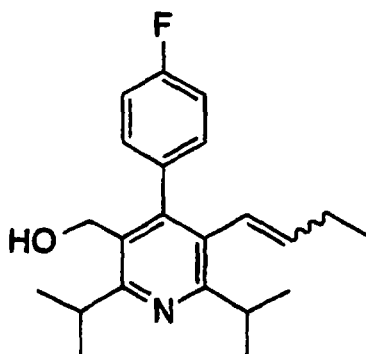
**2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-hexenyl)-pyridine**

The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and pentyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. The product was obtained as a mixture 6:4 trans:cis isomers; gummy oil. ^1H NMR (300 MHz, CDCl_3): δ 7.10 (m, 4 H), 5.98 (m, 1 H), 5.42 (dt, $J = 7, 11.4$ Hz, 0.4 H), 5.29 (dt, $J = 7, 16.2$ Hz, 0.6 H), 4.40 (d, $J = 5.5$ Hz, 2 H), 3.44 (m, 1 H), 3.36 (sept, $J = 6.6$ Hz, 0.6 H), 3.24 (sept, $J = 6.6$ Hz, 0.4 H), 1.94 (m, 1 H), 1.36 (m, 6 H), 1.23 (m, 8 H), 1.12 (m, 4 H), 0.82 (m, 3 H). FAB-

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- 0 MS: calculated for (C₂₄H₃₂FNO) 369, found 370 (M+H). R_f = 0.4 (20% ethyl acetate/hexane).

EXAMPLE 20



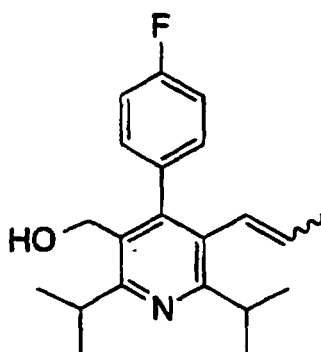
5

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-butenyl)-pyridine

- The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and propyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. The product was obtained as a mixture 1:1 trans:cis isomers; gummy oil. ¹H NMR (300 MHz, CDCl₃): δ 7.10 (m, 4 H), 5.97 (m, 1 H), 5.39 (dt, J = 7, 11.4 Hz, 0.5 H), 5.32 (dt, J = 7, 16.2 Hz, 0.5 H), 4.41 (d, J = 5.5 Hz, 2 H), 3.45 (m, 1 H), 3.36 (sept, J = 6.6 Hz, 0.5 H), 3.24 (sept, J = 6.6 Hz, 0.5 H), 1.95 (m, 1 H), 1.70 (m, 1 H), 1.35 (d, J = 6.6 Hz, 3 H), 1.34 (d, J = 6.6 Hz, 3 H), 1.25 (m, 7 H), 0.79 (t, J = 7.5 Hz, 1.5 H), 0.78 (t, J = 7.5 Hz, 1.5 H). FAB-MS: calculated for (C₂₂H₂₈FNO) 341, found 342 (M+H). R_f = 0.4 (20% ethyl acetate/hexane).

15

EXAMPLE 21



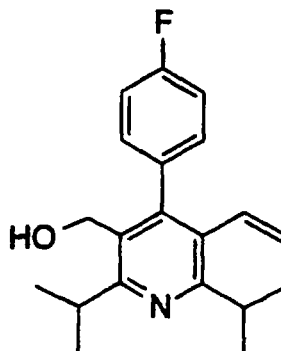
20

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-propenyl)-pyridine

The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and ethyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. The product was obtained as a

- 0 mixture 1:1 trans:cis isomers. ^1H NMR (300 MHz, CDCl_3): δ 7.11 (m, 4 H), 6.04 (d, $J = 11.7$ Hz, 0.5 H), 5.96 (d, $J = 16.1$ Hz, 0.5 H), 5.53 (m, 0.5 H), 5.33 (m, 0.5 H), 4.41 (m, 3 H), 3.42 (m, 1.5 H), 3.20 (sept, $J = 6.6$ Hz, 0.5 H), 1.61 (d, $J = 6$ Hz, 2 H), 1.3 (m, 13 H). FAB-MS: calculated for $(\text{C}_{21}\text{H}_{26}\text{FNO})$ 327, found 328 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{FNO}$: C, 77.03; H, 8.00; N, 4.28. Found: C, 77.15; H, 8.07; N, 4.11. mp
- 5 46-47°C. $R_f = 0.4$ (20% ethyl acetate/hexane).

EXAMPLE 22

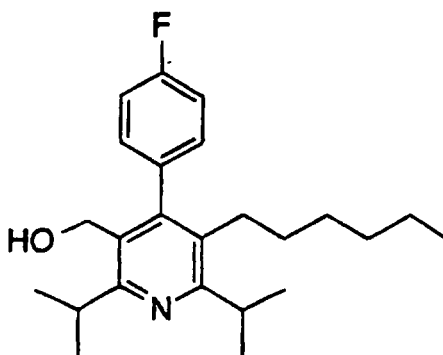


10

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-ethenylpyridine

- The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and methyl triphenylphosphonium bromide/sodium amide according to the procedures described in Example 1, Steps A-G. ^1H NMR (300
- 15 MHz, CDCl_3): δ 7.12 (m, 4 H), 6.35 (dd, $J = 11.5, 18$ Hz, 1 H), 5.24 (dd, $J = 1.5, 11.4$ Hz, 1 H), 4.97 (dd, $J = 1.5, 18$ Hz, 1 H), 4.41 (d, $J = 5.5$ Hz, 2 H), 3.44 (sept, $J = 6.6$ Hz, 2 H), 1.35 (d, $J = 6.6$ Hz, 6 H), 1.28 (d, $J = 6.6$ Hz, 6 H), 1.25 (m, 1 H). FAB-MS: calculated for $(\text{C}_{20}\text{H}_{24}\text{FNO})$ 313, found 314 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{FNO}$: C, 76.65; H, 7.72; N, 4.47. Found: C, 76.87; H, 7.79; N, 4.33. mp 119-120°C. $R_f = 0.4$
- 20 (20% ethyl acetate/hexane).

EXAMPLE 23

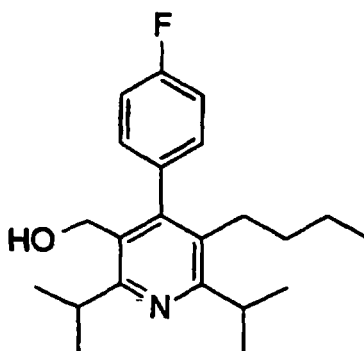


0

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-hexylpyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-hexenyl)pyridine (Example 19) according to the procedure described in Example 1, Step H. ¹H NMR (300 MHz, CDCl₃): δ 7.14 (m, 4 H), 4.33 (s, 2 H), 3.41 (sept, *J* = 6.6 Hz, 1 H), 3.23 (sept, *J* = 6.6 Hz, 1 H), 2.26 (m, 2 H), 1.33 (d, *J* = 6.6 Hz, 6 H), 1.30 (d, *J* = 6.6 Hz, 6 H), 1.26 (m, 1 H), 1.14 (m, 7 H), 0.82 (t, *J* = 7 Hz, 3 H). FAB-MS: calculated for (C₂₄H₃₄FNO) 371, found 372 (M+H). mp 93-95°C. R_f = 0.4 (20% ethyl acetate/hexane).

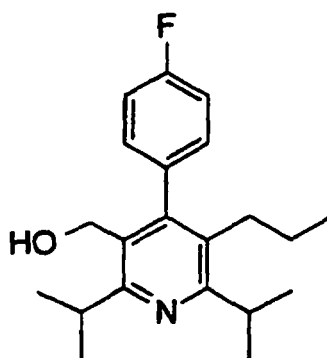
10

EXAMPLE 242,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-butylpyridine

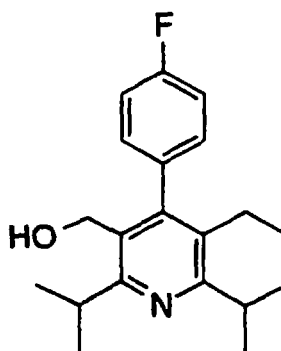
The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-butenyl)pyridine (Example 20) according to the procedure described in Example 1, Step H. ¹H NMR (300 MHz, CDCl₃): δ 7.15 (m, 4 H), 4.33 (d, *J* = 5.2 Hz, 2 H), 3.41 (sept, *J* = 6.6 Hz, 1 H), 3.23 (sept, *J* = 6.6 Hz, 1 H), 2.27 (m, 2 H), 1.34 (d, *J* = 6.6 Hz, 6 H), 1.30 (d, *J* = 6.6 Hz, 6 H), 1.27 (m, 1 H), 1.16 (m, 3 H), 0.73 (t, *J* = 7 Hz, 3 H). FAB-MS: calculated for (C₂₂H₃₀FNO) 343, found 344 (M+H). Anal. Calcd for C₂₂H₃₀FNO: C, 76.93; H, 8.80; N, 4.08. Found: C, 76.93; H, 8.70; N, 3.96. mp 45-50°C. R_f = 0.4 (20% ethyl acetate/hexane).

25

30

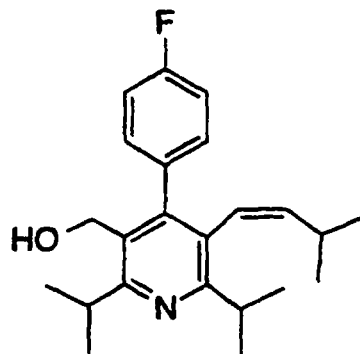
EXAMPLE 252,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-propylpyridine

5 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-propenyl)pyridine (Example 21) according to the procedure described in Example 1, Step H. ^1H NMR (300 MHz, CDCl_3): δ 7.15 (m, 4 H), 4.33 (s, 2 H), 3.41 (sept, $J = 6.6$ Hz, 1 H), 3.23 (sept, $J = 6.6$ Hz, 1 H), 2.25 (m, 2 H), 1.33 (d, $J = 6.6$ Hz, 6 H), 1.30 (d, $J = 6.6$ Hz, 6 H), 1.27 (m, 1 H), 1.19 (m, 1 H), 0.76 (t, $J = 7$ Hz, 3 H). FAB-MS: calculated for ($\text{C}_{21}\text{H}_{28}\text{FNO}$) 329, found 330 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{FNO}$: C, 76.56; H, 8.57; N, 4.25. Found: C, 76.55; H, 8.48; N, 4.11. mp 49-54 °C. $R_f = 0.4$ (20% ethyl acetate/hexane).

EXAMPLE 262,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-ethylpyridine

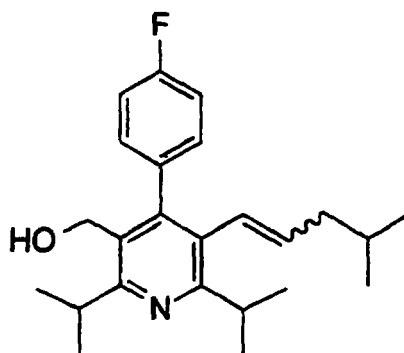
20 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-ethenylpyridine (Example 22) according to the procedure described in Example 1, Step H. ^1H NMR (300 MHz, CDCl_3): δ 7.15 (m, 4 H), 4.33 (d, $J = 3.6$ Hz, 2 H), 3.41 (sept, $J = 6.6$ Hz, 1 H), 3.26 (sept, $J = 6.6$ Hz, 1 H), 2.34 (q, $J = 7.35$ Hz, 2 H), 1.33 (d, $J = 6.6$ Hz, 6 H), 1.31 (d, $J = 6.6$ Hz, 6 H), 1.19 (m, 1 H), 0.93 (t, $J = 7.35$ Hz, 3 H). FAB-MS: calculated for ($\text{C}_{20}\text{H}_{26}\text{FNO}$) 315, found 316 ($\text{M}+\text{H}$). Anal.

- 0 Calcd for $C_{20}H_{26}FNO$: C, 76.16; H, 8.31; N, 4.44. Found: C, 75.74; H, 8.50; N, 4.27.
mp 126-129°C. R_f = 0.4 (20% ethyl acetate/hexane).

EXAMPLE 27

5
(Z)-2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(3-methyl-1-butenyl)pyridine

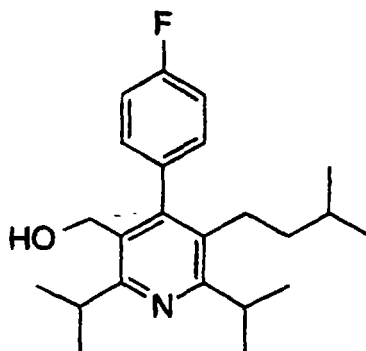
- The title compound was prepared from ethyl isobutyrylacetate,
10 4-fluorobenzaldehyde and isobutyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. 1H NMR (300 MHz, $CDCl_3$): δ 7.07 (m, 4 H), 5.92 (d, J = 10.7 Hz, 1 H), 5.20 (dd, J = 10.7, 11.4 Hz, 1 H), 4.42 (bs, 2 H), 3.45 (sept, J = 6.6 Hz, 1 H), 3.30 (sept, J = 6.6 Hz, 1 H), 2.06 (m, 1 H), 1.35 (d, J = 6.6 Hz, 6 H), 1.31 (m, 1 H), 1.24 (m, 5 H), 0.69 (bs, 6 H). FAB-MS: calculated for ($C_{23}H_{30}FNO$) 355, found 356 ($M+H$). Anal. Calcd for $C_{23}H_{30}FNO$: C, 77.71; H, 8.51; N, 3.94. Found: C, 77.94; H, 8.59; N, 3.79. mp 112°C. R_f = 0.3 (20% ethyl acetate/hexane).

EXAMPLE 28

20
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(4-methyl-1-pentenyl)pyridine

0 The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and isoamyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. The product is obtained as a 6:4 mixture of trans:cis isomers. ¹H NMR (300 MHz, CDCl₃): δ 7.11 (m, 4 H), 6.04 (dt, J = 1.5, 11 Hz, 0.4 H), 5.96 (dt, J = 1.5, 16 Hz, 0.6 H), 5.47 (dt, J = 7, 11 Hz, 0.4 H), 5.32 (dt, J = 7, 16 Hz, 0.6 H), 4.41 (m, 2 H), 3.44 (m, 0.8 H), 3.38 (sept, J = 6.6 Hz, 0.6 H), 3.24 (sept, J = 6.6 Hz, 0.6 H), 1.84 (m, 1 H), 1.45 (m, 1 H), 1.35 (m, 6 H), 1.24 (m, 7 H), 0.79 (d, J = 6.6 Hz, 2.4 H), 0.73 (d, J = 6.6 Hz, 3.6 H). FAB-MS: calculated for (C₂₄H₃₂FNO) 369, found 370 (M+H). Anal. Calcd for C₂₄H₃₂FNO: C, 78.01; H, 8.73; N, 3.79. Found: C, 78.14; H, 8.62; N, 3.50. mp 48-50°C. R_f = 0.3 (20% ethyl acetate/hexane).

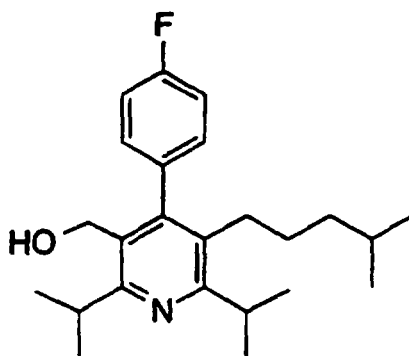
EXAMPLE 29



2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(3-methylbutyl)pyridine

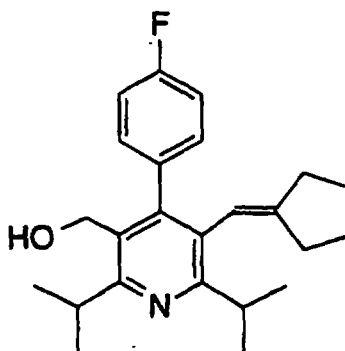
15 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(3-methyl-1-butenyl)pyridine (Example 27) according to the procedure described in Example 1, Step H. ¹H NMR (300 MHz, CDCl₃): δ 7.14 (m, 4 H) 4.33 (d, J = 5.5 Hz, 2 H), 3.41 (sept, J = 6.6 Hz, 1 H), 3.22 (sept, J = 6.6 Hz, 1 H), 2.27 (m, 2 H), 1.35 (m, 1 H), 1.33 (d, J = 7 Hz, 6 H), 1.30 (d, J = 7 Hz, 6 H), 1.17 (m, 3 H), 0.70 (d, J = 6.6 Hz, 6 H). FAB-MS: calculated for (C₂₃H₃₂FNO) 357, found 358 (M+H). Anal. Calcd for C₂₃H₃₂FNO: C, 77.27; H, 9.02; N, 3.92. Found: C, 77.34; H, 9.15; N, 3.69. mp 43-45°C. R_f = 0.2 (20% ethyl acetate/hexane).

0

EXAMPLE 302,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(4-methylpentyl)pyridine

5 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(4-methyl-1-pentenyl)pyridine (Example 28) according to the procedure described in Example 1, Step H. ^1H NMR (300 MHz, CDCl_3): δ 7.14 (m, 4 H), 4.33 (d, $J = 5$ Hz, 2 H), 3.41 (sept, $J = 6.6$ Hz, 1 H), 3.22 (sept, $J = 6.6$ Hz, 1 H), 2.23 (m, 2 H), 1.38 (m, 1 H), 1.33 (d, $J = 6.6$ Hz, 6 H), 1.30 (d, $J = 6.6$ Hz, 6 H), 1.27 (m, 10 1 H), 1.17 (m, 1 H), 1.00 (m, 3 H), 0.76 (d, $J = 6.6$ Hz, 6 H). FAB-MS: calculated for ($\text{C}_{24}\text{H}_{34}\text{FNO}$) 371, found 372 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{24}\text{H}_{34}\text{FNO}$: C, 77.59; H, 9.22; N, 3.77. Found: C, 77.63; H, 9.39; N, 3.58. mp 101-103°C. $R_f = 0.3$ (20% ethyl acetate/hexane).

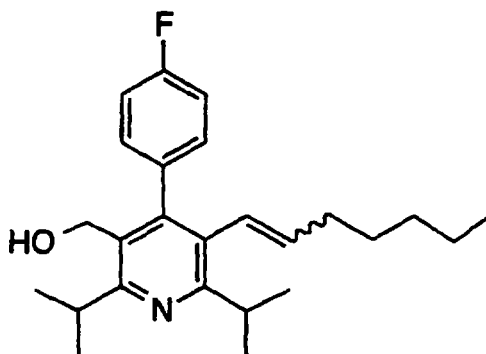
15

EXAMPLE 312,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(cyclopentylidenemethylene)pyridine

20 The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and cyclopentyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. ^1H NMR (300 MHz, CDCl_3): δ 7.13 (m, 2 H), 7.07 (m, 2 H), 5.88 (s, 1 H), 4.43 (d, $J = 5.5$ Hz, 2 H), 3.44 (sept, $J = 6.6$

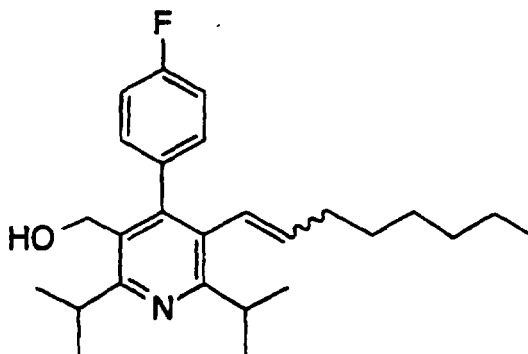
0 Hz, 1 H), 3.21 (sept, $J = 6.6$ Hz, 1 H), 2.11 (m, 2 H), 1.75 (m, 2 H), 1.47 (m, 4 H), 1.34 (d, $J = 6.6$ Hz, 6 H), 1.29 (m, 1 H), 1.21 (d, $J = 6.6$ Hz, 6 H). FAB-MS: calculated for ($C_{24}H_{30}FNO$) 367, found 368 (M+H). Anal. Calcd for $C_{24}H_{30}FNO$: C, 78.44; H, 8.23; N, 3.81. Found: C, 78.46; H, 8.18; N, 3.63. mp 97-98°C. $R_f = 0.3$ (20% ethyl acetate/hexane).

5

EXAMPLE 3210 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-heptenyl)-pyridine

The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and n-hexyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. The product was obtained as a mixture 1:1 trans:cis isomers; gummy oil. 1H NMR (300 MHz, $CDCl_3$): δ 7.11 (m, 4

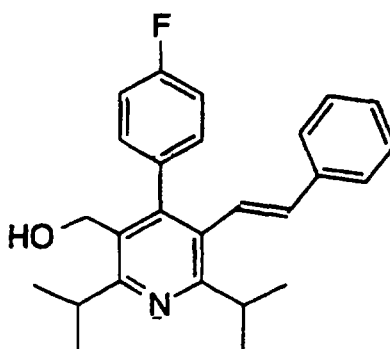
15 H), 5.99 (m, 1 H), 5.42 (dt, $J = 7, 11$ Hz, 0.5 H), 5.30 (dt, $J = 7, 16$ Hz, 0.5 H), 4.41 (d, $J = 5.5$ Hz, 2 H), 3.45 (m, 1 H), 3.37 (sept, $J = 6.6$ Hz, 0.5 H), 3.24 (sept, $J = 6.6$ Hz, 0.5 H), 1.94 (m, 1 H), 1.35 (m, 6 H), 1.29 (m, 1 H), 1.26 (d, $J = 6.6$ Hz, 3 H), 1.22 (m, 6 H), 1.15 (m, 4 H), 0.86 (m, 3 H). FAB-MS: calculated for ($C_{25}H_{34}FNO$) 383, found 384 (M+H). Anal. Calcd for $C_{25}H_{34}FNO$: C, 78.29; H, 8.93; N, 3.65. Found: C, 78.37; 20 H, 8.88; N, 3.57. $R_f = 0.4$ (20% ethyl acetate/hexane).

EXAMPLE 33

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2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-octenyl)-pyridine

The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and n-heptyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. The product was obtained as a mixture 1:1 trans:cis isomers; gummy oil. ¹H NMR (300 MHz, CDCl₃): δ 7.11 (m, 4 H), 5.98 (m, 1 H), 5.42 (dt, J = 7, 11 Hz, 0.5 H), 5.30 (dt, J = 7, 16 Hz, 0.5 H), 4.41 (d, J = 5.5 Hz, 2 H), 3.44 (m, 1 H), 3.37 (sept, J = 6.6 Hz, 0.5 H), 3.24 (sept, J = 6.6 Hz, 0.5 H), 1.94 (m, 1 H), 1.35 (m, 6 H), 1.30 (m, 1 H), 1.26 (d, J = 6.6 Hz, 6 H), 1.22 (m, 4 H), 1.16 (m, 5 H), 0.87 (m, 3 H). FAB-MS: calculated for (C₂₆H₃₆FNO) 397, found 398 (M+H). Anal. Calcd for C₂₆H₃₆FNO: C, 78.55; H, 9.13; N, 3.52. Found: C, 78.63; H, 9.16; N, 3.48. R_f = 0.4 (20% ethyl acetate/hexane)

EXAMPLE 34

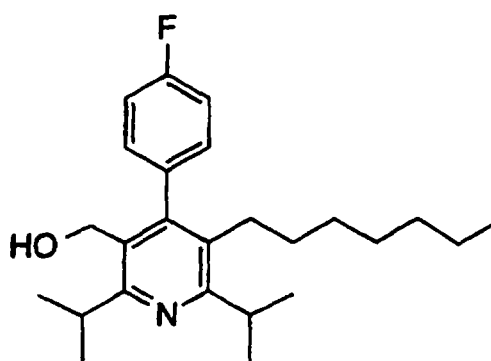
15

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[2(E)-phenyl-ethenyl]pyridine

The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and benzyl triphenylphosphonium bromide/sodium amide according to the procedures described in Example 1, Steps A-G. ¹H NMR (300 MHz, CDCl₃): δ 7.21 (m, 9 H), 6.70 (d, J = 16.5 Hz, 1 H), 6.26 (d, J = 16.5 Hz, 1 H), 4.45 (d, J = 5.5 Hz, 2 H), 3.48 (sept, J = 6.6 Hz, 2 H), 1.37 (d, J = 6.6 Hz, 6 H), 1.31 (d, J = 6.6 Hz, 6 H), 1.29 (m, 1 H). FAB-MS: calculated for (C₂₆H₂₈FNO) 389, found 390 (M+H). Anal. Calcd for C₂₆H₂₈FNO: C, 80.17; H, 7.25; N, 3.60. Found: C, 79.89; H, 7.28; N, 3.49. mp 107-110°C. R_f = 0.3 (20% ethyl acetate/hexane).

30

0

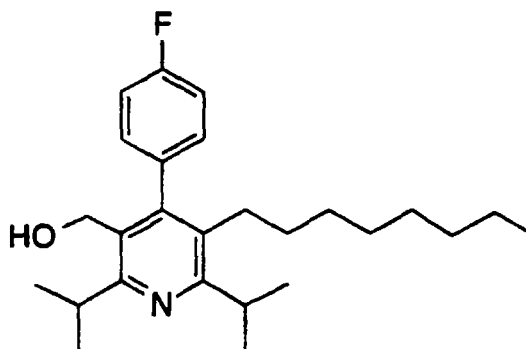
EXAMPLE 35**2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-heptylpyridine**

5 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-heptenyl)pyridine (Example 32) according to the procedure described in Example 1, Step H. ¹H NMR (300 MHz, CDCl₃): δ 7.13 (m, 4 H), 4.33 (s, 2 H), 3.41 (sept, *J* = 6.6 Hz, 1 H), 3.22 (sept, *J* = 6.6 Hz, 1 H), 2.26 (m, 2 H), 1.33 (d, *J* = 6.6 Hz, 6 H), 1.30 (d, *J* = 6.6 Hz, 6 H), 1.22 (m, 3 H), 1.11 (m, 8 H), 0.85 (t, *J* = 7 Hz, 3 H). FAB-MS: calculated for (C₂₅H₃₆FNO) 385, found 386 (M+H). Anal. Calcd for C₂₅H₃₆FNO: C, 77.88; H, 9.41; N, 3.63. Found: C, 77.86; H, 9.66; N, 3.59. mp 73-75°C. R_f = 0.3 (20% ethyl acetate/hexane).

10

EXAMPLE 36

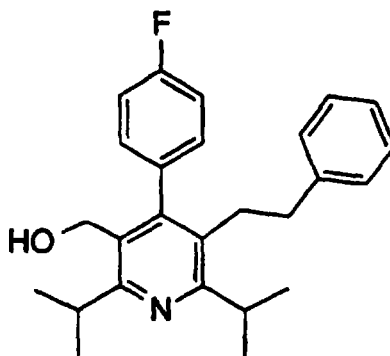
15

**2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-octylpyridine**

20 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-octenyl)pyridine (Example 33) according to the procedure described in Example 1, Step H. ¹H NMR (300 MHz, CDCl₃): δ 7.14 (m, 4 H), 4.33 (d, *J* = 5.5 Hz, 2 H), 3.41 (sept, *J* = 6.6 Hz, 1 H), 3.23 (sept, *J* = 6.6 Hz, 1 H), 2.26 (m, 2 H), 1.33 (d, *J* = 6.6 Hz, 6 H), 1.30 (d, *J* = 6.6 Hz, 6 H), 1.25 (m, 3 H), 1.15 (m, 10 H), 0.87 (t, *J* = 7 Hz, 3 H). FAB-MS: calculated for (C₂₆H₃₈FNO) 399, found 400 (M+H).

- 0 Anal. Calcd for $C_{26}H_{38}FNO$: C, 78.15; H, 9.59; N, 3.51. Found: C, 78.27; H, 9.81; N, 3.43. Gummy oil; $R_f = 0.3$ (20% ethyl acetate/hexane).

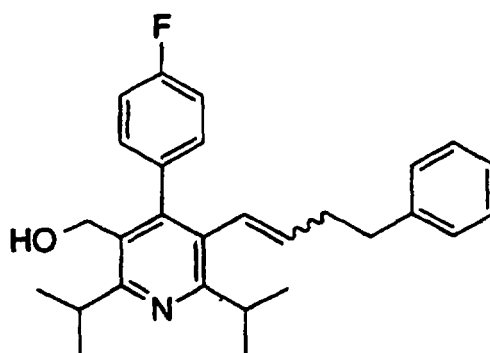
EXAMPLE 37



5 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(2-phenylethyl)pyridine

- The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[2(E)-phenylethenyl]pyridine (Example 34) according to the procedure described in Example 1, Step H. 1H NMR (300 MHz, $CDCl_3$): δ 7.19 (m, 7 H), 6.86 (m, 2 H), 4.36 (d, $J = 5.5$ Hz, 2 H), 3.44 (sept, $J = 6.6$ Hz, 1 H), 3.35 (sept, $J = 6.6$ Hz, 1 H), 2.58 (m, 4 H), 1.35 (d, $J = 6.6$ Hz, 6 H), 1.34 (d, $J = 6.6$ Hz, 6 H), 1.19 (t, $J = 5.5$ Hz, 1 H). FAB-MS: calculated for $(C_{26}H_{30}FNO)$ 391, found 392 ($M+H$). Anal. Calcd for $C_{26}H_{30}FNO$: C, 79.76; H, 7.72; N, 3.58. Found: C, 79.57; H, 7.61; N, 3.44. mp 158-159°C. $R_f = 0.3$ (20% ethyl acetate/hexane).

EXAMPLE 38

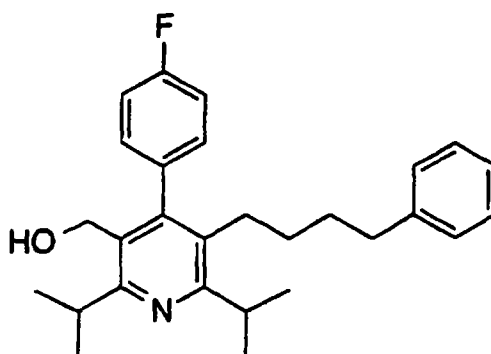


20 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(4-phenyl-1-butenyl)pyridine

The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and 3-phenylpropyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. The product was obtained as a mixture 5:1 trans:cis isomers; gummy oil. 1H NMR (300 MHz,

- 0 CDCI₃): δ 7.26 (m, 2 H), 7.19 (m, 1 H), 7.09 (m, 6 H), 6.05 (d, J = 11 Hz, 0.2 H), 5.98 (d, J = 16 Hz, 0.8 H), 5.47 (dt, J = 7, 11 Hz, 0.2 H), 5.33 (dt, J = 7, 16 Hz, 0.8 H), , 4.40 (d, J = 5 Hz, 2 H), 3.43 (m, 1 H), 3.26 (sept, J = 6.6 Hz, 1 H), 2.51 (m, 2 H), 2.29 (m, 1.6 H), 2.05 (m, 0.4 H), 1.34 (m, 6 H), 1.25 (m, 1 H), 1.22 (d, J = 6.6 Hz, 6 H). FAB-MS: calculated for (C₂₈H₃₂FNO) 417, found 418 (M+H). Anal. Calcd for C₂₈H₃₂FNO: C, 80.54; H, 7.72; N, 3.35. Found: C, 80.56; H, 7.56; N, 3.32. R_f = 0.3 (20% ethyl acetate/hexane).
- 5

EXAMPLE 39

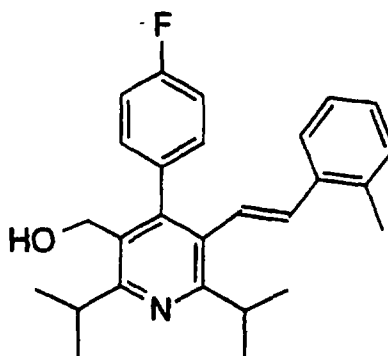


10

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(4-phenylbutyl)pyridine

- The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(4-phenyl-1-butenyl)pyridine (Example 38) according to the
- 15 procedure described in Example 1, Step H. Gummy oil; ¹H NMR (300 MHz, CDCl₃): δ 7.24 (m, 3 H), 7.08 (m, 6 H), 4.31 (d, J = 5.5 Hz, 2 H), 3.40 (sept, J = 6.6 Hz, 1 H), 3.17 (sept, J = 6.6 Hz, 1 H), 2.46 (t, J = 7.5 Hz, 2 H), 2.29 (m, 2 H), 1.47 (m, 2 H), 1.32 (d, J = 6.6 Hz, 6 H), 1.30 (m, 2 H), 1.27 (d, J = 6.6 Hz, 6 H), 1.15 (t, J = 5.5 Hz, 1 H). FAB-MS: calculated for (C₂₈H₃₄FNO) 419, found 420 (M+H). Anal. Calcd for
- 20 C₂₈H₃₄FNO: C, 80.15; H, 8.17; N, 3.34. Found: C, 80.06; H, 7.94; N, 3.28. R_f = 0.3 (20% ethyl acetate/hexane).

EXAMPLE 40

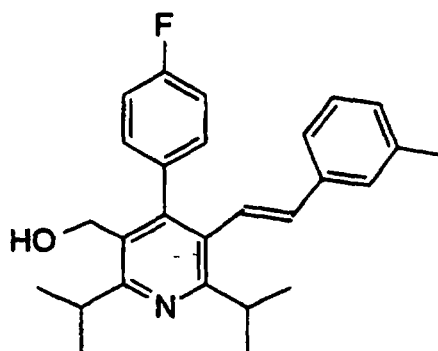


0 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[2(E)-(2-methyl-phenyl)ethenyl]pyridine

The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and 2-methylbenzyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. ¹H NMR (300
5 MHz, CDCl₃): δ 7.22 (m, 3 H), 7.10 (m, 5 H), 6.62 (d, J = 17 Hz, 1 H), 6.45 (d, J = 17 Hz, 1 H), 4.45 (d, J = 5.5 Hz, 2 H), 3.48 (m, 2 H), 2.12 (s, 3 H), 1.37 (d, J = 6.6 Hz, 6 H), 1.33 (d, J = 6.6 Hz, 6 H), 1.31 (m, 1 H). FAB-MS: calculated for (C₂₇H₃₀FNO) 403, found 404 (M+H). Anal. Calcd for C₂₇H₃₀FNO: C, 80.36; H, 7.49; N, 3.47. Found: C, 80.23; H, 7.23; N, 3.44. mp 108-111°C. R_f = 0.3 (20% ethyl acetate/hexane).

10

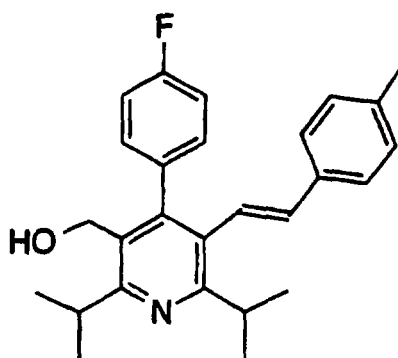
EXAMPLE 41



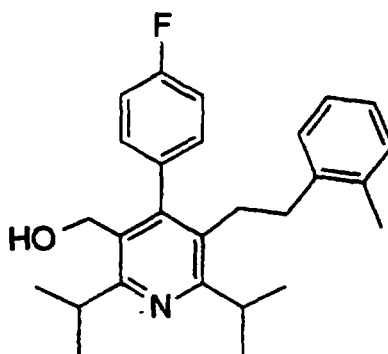
15 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[2(E)-(3-methyl-phenyl)ethenyl]pyridine

The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and 3-methylbenzyl triphenylphosphonium chloride according to the procedures described in Example 1, Steps A-G. ¹H NMR (300
20 MHz, CDCl₃): δ 7.18 (m, 3 H), 7.11 (m, 2 H), 7.00 (m, 3 H), 6.68 (d, J = 17 Hz, 1 H), 6.23 (d, J = 17 Hz, 1 H), 4.44 (d, J = 5.5 Hz, 2 H), 3.47 (m, 2 H), 2.32 (s, 3 H), 1.37 (d, J = 6.6 Hz, 6 H), 1.31 (d, J = 6.6 Hz, 6 H), 1.28 (m, 1 H). FAB-MS: calculated for (C₂₇H₃₀FNO) 403, found 404 (M+H). Anal. Calcd for C₂₇H₃₀FNO: C, 80.36; H, 7.49; N, 3.47. Found: C, 80.38; H, 7.45; N, 3.45. mp 97-99°C. R_f = 0.3 (20% ethyl
25 acetate/hexane).

30

EXAMPLE 422,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[2(E)-(4-methylphenyl)ethenyl]pyridine

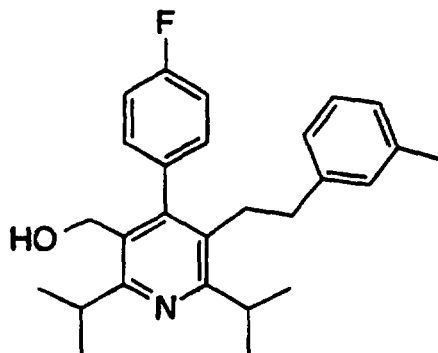
The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and 4-methylbenzyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. ¹H NMR (300 MHz, CDCl₃): δ 7.18 (m, 2 H), 7.08 (m, 6 H), 6.63 (d, J = 17 Hz, 1 H), 6.23 (d, J = 17 Hz, 1 H), 4.43 (d, J = 5 Hz, 2 H), 3.47 (sept, J = 6.6 Hz, 2 H), 2.31 (s, 3 H), 1.36 (d, J = 6.6 Hz, 6 H), 1.30 (d, J = 6.6 Hz, 6 H), 1.26 (m, 1 H). FAB-MS: calculated for (C₂₇H₃₀FNO) 403, found 404 (M+H). Anal. Calcd for C₂₇H₃₀FNO: C, 80.36; H, 7.49; N, 3.47. Found: C, 79.93; H, 7.34; N, 3.47. mp 131-133°C. R_f = 0.3 (20% ethyl acetate/hexane).

EXAMPLE 432,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[2-(2-methylphenyl)ethyl]pyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[2(E)-(2-methylphenyl)ethenyl]pyridine (Example 40) according to the procedure described in Example 1, Step H. ¹H NMR (300 MHz, CDCl₃): δ

0 7.16 (m, 4 H), 7.06 (m, 3 H), 6.81 (m, 1 H), 4.35 (d, $J = 4$ Hz, 2 H), 3.42 (sept, $J = 6.6$ Hz, 2 H), 2.57 (m, 4 H), 1.97 (s, 3 H), 1.36 (d, $J = 6.6$ Hz, 6 H), 1.35 (d, $J = 6.6$ Hz, 6 H), 1.19 (m, 1 H). FAB-MS: calculated for (C₂₇H₃₂FNO) 405, found 406 (M+H). Anal. Calcd for C₂₇H₃₂FNO: C, 79.96; H, 7.95; N, 3.45. Found: C, 80.08; H, 8.05; N, 3.46. mp 125-126°C. $R_f = 0.3$ (20% ethyl acetate/hexane).

5

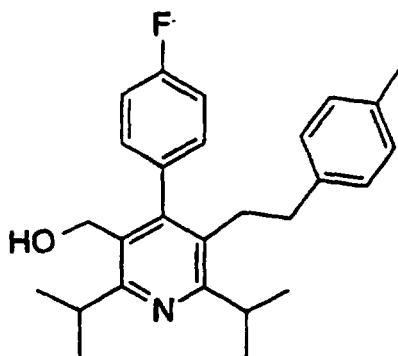
EXAMPLE 44

10 **2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[2-(3-methylphenyl)ethyl]pyridine**

The title compound was prepared 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[2(E)-(3-methylphenyl)ethenyl]pyridine (Example 41) according to the procedure described in Example 1, Step H. ¹H NMR (300 MHz, CDCl₃): δ 7.18

15 (d, $J = 7$ Hz, 4 H), 7.10 (m, 1 H), 6.97 (m, 1 H), 6.65 (m, 2 H), 4.36 (s, 2 H), 3.44 (sept, $J = 6.6$ Hz, 1 H), 3.35 (d, $J = 6.6$ Hz, 1 H), 2.57 (m, 4 H), 2.28 (s, 3 H), 1.35 (d, $J = 6.6$ Hz, 6 H), 1.34 (d, $J = 6.6$ Hz, 6 H), 1.20 (m, 1 H). FAB-MS: calculated for (C₂₇H₃₂FNO) 405, found 406 (M+H). Anal. Calcd for C₂₇H₃₂FNO: C, 79.96; H, 7.95; N, 3.45. Found: C, 79.30; H, 8.10; N, 3.36. mp 148-150°C. $R_f = 0.3$ (20% ethyl acetate/hexane).

20

EXAMPLE 45

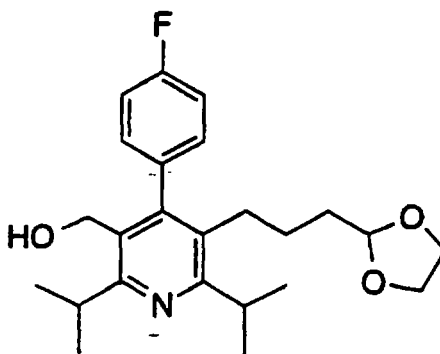
0

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[2-(4-methylphenyl)ethyl]pyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[2(E)-(4-methylphenyl)ethenyl]pyridine (Example 42) according to the procedure described in Example 1, Step H. ¹H NMR (300 MHz, CDCl₃): δ 7.17 (m, 4 H), 7.02 (d, J = 7.7 Hz, 2 H), 6.75 (d, J = 7.7 Hz, 2 H), 4.36 (d, J = 4 Hz, 2 H), 3.43 (sept, J = 6.6 Hz, 1 H), 3.34 (sept, J = 6.6 Hz, 1 H), 2.55 (m, 4 H), 2.29 (s, 3 H), 1.34 (d, J = 6.6 Hz, 6 H), 1.33 (d, J = 6.6 Hz, 6 H), 1.20 (m, 1 H). FAB-MS: calculated for (C₂₇H₃₂FNO) 405, found 406 (M+H). Anal. Calcd for C₂₇H₃₂FNO: C, 79.96; H, 7.95; N, 3.45. Found: C, 79.40; H, 7.84; N, 3.44. mp 121-123°C. R_f = 0.3 (20% ethyl acetate/hexane).

10

EXAMPLE 46



15

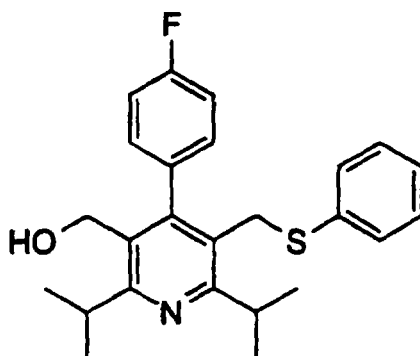
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[3-(1,3-dioxolan-2-yl)propyl]pyridine

The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide according to the procedures described in Example 1, Steps A-G. ¹H NMR (300 MHz, CDCl₃): δ 7.16 (m, 4 H), 4.63 (t, J = 4 Hz, 1 H), 4.33 (d, J = 5 Hz, 2 H), 3.88 (m, 2 H), 3.77 (m, 2 H), 3.41 (bm, 1 H), 3.24 (bm, 1 H), 2.34 (m, 2 H), 1.47 (m, 4 H), 1.32 (m, 12 H), 1.18 (m, 1 H). FAB-MS: calculated for (C₂₄H₃₂FNO₃) 401, found 402 (M+H). mp 90-91°C. R_f = 0.2 (20% ethyl acetate/hexane).

25

30

0

EXAMPLE 47

5

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(phenylthio)methyl]pyridineStep A: Methyl 2,6-diisopropyl-4-(4-fluorophenyl)-5-hydroxymethyl-3-pyridinecarboxylate

10 Prepared from methyl isobutyrylacetate, 4-fluorobenzaldehyde and ammonium acetate by the procedures described in Example 1, Steps A-D.

Step B: Methyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-bromomethyl-3-pyridinecarboxylate

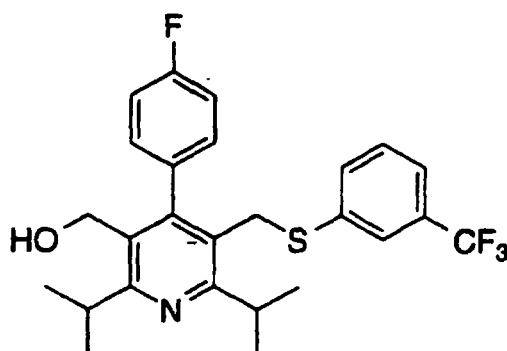
15 A solution of the intermediate obtained in Step A (20 g, 57.9 mmol) in acetonitrile (500 mL) was stirred at 0°C and treated with dibromotriphenylphosphorane (36.7 g, 86.9 mmol) in portions. The suspension was then allowed to warm to room temperature and stirred for 2 hr. The solvent was removed *in vacuo* and the residue partitioned between diethyl ether (400 mL) and
 20 water (350 mL). The ether layer was washed with brine (150 mL), dried (MgSO₄) and concentrated. Purification by chromatography through silica (5% diethyl ether/hexane) gave a white solid (20.6 g, 50.5 mmol, 87%). ¹H NMR (300 MHz, CDCl₃): δ 7.31 (m, 2 H), 7.12 (m, 2 H), 4.29 (s, 2 H), 3.49 (s, 3H), 3.41 (sept, J = 6.6 Hz, 1 H), 3.06 (sept, J = 6.6 Hz, 1 H), 1.33 (m, 12 H). mp 109-111°C. R_f = 0.6 (50%
 25 CH₂Cl₂/hexane).

Step C: 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(phenylthio)methyl]pyridine

30 A solution of the intermediate obtained in Step B (200 mg, 0.47 mmol) in anhydrous THF (5 mL), stirred under argon, was treated with benzenethiol (73 μL,

0 0.71 mmol) and *N*-methylmorpholine (0.26 mL, 2.4 mmol). The reaction mixture was stirred at reflux for 14 hr, allowed to cool to room temperature and treated with lithium aluminum hydride (1.9 mL, 1.9 mmol, 1.0M in THF). The reaction mixture was heated at reflux for 1 hr then allowed to cool to room temperature. The mixture was quenched by the successive addition of water (80 μ L), 20% NaOH
 5 (80 μ L) and water (240 μ L). The resulting suspension was filtered through a cake of celite and concentrated. Purification by flash silica gel chromatography (5% ethyl acetate/hexane) afforded a white solid (160 mg, 0.39 mmol, 83%). ^1H NMR (300 MHz, CDCl_3): δ 7.23 (m, 5 H), 7.11 (m, 4 H), 4.36 (d, J = 5.5 Hz, 2 H), 3.81 (s, 2 H), 3.45 (sept, J = 6.6 Hz, 1 H), 3.43 (sept, J = 6.6 Hz, 1 H), 1.35 (d, J = 6.6 Hz, 6 H), 1.33
 10 (d, J = 6.6 Hz, 6 H), 1.21 (t, J = 5.5 Hz, 1 H). FAB-MS calcd for ($\text{C}_{25}\text{H}_{28}\text{FNOS}$) 409, found 410 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{25}\text{H}_{28}\text{FNOS}$: C, 73.32; H, 6.89; N, 3.42; S, 7.83. Found: C, 73.24; H, 6.90; N, 3.35; S, 8.01. mp 119-121°C. R_f = 0.3 (20% ethyl acetate/hexane).

15

EXAMPLE 48

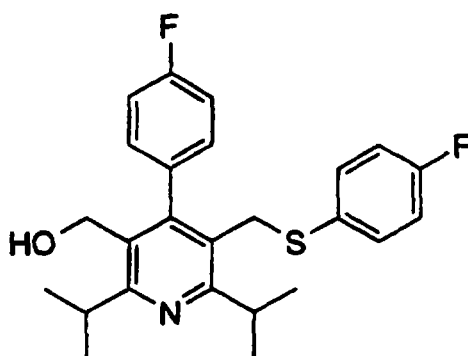
20

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(((3-trifluoromethyl)phenyl)thio)methylpyridine

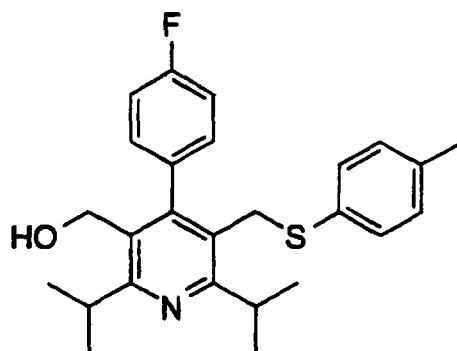
25

The title compound was prepared from 3-trifluoromethyl-thiophenol according to the procedures described in Example 47. ^1H NMR (300 MHz, CDCl_3): δ 7.34 (m, 2 H), 7.24 (m, 4 H), 7.10 (m, 2 H), 4.36 (d, J = 5.5 Hz, 2 H), 3.85 (s, 2 H), 3.45 (sept, J = 6.6 Hz, 1 H), 3.38 (sept, J = 6.6 Hz, 1 H), 1.35 (d, J = 6.6 Hz, 6 H), 1.34
 25 (d, J = 6.6 Hz, 6 H), 1.23 (t, J = 5.5 Hz, 1 H). FAB-MS calcd for ($\text{C}_{26}\text{H}_{27}\text{F}_4\text{NOS}$) 477, found 478 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{26}\text{H}_{27}\text{F}_4\text{NOS}$: C, 65.39; H, 5.70; N, 2.93; S, 6.71. Found: C, 65.39; H, 5.76; N, 2.88; S, 6.62. mp 110-111°C. R_f = 0.3 (20% ethyl acetate/hexane).

30

EXAMPLE 49**2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(4-fluorophenyl)thio]methylpyridine**

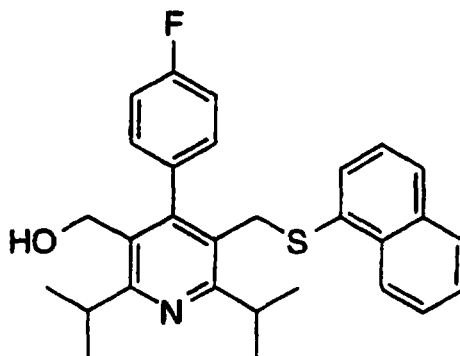
The title compound was prepared from 4-fluorothiophenol according to the procedures described in Example 47. ^1H NMR (300 MHz, CDCl_3): δ 7.24 (m, 2 H), 7.12 (m, 4 H), 6.93 (m, 2 H), 4.35 (d, $J = 5.5$ Hz, 2 H), 3.76 (s, 2 H), 3.44 (sept, $J = 6.6$ Hz, 1 H), 3.40 (sept, $J = 6.6$ Hz, 1 H), 1.34 (d, $J = 6.6$ Hz, 6 H), 1.33 (d, $J = 6.6$ Hz, 6 H), 1.22 (t, $J = 5.5$ Hz, 1 H). FAB-MS calcd for $(\text{C}_{25}\text{H}_{27}\text{F}_2\text{NOS})$ 427, found 428 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{25}\text{H}_{27}\text{F}_2\text{NOS}$: C, 70.23; H, 6.37; N, 3.28; S, 7.50. Found: C, 70.22; H, 6.41; N, 3.22; S, 7.39. mp 119-121°C. $R_f = 0.3$ (20% ethyl acetate/hexane).

EXAMPLE 50**2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(4-methylphenyl)thio]methylpyridine**

The title compound was prepared from *p*-thiocresol according to the procedures described in Example 47. ^1H NMR (300 MHz, CDCl_3): δ 7.27 (m, 2 H), 7.13 (m, 2 H), 7.03 (m, 4 H), 4.35 (d, $J = 5.5$ Hz, 2 H), 3.77 (s, 2 H), 3.44 (m, 2 H), 2.31 (s, 3 H), 1.34 (d, $J = 6.6$ Hz, 6 H), 1.33 (d, $J = 6.6$ Hz, 6 H), 1.22 (t, $J = 5.5$ Hz, 1 H). FAB-MS calcd for $(\text{C}_{26}\text{H}_{30}\text{FNOS})$ 423, found 424 ($\text{M}+\text{H}$). Anal. Calcd for

- 0 C₂₆H₃₀FNOS: C, 73.72; H, 7.14; N, 3.31; S, 7.57. Found: C, 74.00; H, 7.15; N, 3.36; S, 7.32. mp 90-91°C. R_f = 0.3 (20% ethyl acetate/hexane).

EXAMPLE 51

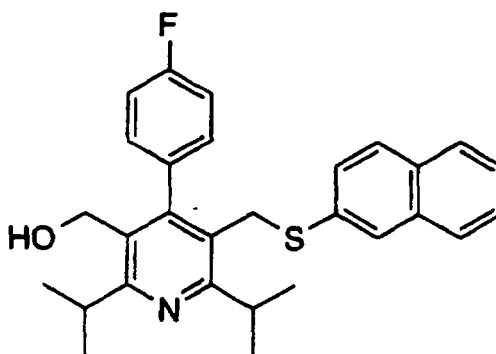


5

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-naphthylthio)-methylpyridine

- The title compound was prepared from 1-naphthalenethiol according to the procedures described in Example 47. ¹H NMR (300 MHz, CDCl₃): δ 8.01 (d, J = 8.5 Hz, 1 H), 7.82 (d, J = 8.5 Hz, 1 H), 7.74 (d, J = 8 Hz, 1 H), 7.46 (m, 3 H), 7.34 (m, 1 H), 7.20 (m, 2 H), 7.06 (m, 2 H), 4.34 (d, J = 5.5 Hz, 2 H), 3.82 (s, 2 H), 3.51 (sept, J = 6.6 Hz, 1 H), 3.45 (sept, J = 6.6 Hz, 1 H), 1.36 (d, J = 6.6 Hz, 6 H), 1.35 (d, J = 6.6 Hz, 6 H), 1.19 (t, J = 5.5 Hz, 1 H). FAB-MS calcd for (C₂₉H₃₀FNOS) 459, found 460 (M+H).
- 15 Anal. Calcd for C₂₉H₃₀FNOS: C, 75.78; H, 6.58; N, 3.05; S, 6.98. Found: C, 75.36; H, 6.52; N, 2.91; S, 6.74. mp 77-79°C. R_f = 0.4 (20% ethyl acetate/hexane).

EXAMPLE 52

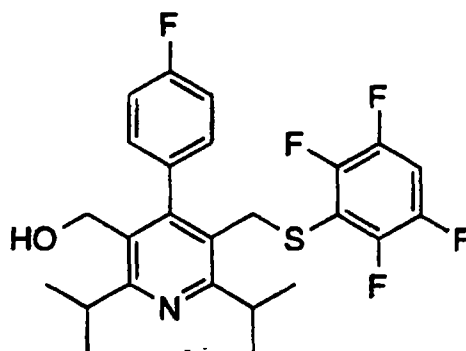


20

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(2-naphthylthio)methylpyridine

- 0 The title compound was prepared from 2-naphthalenethiol according to the procedures described in Example 47. ^1H NMR (300 MHz, CDCl_3): δ 7.77 (d, $J = 9$ Hz, 1 H), 7.68 (d, $J = 9$ Hz, 2 H), 7.52 (d, $J = 1.5$ Hz, 1 H), 7.45 (m, 2 H), 7.25 (m, 2 H), 7.17 (dd, $J = 1.8, 8.5$ Hz, 1 H), 7.07 (m, 2 H), 4.35 (d, $J = 5.5$ Hz, 2 H), 3.91 (s, 2 H), 3.45 (sept, $J = 6.6$ Hz, 2 H), 1.35 (d, $J = 6.6$ Hz, 6 H), 1.34 (d, $J = 6.6$ Hz, 6 H), 1.21 (t, $J = 5.5$ Hz, 1 H). FAB-MS calcd for ($\text{C}_{29}\text{H}_{30}\text{FNOS}$) 459, found 460 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{29}\text{H}_{30}\text{FNOS}$: C, 75.78; H, 6.58; N, 3.05; S, 6.98. Found: C, 75.55; H, 6.60; N, 2.95; S, 6.91. mp 127-129°C. $R_f = 0.4$ (20% ethyl acetate/hexane).

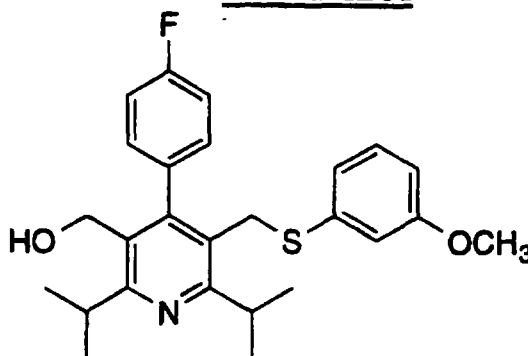
EXAMPLE 53



2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(2,3,5,6-tetrafluorophenyl)thio]methylpyridine

- 15 The title compound was prepared from pentafluorothiophenol according to the procedures described in Example 47. ^1H NMR (300 MHz, CDCl_3): δ 7.27 (m, 2 H), 7.11 (m, 2 H), 6.99 (m, 1 H), 4.35 (d, $J = 5.5$ Hz, 2 H), 3.84 (s, 2 H), 3.44 (sept, $J = 6.6$ Hz, 1 H), 3.43 (sept, $J = 6.6$ Hz, 1 H), 1.34 (d, $J = 6.6$ Hz, 6 H), 1.33 (d, $J = 6.6$ Hz, 6 H), 1.23 (t, $J = 5.5$ Hz, 1 H). FAB-MS calcd for ($\text{C}_{25}\text{H}_{24}\text{F}_5\text{NOS}$) 481, found 482 ($\text{M}+\text{H}$). Anal. Calcd for $\text{C}_{25}\text{H}_{24}\text{F}_5\text{NOS}$: C, 62.36; H, 5.02; N, 2.91; S, 6.66; F, 19.73. Found: C, 62.40; H, 4.96; N, 2.82; S, 6.74; F, 19.49. mp 109-110°C. $R_f = 0.4$ (20% ethyl acetate/hexane).

EXAMPLE 54

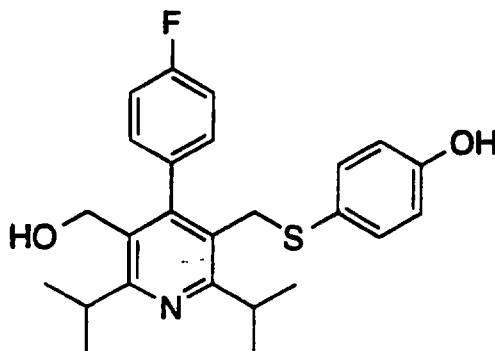


0 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(3-methoxy-phenyl)thio]methylpyridine

The title compound was prepared from 3-methoxybenzenethiol according to the procedures described in Example 47. ¹H NMR (300 MHz, CDCl₃): δ 7.24 (m, 2 H), 7.13 (m, 3 H), 6.72 (m, 2 H), 6.62 (m, 1 H), 4.35 (d, *J* = 5.5 Hz, 2 H), 3.81 (s, 2 H),
 5 3.75 (s, 3 H), 3.44 (sept, *J* = 6.6 Hz, 1 H), 3.42 (sept, *J* = 6.6 Hz, 1 H), 1.34 (d, *J* = 6.6 Hz, 6 H), 1.33 (d, *J* = 6.6 Hz, 6 H), 1.23 (t, *J* = 5.5 Hz, 1 H). FAB-MS calcd for (C₂₆H₃₀FNO₂S) 339, found 440 (M+H). Anal. Calcd for C₂₆H₃₀FNO₂S: C, 71.04; H, 6.88; N, 3.19; S, 7.29. Found: C, 70.94; H, 6.77; N, 2.96; S, 7.41. mp 93-94°C. R_f = 0.4 (20% ethyl acetate/hexane).

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EXAMPLE 55



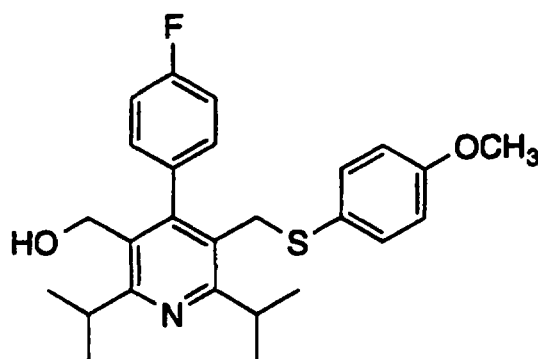
15 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(4-hydroxy-phenyl)thio]methylpyridine

The title compound was prepared from 4-hydroxythiophenol according to the procedures described in Example 47. ¹H NMR (300 MHz, 5:1 CDCl₃/CD₃OD): δ 7.15 (m, 2 H), 7.06 (m, 2 H), 6.97 (d, *J* = 8.5 Hz, 2 H), 6.64 (d, *J* = 8.5 Hz, 2 H), 4.27
 20 (s, 2 H), 3.66 (s, 2 H), 3.40 (m, 2 H), 1.29 (d, *J* = 6.6 Hz, 6 H), 1.28 (d, *J* = 6.6 Hz, 6 H). FAB-MS calcd for (C₂₅H₂₈FNO₂S) 425, found 426 (M+H). Anal. Calcd for C₂₅H₂₈FNO₂S: C, 70.56; H, 6.63; N, 3.29; S, 7.53. Found: C, 70.29; H, 6.34; N, 3.12; S, 7.44. mp 178-179°C. R_f = 0.3 (30% ethyl acetate/hexane).

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EXAMPLE 56

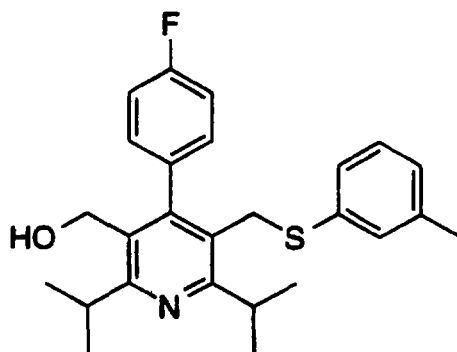
5

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(4-methoxyphenyl)thio]methylpyridine

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The title compound was prepared from 4-methoxybenzenethiol according to the procedures described in Example 47. ¹H NMR (300 MHz, CDCl₃): δ 7.23 (m, 2 H), 7.12 (m, 4 H), 6.77 (d, *J* = 9 Hz, 2 H), 4.35 (d, *J* = 5.5 Hz, 2 H), 3.79 (s, 3 H), 3.73 (s, 2 H), 3.44 (sept, *J* = 6.6 Hz, 2 H), 1.34 (d, *J* = 6.6 Hz, 6 H), 1.33 (d, *J* = 6.6 Hz, 6 H), 1.21 (t, *J* = 5.5 Hz, 1 H). FAB-MS calcd for (C₂₆H₃₀FN₂O₂S) 339, found 440 (M+H). Anal. Calcd for C₂₆H₃₀FN₂O₂S: C, 71.04; H, 6.88; N, 3.19; S, 7.29. Found: C, 70.96; H, 6.90; N, 3.15; S, 7.35. mp 92-93°C. R_f = 0.4 (20% ethyl acetate/hexane).

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EXAMPLE 572,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(3-methylphenyl)thio]methylpyridine

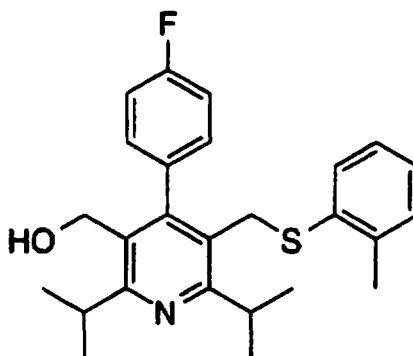
20

The title compound was prepared from *m*-thiocresol according to the procedures described in Example 47. ¹H NMR (300 MHz, CDCl₃): δ 7.25 (m, 2 H), 7.11 (m, 3 H), 7.00 (m, 1 H), 6.94 (m, 2 H), 4.36 (d, *J* = 5.5 Hz, 2 H), 3.81 (s, 2 H), 3.45 (sept, *J* = 6.6 Hz, 1 H), 3.43 (sept, *J* = 6.6 Hz, 1 H), 2.28 (s, 3 H), 1.35 (d, *J* = 6.6 Hz, 6 H), 1.34 (d, *J* = 6.6 Hz, 6 H), 1.22 (t, *J* = 5.5 Hz, 1 H). FAB-MS calcd for

- 0 (C₂₆H₃₀FNOS) 423, found 424 (M+H). Anal. Calcd for C₂₆H₃₀FNOS: C, 73.72; H, 7.14; N, 3.31; S, 7.57. Found: C, 73.76; H, 7.09; N, 3.27; S, 7.42. mp 92-93°C. R_f = 0.4 (20% ethyl acetate/hexane).

EXAMPLE 58

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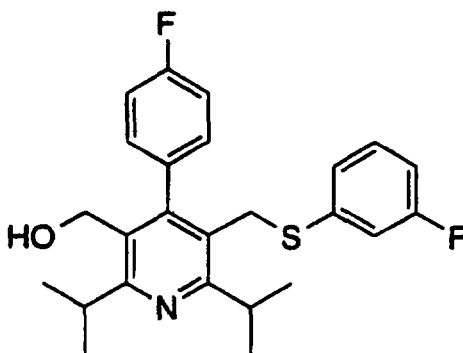


2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(2-methylphenyl)thio]methylpyridine

- 10 The title compound was prepared from *o*-thiocresol according to the procedures described in Example 47. ¹H NMR (300 MHz, CDCl₃): δ 7.25 (m, 2 H), 7.11 (m, 6 H), 4.36 (d, *J* = 5.5 Hz, 2 H), 3.74 (s, 2 H), 3.45 (sept, *J* = 6.6 Hz, 2 H), 2.26 (s, 3 H), 1.35 (d, *J* = 6.6 Hz, 12 H), 1.21 (t, *J* = 5.5 Hz, 1 H). FAB-MS calcd for (C₂₆H₃₀FNOS) 423, found 424 (M+H). Anal. Calcd for C₂₆H₃₀FNOS: C, 73.72; H, 7.14; N, 3.31; S, 7.57. Found: C, 73.54; H, 7.09; N, 3.06; S, 7.37. mp 140-141°C. R_f = 0.4 (20% ethyl acetate/hexane).

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EXAMPLE 59

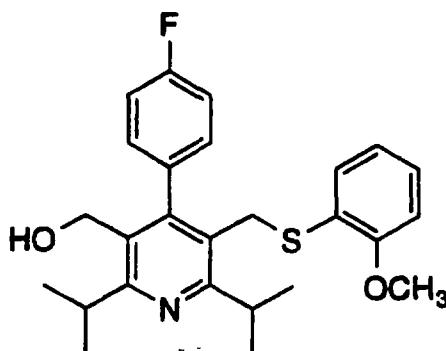


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2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(3-fluorophenyl)thio]methylpyridine

- 0 The title compound was prepared from 3-fluorothiophenol according to the procedures described in Example 47. ¹H NMR (300 MHz, CDCl₃): δ 7.27 (m, 3 H), 7.11 (m, 2 H), 6.87 (m, 2 H), 6.78 (m, 1 H), 4.36 (d, *J* = 5.5 Hz, 2 H), 3.82 (s, 2 H), 3.45 (sept, *J* = 6.6 Hz, 1 H), 3.38 (sept, *J* = 6.6 Hz, 1 H), 1.35 (d, *J* = 6.6 Hz, 6 H), 1.33 (d, *J* = 6.6 Hz, 6 H), 1.23 (t, *J* = 5.5 Hz, 1 H). FAB-MS calcd for (C₂₅H₂₇F₂NOS) 427, found 428 (M+H). Anal. Calcd for C₂₅H₂₇F₂NOS: C, 70.23; H, 6.37; N, 3.28; S, 7.50. Found: C, 70.22; H, 6.31; N, 3.20; S, 7.41. mp 99-100°C. R_f = 0.4 (20% ethyl acetate/hexane).

EXAMPLE 60



2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(2-methoxyphenyl)thio]methylpyridine

- 15 The title compound was prepared from 2-methoxythiophenol according to the procedures described in Example 47. ¹H NMR (300 MHz, CDCl₃): δ 7.22 (m, 3 H), 7.07 (m, 3 H), 6.83 (m, 2 H), 4.34 (d, *J* = 5.5 Hz, 2 H), 3.78 (s, 3 H), 3.75 (s, 2 H), 3.49 (sept, *J* = 6.6 Hz, 1 H), 3.43 (sept, *J* = 6.6 Hz, 1 H), 1.34 (d, *J* = 6.6 Hz, 12 H), 1.19 (t, *J* = 5.5 Hz, 1 H). FAB-MS calcd for (C₂₆H₃₀FNO₂S) 339, found 440 (M+H). Anal. Calcd for C₂₆H₃₀FNO₂S: C, 71.04; H, 6.88; N, 3.19; S, 7.29. Found: C, 70.93; H, 6.67; N, 3.12; S, 7.48. mp 129-131°C. R_f = 0.4 (20% ethyl acetate/hexane).

EXAMPLE 61

