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(54) Title: COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract
Aminophosphonates alpha substituted by phenol groups of formula (I) have lipoprotein(s) lowering activity.

![Chemical Structure](attachment:image.png)
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Compounds and Pharmaceutical Compositions containing them

This invention relates to a new therapeutic use of aminophosphonate compounds for lowering plasma and tissue levels of lipoprotein(a). In particular, this invention provides a new use of aminophosphonate derivatives, for the preparation of pharmaceutical compositions useful in the treatment of diseases or disorders associated with high plasma and tissue concentrations of lipoprotein(a); such as, for instance atherosclerosis, thrombosis, restenosis after angioplasty and stroke. This invention also provides a method for increasing thrombolysis and preventing thrombosis and a method of treatment of restenosis after angioplasty by administering to a patient in need thereof an aminophosphonate compound at a dose effective for lowering plasma and tissue lipoprotein(a) levels. In addition, this invention also provides a group of new aminophosphonate compounds for use in the above mentioned uses and compositions.

Recent epidemiologic studies have shown a strong association between elevated lipoprotein(a) [Lp(a)] plasma levels and the occurrence of coronary heart disease, stroke and peripheral artery disease. Lp(a) is now recognized as an independent risk factor for cardiovascular diseases; in addition its role in promoting thrombosis by decreasing thrombolysis is increasingly acknowledged, see for instance "Lipoprotein(a) as A Risk Factor for Preclinical Atherosclerosis" P.J. Schreiner, J.D. Morrisett, A.R. Sharrett, W. Patsch, H.A. Tyroler, K.Wu and G. Heiss; Arteriosclerosis and Thrombosis 13, p. 826-833 (1993); "Detection and Quantification of Lipoprotein(a) in the Arterial Wall of 107 Coronary Bypass Patients" M. Rath, A. Niendorf, T. Reblin, M. Dietel, H.J. Krebber and U. Beisiegel; Arteriosclerosis 2, p. 579-592 (1989); and "Lipoprotein(a) : Structure, Properties and Possible Involvement in Thrombogenesis and Atherogenesis" A.D. MBewu and P.N. Durrington; Atherosclerosis 85, p. 1-14 (1990).

The potential of thrombosis involvement in vessel occlusion and acute cardiovascular syndrome is being increasingly recognized. One of the mechanisms that mediate thrombosis associated with atherosclerotic plaque rupture involves elevated levels of lipoprotein(a). The structure of Lp(a) consists of a low-density lipoprotein (LDL)-like particle with a glycoprotein, apolipoprotein(a) [apo(a)] that is linked via a disulfide bridge to the apo B-100 moiety of the LDL. Structurally there is striking analogy between apo(a) and plasminogen, the precursor of plasmin which cleaves fibrin to dissolve blood clots. However, unlike plasminogen apo(a) is not a substrate for plasminogen activators. This structural resemblance has led researchers to
postulate and later demonstrate that apo(a) interferes with the normal physiological function of plasminogen, leading to a potential thrombogenic activity of Lp(a) see for instance:

"Activation of Transforming Growth Factor-β is Inversely Correlated with Three Major Risk Factors for Coronary Artery Disease : Lipoprotein(a), LDL-Cholesterol and Plasminogen Activator Inhibitor-1", A. Chauhan, N.R. Williams, J.C. Metcalfe, A.A. Grace, A.C. Liu, R.M. Lawn, P.R. Kemp, P.M. Schofield and D.J. Grainger; Circulation, Vol 90, No. 4, Part 2, p. I-623 (1994); and


On the basis of its suspected thrombogenic activity, Lp(a) has also been implicated in peripheral artery disease, in particular stroke. Recently clinicians have shown that serum Lp(a) levels were significantly higher in stroke patients than in a reference normal population :


Restenosis following percutaneous transluminal angioplasty is a common complication occurring in up to 40% of cases within 3-6 months of the intervention. The main cause for restenosis is believed to be abnormal vascular smooth muscle cell activation and proliferation. The proof that high plasma Lp(a) levels are associated with smooth muscle cell proliferation and activation was established in vitro and in vivo by the two following studies :

"Proliferation of Human Smooth Muscle Cells Promoted by Lipoprotein(a)" D.J. Grainger, H. L. Kirschenlohr, J.C. Metcalfe, P.L. Weissberg, D.P. Wade and R.M. Lawn; Science, Vol 260, p.1655-1658 (1993); and


This observation has led to a hypothesis that associates elevated plasma Lp(a) levels with an increased incidence of restenosis. The hypothesis was confirmed by the results of a recent clinical study showing that, in patients with high plasma Lp(a) levels, a reduction of Lp(a) levels by more than 50% by LDL-apheresis significantly reduced the restenosis rate; see for instance:

The above discussion has established the rationale for decreasing plasma Lp(a) in patients at risk with elevated levels (>20-30mg/dl). The Lp(a) concentration in individuals appears to be highly determined by inheritance and is hardly influenced by dietary regimes. Various hormones (i.e. steroid hormones, growth hormones, thyroid hormones) have been shown to regulate plasma levels of Lp(a) in man. Of particular interest, drugs which effectively lower LDL such as the bile acid sequestrant cholestyramine or the HMGCoA reductase inhibitors lovastatin or pravastatin do not affect Lp(a) levels. The drugs of the fibrate family : clofibrate or bezafibrate and the antioxidant drug probucol are equally ineffective. The only drug reported to lower Lp(a) is nicotinic acid. However at the high doses necessary for efficacy (4g/day) nicotinic acid has several serious side-effects which preclude its wide use : flushing, vasodilation and hepatotoxicity. Therefore the medical need to lower elevated Lp(a) plasma levels, an independent risk factor for cardiovascular disease, is still unmet.

In contrast to LDL, Lp(a) exists only in mammals high in the evolutionary scale (humans and non human primates) and is exclusively synthesized by the liver cells. Cynomolagus monkeys possess Lp(a) that is similar to human Lp(a), including possession of the unique apolipoprotein apo(a). This primate offers an experimental opportunity for studying the synthesis of Lp(a) and the role of Lp(a) in atherosclerosis and thrombosis. Primary cultures of cynomolgus monkey hepatocytes have been selected as the in vitro test for screening aminophosphonate derivatives of formula (I) for their ability to modulate Lp(a) levels. Prior to screening, this assay system had been validated by testing as reference products nicotinic acid and steroid hormones which are known to lower Lp(a) in man.

The present invention relates to the unexpected discovery that aminophosphonate derivatives are effective for lowering plasma and tissue lipoprotein(a). Accordingly, in a first aspect, the present invention provides for the use of a compound of formula (I):
where:

$X^1, X^2$, which may be identical or different, are $H$, a straight or branched alkyl or alkoxy group having from 1 to 8 carbon atoms, a hydroxy group or a nitro group,

$X^3$ is $H$, an alkyl group from 1 to 4 carbon atoms, $X^3O$ and one of the two other substituents $X^1$ or $X^2$ may form an alkylidene dioxy ring having from 1 to 4 carbon atoms,

$R^1, R^2$, identical or different, are $H$, a straight or branched alkyl group having from 1 to 6 carbon atoms,

$B$ is $CH_2, CH_2-CH_2$ or $CH=CH$,

$n$ is zero or 1,

$Z$ is $H$, a straight or branched alkyl group having from 1 to 8 carbon atoms, an acyl group $R^3-CO$ where $R^3$ is an alkyl group from 1 to 4 carbon atoms, a perfluoroalkyl group from 1 to 4 carbon atoms,

$A$ is $H, CH_2-CH=CH_2$, a straight, branched or cyclic alkyl group having from 1 to 8 carbon atoms, or is selected from the following groups:
where \( k \) is an integer from 2 to 4, \( m \) is 0 or an integer from 1 to 5, \( X^4, X^5, X^6 \)
identical or different, are H, a straight or branched alkyl or alkoxy group from 1 to 8
carbon atoms, a hydroxy, trifluoromethyl, nitro, amino, dimethylamino,
diethylamino group, a halogen atom (F, Cl, Br, I), \( X^4 \) and \( X^5 \) may form an
alkylidendioxy ring having from 1 to 4 carbon atoms, \( X^7 \) is H or \( \text{CH}_3 \), R is a straight
or branched alkyl group having from 1 to 6 carbon atoms, an aryl or arylalkyl group from 6 to 9 carbon atoms;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for lowering plasma and tissue lipoprotein(a).


Preferred compounds of formula (I) for use in the manufacture of a medicament for lowering plasma and tissue lipoprotein(a) are those of the formula (Ia):

\[
\begin{align*}
\text{X}^1 & \text{O} \quad \text{X}^2 & \text{O} \\
\quad \quad \quad \quad \quad \text{B}_n & \text{CH} \\
\text{X}^3 & \text{N} \quad \text{CH}_2 & \text{X}^4
\end{align*}
\]

where B, R^1, R^2, X^1, X^2, X^3, X^4, Z, n and m are as hereinbefore defined;

or a pharmaceutically acceptable salt thereof.

Certain compounds within the scope of formula (Ia) are novel and are particularly useful in lowering plasma and tissue lipoprotein(a).

Accordingly, in a further aspect, this invention provides aminophosphonate derivatives of formula (Ia) where:

X^1 is H, C\(_{1-8}\)alkyl or C\(_{1-8}\)alkoxy;

X^2 is C\(_{1-8}\)alkyl or C\(_{1-8}\)alkoxy;

X^3 is H, C\(_{1-4}\)alkyl, or X^3O and one of the two other substituents X^1 or X^2 may form an alkylidene dioxy ring having from 1 to 4 carbon atoms;

R^1, R^2, which may be identical or different, are H or C\(_{1-6}\)alkyl;

B is CH\(_2\)-CH\(_2\), CH=CH or CH\(_2\);

n is zero or 1;

Z is H or C\(_{1-8}\)alkyl;

m is an integer from 0 to 5;

X^4 is H, C\(_{1-8}\)alkyl, C\(_{1-8}\)alkoxy, or halo;
and the pyridyl ring is attached by the ring carbon α- or β- to the nitrogen (2- or 3-pyridyl);
or a salt, preferably a pharmaceutically acceptable salt, thereof; and excluding:

Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-pyridyl) aminomethylphosphonate;
5
Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(2-picolyl) aminomethylphosphonate;
Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-picolyl) aminomethylphosphonate;
10
Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-methyl-N-(3-picolyl) aminomethylphosphonate;
Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(2-pyridylethyl) aminomethylphosphonate, and
Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(4-picolyl) aminomethylphosphonate.
15

Suitably, X\(^1\) is H, C\(_{1-4}\)alkyl or C\(_{1-4}\)alkoxy, preferably C\(_{1-3}\)alkyl or C\(_{1-3}\)alkoxy, more preferably hydrogen, methyl or methoxy.
20
Suitably, X\(^2\) is C\(_{1-4}\)alkyl or C\(_{1-4}\)alkoxy, preferably C\(_{1-3}\)alkyl or C\(_{1-3}\)alkoxy, more preferably methyl or methoxy.

Suitably, X\(^1\) and X\(^2\) are both alkoxy or one of X\(^1\) and X\(^2\) is alkyl and the other is alkoxy, or one of X\(^1\) and X\(^2\) is C\(_{1-4}\)alkyl and the other of X\(^1\) and X\(^2\) is C\(_{1-3}\)alkyl.
25

Suitable combinations of X\(^1\) and X\(^2\) include methoxy and methoxy, methoxy and methyl, n-propyl or iso-butyl, methyl and methyl or t-butyl, respectively.

Preferably, X\(^3\) is hydrogen.
30
Preferably, (B)\(_n\) is a direct bond.

Preferably, R\(^1\) and R\(^2\) is each a C\(_{1-3}\)alkyl group, more preferably, a C\(_2\) or C\(_3\) alkyl group, in particular R\(^1\) and R\(^2\) is ethyl or isopropyl.
35

Preferably, Z is hydrogen.

Preferably, X\(^4\) is hydrogen or methyl which is preferably on the ring carbon adjacent to N.

Preferably, the pyridyl ring is attached by the ring carbon β- to the nitrogen (3-pyridyl).
When used herein, the terms 'alkyl' and 'alkoxy' include both straight and branched groups, for instance, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, s-butyl, t-butyl, etc.

Preferred compounds of formula (Ia) include:
- Diisopropyl \( \alpha\)-(4-hydroxy-3-methoxy-5-methylphenyl)-N-(3-pyridyl)-aminomethylphosphonate;
- Diisopropyl \( \alpha\)-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate;
- Diethyl \( \alpha\)-(3-methyl-4-hydroxy-5-t-butylphenyl)-N-(3-pyridyl)-aminomethylphosphonate;
- Diethyl \( \alpha\)-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate; and
- Diethyl \( \alpha\)-(3,5-dimethyl-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate.

Independently from the previously published activity, the present invention relates to the unexpected discovery that aminophosphonate derivatives of formula (I) are effective for decreasing Lp(a) production by primary cultures of Cynomolgus monkey hepatocytes. Lp(a) of these primates is similar in immunologic properties to human Lp(a) and occurs in an almost identical frequency distribution of plasma concentrations, see for instance: "Plasma Lipoprotein(a) Concentration is Controlled by Apolipoprotein(a) Protein Size and the Abundance of Hepatic Apo(a) mRNA in a Cynomolgus Monkey Model", N. Azrolan, D. Gavish and J. Breslow; J. Biol. Chem., Vol 266, p. 13866-13872 (1991).

Therefore the compounds of this invention are potentially useful for decreasing Lp(a) in man and thus provide a therapeutic benefit.

In particular, this invention provides a new therapeutic use for aminophosphonate compounds of formula (I) as Lp(a) lowering agents. Diseases associated with elevated plasma and tissue levels of lipoprotein(a) include, for instance, coronary heart disease, peripheral artery disease, intermittent claudication, thrombosis, restenosis after angioplasty, extracranial carotid atherosclerosis, stroke and atherosclerosis occurring after heart transplant.
The recently discovered Lp(a) lowering activity of the aminophosphonates of formula (I) is independent from their previously reported pharmacological activities of decreasing plasma cholesterol and blood peroxides. Recent clinical studies have shown that neither the hypocholesterolemic drug pravastatin nor the antioxidant drug probucol can decrease Lp(a) levels in man. See for example:

"Serum Lp(a) Concentrations are Unaffected by Treatment with the HMG-CoA Reductase Inhibitor Pravastatin: Results of a 2-Year Investigation" H.G. Fieseler, V.W. Armstrong, E. Wieland, J. Thiery, E. Schütz, A.K. Walli and D. Seidel; Clinica Chimica Acta, Vol 204, p. 291-300 (1991); and


For therapeutic use the compounds of the present invention will generally be administered in a standard pharmaceutical composition obtained by admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsule, ovules or lozenges either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The choice of form for administration as well as effective dosages will vary depending, inter alia, on the condition being treated.

The choice of mode administration and dosage is within the skill of the art.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions or as solids for example, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agents.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.
A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of structure (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The pharmaceutically acceptable compounds of the invention will normally be administered to a subject in a daily dosage regimen. For an adult patient this may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day.

Compounds of formula (I) may be prepared according to the processes described in European Patent Application EP 0 559 079-A (1993}[corresponding to the US Patent
424 303]. This process which has two variants is shown in the following general scheme:
GENERAL SYNTHESIS SCHEM

Variant 1

\[ \begin{align*}
X^3 &- O - ( B )_n - \text{CHO} + H - N - A \\
\text{X} \quad \text{X} \quad \text{X} \quad \text{X} \quad \text{X} \\
\end{align*} \]

\[ \downarrow \]

\[ \begin{align*}
\text{X} &- O - ( B )_n - \text{CH} = N - A \\
\text{X} \quad \text{X} \quad \text{X} \quad \text{X} \quad \text{X} \\
\end{align*} \]

\[ \downarrow \]

\[ \begin{align*}
&H - \text{P} - \text{OR}_1 \quad \text{or} \quad \text{Na} - \text{P} - \text{OR}_1 \\
\text{X} &- O - ( B )_n - \text{C} - H \\
\text{X} \quad \text{X} \quad \text{X} \quad \text{X} \quad \text{X} \\
\end{align*} \]

\( I \) when Z is H

Variant 2

\[ \begin{align*}
X^3 &- O - ( B )_n - \text{CHO} + H - N - A + H - \text{P} - \text{OR}_1 \\
\text{X} \quad \text{X} \quad \text{X} \quad \text{X} \quad \text{X} \\
\end{align*} \]

\[ \downarrow \]

\[ \begin{align*}
&H - \text{P} - \text{OR}_1 \quad \text{or} \quad \text{Na} - \text{P} - \text{OR}_1 \\
\text{X} &- O - ( B )_n - \text{C} - H \\
\text{X} \quad \text{X} \quad \text{X} \quad \text{X} \quad \text{X} \\
\end{align*} \]

\( I \) when Z is not H
Variant 1 is used when Z is H, i.e. when the starting compound is a primary amine. Briefly, the aminophosphonates of formula (I) are prepared by nucleophilic addition of a dialkyl phosphite or its sodium salt obtained in situ by the reaction of dialkyl phosphite and sodium hydride on the imine obtained by condensation of the appropriate aldehyde and a primary amine.

Variant 2 is used when Z is not H, i.e. when the starting compound is a secondary amine. In this case, the aminophosphonates of formula (I) are prepared by reacting equimolar amounts of the appropriate aldehyde and the secondary amine and a dialkyl phosphite. The reaction is advantageously carried out in the presence of p-toluenesulfonic acid as a catalyst in a hydrocarbon solvent such as benzene or toluene with concomittant elimination of water, for instance, by using a Dean-Stark apparatus.

Novel compounds of formula (Ia) in which Z is hydrogen may be prepared by a process which comprises treating an imine of formula (II):

\[
\begin{array}{c}
\text{X}^2\\(B)_n\\\text{CH=N-(CH}_2\text{)}_m\\\text{X}^4
\end{array}
\]

in which B, X\text{\textsuperscript{1}}, X\text{\textsuperscript{2}}, X\text{\textsuperscript{3}}, X\text{\textsuperscript{4}}, m and n are as hereinbefore defined; with a phosphite compound of formula (III):

\[
\text{HPO(OR\text{\textsuperscript{1}})(OR\text{\textsuperscript{2}})}
\]

in which R\text{\textsuperscript{1}} and R\text{\textsuperscript{2}} are as hereinbefore defined; or a trialkyl silyl derivative thereof, preferably the trimethyl silyl phosphite, or a metal salt thereof, for instance the sodium salt, formed in situ by treatment of the compound of formula (III) with a suitable base, for instance sodium hydride, ethoxide or methoxide.

The reaction may be carried out in the presence or absence of a catalyst. Suitable catalysts include amine such as diethylamine or triethylamine. The reaction may be carried out in the absence or presence of a solvent. Suitable solvents include...
petroleum ether, benzene, toluene, diethyl ether, tetrahydrofuran, 1,2-
dimethoxyethane. Suitable reaction temperatures are in the range 30 to 140°C.

The imine compound of formula (II) may be obtained by condensing an aldehyde
compound of formula (V):

\[
\begin{align*}
\text{X}^1 & \quad \text{X}^2 \\
\text{X}^3 & \quad \text{X}^4 \\
\hline
\text{(B),CHO} & \\
\end{align*}
\]  

(V)

in which B, X¹, X², X³ and n are as hereinbefore defined;

with a primary amine of formula (VI):

\[ \text{H}_2\text{NA} \]  

(VI)

in which A is as as hereinbefore defined;

under imine forming conditions.

Suitably, the condensation may be effected with or without a catalyst in a solvent
such as ether, tetrahydrofuran, benzene, toluene or ethanol. Suitable catalysts include
molecular sieve, an acid such as glacial acetic acid, p-toluene sulphonic acid, thionyl
chloride, titanium tetrachloride, boron trifluoride etherate, or a base such as potassium
carbonate. The reaction is suitably carried out at a temperature in the range 0°C to
the boiling point of the solvent being used. For less reactive amines/alddehydes, the
reaction may be usefully carried out in a Dean-Stark apparatus.

Novel compounds of formula (Ia) in which Z is not hydrogen may be prepared by a
process which comprises treating equimolar amounts of an aldehyde of formula (V), a
secondary amine of formula (VII):

\[ \text{HNZA} \]  

(VII)

in which Z is a C(1-8)alkyl group and A is as hereinbefore defined; and
a phosphite of formula (III), suitably in the presence of p-toluenesulfonic acid as a
catalyst, in a hydrocarbon solvent such as petroleum ether, benzene, toluene or
xylene, at a temperature between ambient temperature and the boiling point of the
solvent being used, and with concomitant elimination of water, for instance, by using a Dean-Stark apparatus.

Compounds of formula (Ia) in which m is not zero may also be prepared by a process which comprises treating a compound of formula (VIII):

\[
\begin{array}{c}
\text{O} \\
\text{X}_1 \quad \text{X}_2 \quad \text{X}_3 \quad \text{X}_4 \\
\text{OR}_1 \quad \text{OR}_2 \\
\text{(B)}_n \text{C} \\
\text{NH}_2
\end{array}
\]

(VIII)

in which B, R\(^1\), R\(^2\), X\(^1\), X\(^2\), X\(^3\) and n are as hereinbefore defined; an aldehyde of formula (IX):

\[
\begin{array}{c}
\text{X}_4 \\
\text{(CH}_2\text{)}_{(m-1)} \text{CHO}
\end{array}
\]

(IX)

in which m is an integer from 1 to 5 and X\(^4\) is as hereinbefore defined; under reductive amination conditions.

Suitable such conditions include carrying out the reaction in the presence of sodium cyanoborohydride in an alcoholic solvent, preferably methanol, at a pH between 3 to 6 and at a temperature between 0°C and 25°C.

A compound of formula (VIII) may be obtained according to the process hereinbefore described for a compound of formula (Ia) from an aldehyde of formula (V), a secondary amine of formula (VII) in which Z is protecting group which can be removed by hydrogenolysis, for instance an α substituted benzyl or benzylxycarbonyl and a phosphite of formula (III). This forms an intermediate which is then subjected to hydrogenolysis according to standard conditions, to give a compound of formula (VIII).

Through their amino function, the aminophosphonate ester (I) can form salts of inorganic acids such as HCl, H\(_2\)SO\(_4\) or with organic acids such as oxalic acid, maleic
acid, sulfonic acids, etc. An example of hydrochloride salt of aminophosphonate (I) is provided (example 5). All these salts are integral part of this invention.

Compounds of structure (I) are racemates as they have at least one chiral center which is the carbon atom in position alpha to the phosphonate group. The compounds (I) therefore exist in the two enantiomeric forms. The racemic mixtures (50% of each enantiomer) and the pure enantiomers are comprised in the scope of this application. In certain cases, it may be desirable to separate the enantiomers.

In a further aspect, the present invention provides a process for the enantiomeric synthesis of a derivative of formula (I) which process comprises treating either of the (+) or (-) enantiomer of the α-substituted aminomethylphosphonate of formula (X):

\[
\begin{aligned}
 &X^1 \quad (B) \quad n \quad \text{OR}^1 \\
 &X^2 \quad \text{OR}^2 \\
 &X^3 \quad \text{NH}_2
\end{aligned}
\]

in which B, R^1, R^2, X^1, X^2, X^3 and n are as hereinbefore defined; with an aldehyde of formula (XI):

\[
R^3-\text{CHO}
\]

in which R^3 is as hereinbefore defined; under reductive amination conditions.

Suitable such conditions include carrying out the reaction in the presence of sodium cyanoborohydride in an alcoholic solvent, preferably methanol, at a pH between 3 to 6 and at a temperature between 0°C and 25°C.

The key α-substituted primary aminomethylphosphonate of formula (X) is obtained by treating an aldehyde of formula (V), as hereinbefore defined, with (+) or (-)α-methylbenzylamine to form an intermediate imine which is then reacted with a phosphite ester HPO(OR^1)(OR^2) to give a mixture of diastereoisomers which may be separated by conventional techniques, for instance fractional crystallisation or chromatography. Hydrogenolysis can then be used to remove the benzyl group from nitrogen, to give the α-substituted primary aminomethyl-phosphonate of formula (X). This approach is illustrated by the preparation of enantiomers of compounds No. 7
and 15 of Table 1. Alternately, the resolution of the aminophosphonate racemates can be effected by preparative chiral chromatography, in particular chiral HPLC. The experimental conditions for chromatographic separation of enantiomers of compound No. 20 are provided. With either separation method, final enantiomeric purity can be ascertained by measuring the specific rotations of the separated isomers.

The structure of compounds of formula (I) were established by their elemental analysis, their infrared (IR), mass (MS) and nuclear magnetic resonance (NMR) spectra. The purity of the compounds was checked by thin layer, gas liquid or high performance liquid chromatographies.

The invention is further described in the following examples which are intended to illustrate the invention without limiting its scope. In the tables, n is normal, i is iso, s is secondary and t is tertiary. In the description of the NMR spectra, respectively s is singlet, d doublet, t triplet and m multiplet. TsOH is p-toluenesulfonic acid monohydrate. The temperatures were recorded in degrees Celsius and the melting points are not corrected. In the measurement of optical activity, an enantiomer which rotates the plane of polarized light to the right is called dextrorotatory and is designated (+) or (D). Conversely, levorotatory defines an enantiomer which rotates the plane of polarized light to the left, designated (-) or (L). Unless otherwise indicated, the physical constants and biological data given for aminophosphonates of formula (I) refer to racemates.
Example 1 - Dimethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-pyridyl)-amino-methylphosphonate

A mixture of 50g (0.206mol) of 3,5-di-tert-butyl-4-hydroxybenzaldehyde and 20.3 g (2.16 mol) of 3-aminopyridine dissolved in 300 ml toluene and a catalytic amount of p-toluenesulfonic acid (ca. 50 mg) contained in a flask connected to a Dean Stark apparatus was refluxed for 17 h. The solution was evaporated to dryness to give a solid which was purified by recrystallisation from ligroin : mp = 125-130°, IR (KBr) = 1590 cm⁻¹ : CH=N.

Dimethyl phosphite (63.8 g, 0.58 mol) was added to 60 g (0.19 mol) of the previously described imine dissolved in 230 ml THF and the mixture was refluxed for 6 h. The solvent was evaporated and the residue was purified by column chromatography (SiO₂, 9/1 CHCl₃/MeOH). Recrystallisation from a mixture of methyl-tert-butyl ether/petroleum ether gave a white solid, mp = 168-170°C.

IR (KBr) = 3300 cm⁻¹ : NH, 1240 : P=O, 1030 : P-O-C
NMR (CDCl₃) : δ = 8.06, 7.96, 7.4 and 6.9 (4m, 1H each) : aromatic H, 3-pyridyl, 7.2 (d, J p-H = 2Hz, 2H) : aromatic H, substituted phenyl, 5.24 (s, 1H) : OH, 4.66 (d, Jp-H = 22Hz, 1H) : CH-PO₃Me₂, 4.75 - 4.68 (m, 1H) : NH, 3.74 and 3.39 = (two d, J = 11Hz) : P-O-CH₃, 1.42 (s, 18H) : tert-Bu

MS : m/e = 419 : M⁺-1, 311 (100%) : M⁺- PO₃Me₂

Example 2 - Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(2-pyridyl)-amino-methylphosphonate

The process described in example 1 was employed using 2-aminopyridine as the amine and diethyl phosphite as the phosphonate reagent. The title compound was purified by column chromatography (95/5 CHCl₃/MeOH) to yield a solid (61%); mp = 116-118° (AcOEt-ligroin)

MS (m/e) = 448 : M⁺, 311 : M⁺- PO₃Et₂, 78 (100%) : C₅H₄N
\[ \delta = 8.09, 7.38 \text{ and } 6.57 \text{ and } 6.44 \text{ (4m, 1H each): aromatic H, 2-pyridyl, 7.28 (d, J } p-H=2Hz, 2H): \text{aromatic H, substituted phenyl, 5.46 (dd, } J=9 \text{ and } 22 \text{ Hz, 1H): CH-PO_3Et_2, 5.3 (m, 1H): N-H, 4.14-3.66 (3m, 4H total): P-O-CH_2-CH_3, 1.42 (s, 18H): tert-Bu, 1.21 \text{ and 1.16 (2t, 3H each): P-O-CH_2-CH_3} \]

**Example 3** - Diethyl \( \alpha-(3,5\text{-di-tert-butyl-4-hydroxyphenyl})\text{-N-(5-(2-chloro pyridyl))-aminomethylphosphonate} \)

\[
\text{HO-} \quad \text{Cl} \\
\text{CH} \\
\text{NH} \\
\text{PO_3Et_2} \\
\text{t-Bu} \\
\text{t-Bu}
\]

The process described in example 1 was employed using 5-amino-2-chloropyridine as the amine and diethyl phosphite as the phosphonate reagent. The title compound was obtained in 50% yield after column chromatography (98/2 CHCl_3/MeOH) and trituration in petroleum ether; \( mp = 124-126^\circ \text{C} \)

MS (m/e) = 483: M^+ + 1, 345 (100%), 347 (30%): M^+ - PO_3Et_2

NMR (CDCl_3): \( \delta = 7.78, 7.05 \text{ and 6.09 (3H): aromatic H, 3-pyridyl, 7.18 (d,}\)

\( J=2Hz, 2H): \text{aromatic H, substituted phenyl, 5.22 (s, 1H): OH, 4.83 (t, } J=8Hz): \text{N-H, 4.57 (dd, } J=7.5 \text{ and 22.5Hz): CH-PO_3Et_2, 4.1, 3.86 \text{ and 3.56 (3m, 4H): P-O-CH_2-CH_3, 1.40 (s, 18H): t-Bu, 1.28 \text{ and 1.05 (2t, } J=7Hz): P-O-CH_2-CH_3} \)

**Example 4** - Diethyl \( \alpha-(3,5\text{-di-tert-butyl-4-hydroxyphenyl})\text{-N-acetyl-N-(4-picolyl)-aminomethylphosphonate} \)

\[
\text{HO-} \quad \text{CO-CH_3} \\
\text{CH} \\
\text{NH} \\
\text{PO_3Et_2} \\
\text{t-Bu} \\
\text{t-Bu}
\]

A mixture of acetic anhydride (1.4g, 14 mmol), diethyl \( \alpha-(3,5\text{-di-tert-butyl-4-hydroxyphenyl})\text{-N-(4-picolyl)-aminomethylphosphonate} \) (6 g, 13 mmol) and triethyl amine (1.9 ml, 14 mmol) in 20 ml toluene was refluxed for 16 h. The reaction mixture was extracted with brine, dried and evaporated to dryness. The residue was recrystallized in a mixture of dichloromethane and petroleum ether to give 3.7 g (57% yield); \( mp = 160-162^\circ \text{C} \).

MS (m/e): 504: M^+, 461: M^+ - COCH_3, 367: M^+ - PO_3Et_2, 325 (100%): M^+ + 1 - PO_3Et_2 - COCH_3
Example 5 - Hydrochloride salt of diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-pyridyl)aminomethylphosphonate

\[
\begin{align*}
&\text{HO-} \\
&\text{Bu} \quad \text{Bu} \\
&\text{PO}_{3} \text{Et}_{2} \\
&\text{NH} \\
&\text{HCl}
\end{align*}
\]

5 Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-pyridyl) aminomethylphosphonate (3 g, 6.7 mmol) was dissolved with slight warming in 60 ml toluene and the resulting solution was saturated with gaseous hydrogen chloride. After 16 h at 0°C the mixture was evaporated to dryness and the residue was recrystallized in EtOH; mp = 193-194°C.

Elemental analysis: C_{24}H_{38}ClN_{2}O_{4}P
% Calc. C 59.43 H 7.90 Cl 7.31 N 5.78 P 6.39
% Found C 59.53 H 8.10 Cl 7.02 N 5.72 P 6.21

Example 6 - Diethyl α-(3,4-methylene dioxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate

\[
\begin{align*}
&\text{O} \\
&\text{Bu} \quad \text{Bu} \\
&\text{PO}_{3} \text{Et}_{2} \\
&\text{NH} \\
&\text{H}
\end{align*}
\]

The process described in example 8 was followed. The title compound was purified by column chromatography (9/1 CHCl_{3}/MeOH); 60% yield, mp = 98-99°C, C_{17}H_{21}N_{2}O_{5}P.

15 IR (KBr) = 1240 cm^{-1}: P=O, 1030: P-O-C
MS (m/e) = 365 M^{+}+1, 227 (100%); M^{+} - PO_{3}Et_{2}
NMR (CDCl_{3}) \delta = 8.1, 7.95, 7.05 and 6.95 (4m, 1H each): aromatic H, 3-pyridyl, 6.90, 6.85, 6.75 (3m, 3H): aromatic H, substituted phenyl, 5.95 (2H): = O-CH_{2}-O, 4.86 (d x d, 1H, J=8 and 10Hz): N-H, 4.63 (d x d, 1H, J=8 and 24 Hz): CH-PO_{3}Et_{2},

4.18-3.70 (3m, 4H total): P-O-CH_{2}-CH_{3}, 1.31 and 1.16: (2t, J=7Hz): P-O-CH_{2}-CH_{3}

Example 7 - Diethyl α-(4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate
4-Hydroxybenzaldehyde (6 g, 49 mmol) was reacted at room temperature with 3-
aminopyridine (4.5 g, 52 mmol) in 30 ml THF at room temperature to give 9.9 g of a
light brown solid. The imine so obtained (5.9 g, 30 mmol) was dissolved in 50 ml
THF, diethyl phosphite was added in two portions, one at the beginning of the
reaction and the other after 6 h at reflux, (total amount: 8.2 g, 60 mmol). The
reaction mixture was refluxed overnight. Filtration of the precipitate formed gave 7.5
g (75%) of a tan solid, mp = 210-212°C (EtOH).
MS (m/e) = 337 : M⁺ + 1, 199 (100%): M⁺ - PO₃Et₂
NMR (DMSO-d₆): δ=9.35 (s, 1H): OH, 8.15, 7.7, 7.1 and 7.0 (4m, 1H each):
aromatic H, 3-pyridyl, 6.5 (dxd, 1H): N-H, 7.3 and 6.7 (2m, 2H each): aromatic H,
4-hydroxyphenyl, 4.93 (dxd, 1H): CH₃-PO₃Et₂, 4.1-3.6 (3m, 4H total): P-O-CH₂-
CH₃, 1.15 and 1.02 (2t, 3H each): P-O-CH₂-CH₃

Example 8 - Diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)amino-
methylphosphonate

A mixture of 3 g (16.4 mmol) of syringaldehyde and 1.63 g (17.3 mmol) of 3-
aminopyridine dissolved in 10 ml toluene and a catalytic amount of p-toluenesulfonic
acid (ca. 5 mg) contained in a flask connected to a Dean Stark apparatus was refluxed
for 17 h. The solution was evaporated to dryness to give 4.2 g (100%) of the crude
imine. Diethyl phosphite (4.8 g, 35 mmol) was added to 4.2 g (17.3 mmol) of the
previously described imine dissolved in 10 ml THF and the mixture was refluxed for
7 h. Another amount of diethyl phosphite (4.8 g, 35 mmol) was added and the
mixture was refluxed overnight (total reaction time: 17 h). The solvent and the
excess of diethyl phosphite were evaporated and the residue was recrystallized from a
mixture of ethanol and dichloromethane to give 4.2 g (61%) of a white solid, mp =
181-183°C.
IR (KBr) = 1240 cm⁻¹ : P=O and 1030 : P-O-C
MS (m/e) = 397 : M⁺ + 1, 259 (100%): M⁺ - PO₃Et₂
NMR (CDCl₃): δ = 8.08, 7.98, 7.04 and 6.84 (4m, 1H each): aromatic H, 3-pyridyl, 6.69 (d, J = 2Hz, 2H): aromatic H, substituted phenyl, 5.8 (broad, 1H): O-H, 4.84 (d x d, 1H, J = 7 and 10Hz): N-H, 4.62 (d x d, 1H, J = 7 and 23 Hz): CH-PO₃Et₂, 4.18-3.65 (3m, 4H total): P-O-CH₂-CH₃, 3.86 (s, 6H): OCH₃, 1.31 and 1.16: (2t, J = 7Hz): P-O-CH₂-CH₃

Elemental analysis: C₁₈H₂₅N₂O₅P
%
Calc.    C 54.54    H 6.36    N 7.07    P 7.81
Found    C 54.50    H 6.38    N 6.99    P 7.65

Example 9 - Diethyl α-(3,4,5-trimethoxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate

A mixture of 3,4,5-trimethoxybenzaldehyde (10 g, 51 mmol) and 3-aminopyridine (4.8 g, 51 mmol) and a catalytic amount of TsOH in 50 ml toluene was refluxed for 16 h in a flask connected to a Dean-Stark trap. Evaporation of toluene gave 12.9 g (93%) of the crude imine which was used directly in the next reaction.

A 50 ml THF mixture containing the imine (6g, 22 mmol) and diethyl phosphite (6.1g introduced at the beginning and 6.1 g after 4 h, total amount = 12.2 g, 88 mmol) was refluxed for 8 h. The residue after evaporation of THF and excess of HPO₃Et₂ was triturated in petroleum ether to give 7.12 g (79%) of a white solid, mp = 135-137°C.

MS (m/e) = 410 : M⁺, 273 (100%) : M⁺ - PO₃Et₂

NMR (CDCl₃): δ = 8.1, 8.0, 7.05 and 6.85 (4m, 1H each): aromatic H, 3-pyridyl, 6.69 and 6.68: (d, J = 2Hz, 2H): aromatic H, substituted phenyl, 4.86 (d x d, 1H, J = 8 and 10Hz): N-H, 4.63 (d x d, 1H, J = 7 and 23 Hz): CH-PO₃Et₂, 4.18-3.70 (3m, 4H total): P-O-CH₂-CH₃, 3.86 (two s, 9H): OCH₃, 1.31 and 1.16: (2t, J = 7Hz): P-O-CH₂-CH₃

Example 10 - Diethyl α-(3-ethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate
A 50 ml toluene solution containing 3-ethoxy-4-hydroxybenzaldehyde (10 g, 60 mmol), 3-aminopyridine (5.6 g, 60 mmol) and 50 mg of TsOH placed in a flask connected to a Dean-Stark trap was refluxed for 4 h to give 14.62 g (95%) of the corresponding imine.

To a suspension of sodium hydride (1.19 g of a 60% mixture, 30 mmol) in 20 ml dry THF was added HPO₃Et₂ (9.12 g, 66 mmol) under nitrogen and the resulting mixture was stirred until the initial turbid suspension became completely clear. To this solution of NaPO₃Et₂ was added the above imine (8 g, 33 mmol) dissolved in 10 ml THF and the resulting solution was refluxed for 2 h. THF was evaporated and the residue was partitioned into H₂O and CH₂Cl₂. Evaporation of the dried organic phase gave 3.1 g of a white solid, mp = 184-187°C.

MS : (m/e) = 380 : M⁺, 243 : M⁺ - PO₃Et₂
NMR (DMSO-d6): δ = 8.9 (s, 1H): OH, 8.15, 7.3, 7.0 and 6.9 (1H each): aromatic H, 3-pyridyl, 7.1 (m, 2H) and 6.68 (d, J = 8 Hz, 1H): aromatic H, phenyl, 6.5 (dxd, J = 6 and 10 Hz): NH, 4.92 (dxd, J = 10 and 24 Hz): CH⁻PO₃Et₂, 4.05-3.6 (4m, 6H total): P-O-CH₂-CH₃ and OCH₂CH₃, 1.29 (t, J = 7Hz, 3H): O-CH₂-CH₃, 1.16 and 1.04 (2t, J = 7Hz, 3H each): P-O-CH₂-CH₃

Example 11 - Diethyl α-(4-hydroxy-3-methoxyphenyl)-N-(3-pyridyl)aminomethylphosphonate

The procedure described in example 10 was followed, using 4-hydroxy-3-methoxybenzaldehyde as the starting material. The title compound is a white solid, mp = 170-173°C.

MS (m/e) = 366: M⁺, 229: M⁺ - PO₃Et₂
NMR (DMSO-d6) δ = 8.9 (s, 1H): OH, 8.15, 7.75, 7.0 and 6.9 (4m, 4H): aromatic H, 3-pyridyl, 7.1 (m, 2H) and 6.7 (d, J = 8 Hz, 1H): aromatic H, phenyl, 6.5 (dxd, J = 6
and 10 Hz): NH, 4.92 (dxd, J = 10 and 24 Hz): CH$_3$-PO$_3$Et$_2$, 4.05-3.6 (3m, 4H total): P-O-CH$_2$-CH$_3$, 3.72 (s, 3H): OCH$_3$, 1.17 and 1.4 (2t, J = 7Hz, 6H): P-O-CH$_2$-CH$_3$

**Example 12 - Diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(4-picoly)-aminomethylphosphonate**

![Chemical Structure](image)

A solution of 2.5 g (13.7 mmol) syringaldehyde and 1.6 g (14.4 mmol) 4-picolyamine dissolved in 100 ml toluene contained in a flask connected to a Dean-Stark apparatus was refluxed for 3 h. Toluene was evaporated under vacuum then the residue dissolved in 10 ml THF was heated with 5.1 g (36.8 mmol) diethyl phosphite for 6 h. THF was evaporated and the residue was purified by column chromatography (SiO$_2$, 95/5 CHCl$_3$/MeOH). Recrystallisation in a mixture of CH$_2$Cl$_2$-petroleum ether gave 3.7 g (45%) of a solid, mp = 124-126°C.

MS (m/e) = 410: M$^+$, 273: M$^+$-PO$_3$Et$_2$

NMR (CDCl$_3$) $\delta$ = 8.55 and 7.22 (2m, 4H): aromatic H, 4-picoly, 6.75 (d, J = 2Hz, 2H): aromatic H, phenyl, 4.15-3.77 (several m, 5H): P-O-CH$_2$-CH$_3$ and CH$_3$-PO$_3$Et$_2$, 3.89 (s, 6H): OCH$_3$, 3.82 and 3.62 (2d, J = 14 Hz): NH-CH$_2$-Py, 1.33 and 1.16 (2t, J = 7Hz, 6H): P-O-CH$_2$-CH$_3$

**Example 13 - Diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-picoly)-aminomethylphosphonate**

![Chemical Structure](image)

The procedure described in example 12 was followed, using 3-picolyamine as the starting material. The title compound was purified by column chromatography (9/1 CHCl$_3$/MeOH) to give a thick yellow oil. Recrystallization from CH$_2$Cl$_2$-petroleum ether gave a tan solid, mp = 99-101°C

MS (m/e): 410: M$^+$, 273 = M$^+$-PO$_3$Et$_2$

NMR (CDCl$_3$) $\delta$ = 8.51, 8.50, 7.64 and 7.25 (4m, 4H): aromatic H, 3-picoly, 6.65 (d, J = 2Hz, 2H): aromatic H, phenyl, 7.75 (broad, 1H): OH, 4.15-3.75 (several m, 5H):
P-O-CH₂-CH₃ and CH-P₀₃Et₂, 3.9 (s, 6H): OCH₃, 3.82 and 3.61 (2d, J = 14Hz, 2H): NH-CH₂-Py, 1.31 and 1.16 (2t, J = 7Hz, 6H): P-O-CH₂-CH₃

**Example 14 - Diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(2-pyridyl)-aminomethylphosphonate**

![Chemical Structure](image)

A mixture of 3.64 g (20 mmol) of syringaldehyde and 1.88 g (20 mmol) of 2-aminopyridine dissolved in 20 ml toluene and a catalytic amount of TsOH contained in a flask connected to a Dean Stark apparatus was refluxed for 24 h. The solution was evaporated to dryness to give 5.2 g (100%) of the crude imine. Diethyl phosphite (5.8 g, 42 mmol) was added to 3.6 g (14 mmol) of the previously described imine dissolved in 25 ml THF and the mixture was refluxed for 20 h. The solvent and the excess of diethyl phosphite were evaporated and the residue was recrystallized from ethanol to give 4.2 g (76%) of a white solid, mp = 163-165°C.

IR (KBr) = 1240 cm⁻¹: P=O and 1030 : P-O-C  
MS (m/e) = 397 : M⁺ + 1, 259 (100%) : M⁺ - PO₃Et₂  
NMR (CDCl₃): δ =8.08, 7.37, 6.60 and 6.41 (4m, 1H each): aromatic H, 2-pyridyl, 6.76 (d, J = 2Hz, 2H): aromatic H, substituted phenyl, 5.6 (s, 1H): OH, 5.39 (m, 1H): N-H, 5.37 (d x d, 1H, J=9 and 28 Hz): CH-P₀₃Et₂, 4.18-3.69 (3m, 4H total): P-O-CH₂-CH₃, 3.87 (s, 6H): OCH₃, 1.24 and 1.15: (2t, J=7Hz): P-O-CH₂-CH₃

**Example 15 - Diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(4-pyridyl)-aminomethylphosphonate**

![Chemical Structure](image)

A 25 ml toluene solution containing syringaldehyde (3.64 g, 20 mmol), 4-aminopyridine (1.9 g, 20 mmol) and 5 mg of TsOH placed in a flask connected to a Dean-Stark trap was refluxed for 48 h to give 5.0 g (95%) of the corresponding imine.
To a suspension of sodium hydride (0.87 g of a 60% mixture, 20 mmol) in 25 ml dry THF was added HPO$_3$Et$_2$ (4.14 g, 30 mmol) under nitrogen and the resulting mixture was stirred until the initial turbid suspension became completely clear. To this solution of NaPO$_3$Et$_2$ was added the above imine (2.6 g, 10 mmol) dissolved in 5 ml THF and the resulting solution was refluxed for 2 h. THF was evaporated and the residue was partitioned into H$_2$O and CH$_2$Cl$_2$. Evaporation of the dried organic phase gave a white solid which was recrystallized in EtOH (1.84 g, 45%); mp = 172-174°C.

MS (m/e) = 396 : M$^+$, 259 (100%) : M$^+$ - PO$_3$Et$_2$

NMR (CDCl$_3$): $\delta$ = 8.18, 8.16, 6.48 and 6.46 (4m, 1H each): aromatic H, 4-pyridyl, 6.67 (d, J = 2Hz, 2H): aromatic H, substituted phenyl, 5.27 (d x d, 1H, J=7 and 10Hz): N-H, 4.66 (d x 3, 1H, J=7 and 23 Hz): CH-P=O$_3$Et$_2$, 4.18-3.60 (3m, 4H total): P=O-CH$_2$-CH$_3$, 3.87 (s, 6H): OCH$_3$, 1.30 and 1.15: (2t, J=7Hz): P-O-CH$_2$-CH$_3$

**Example 16 - Enantiomers of diethyl $\alpha$-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(4-picolyl)-aminomethylphosphonate**

![Diethylaminomethylphosphonate](image)

a) 3,5-Di-tert-butyl-4-hydroxybenzaldehyde (30 g, 123.5 mmol) and (R)-(+-)-1-phenyl-ethylamine (15.7 g, 129.7 mmol) were stirred in 100 ml of THF at room temperature for one day. The solution was dried on MgSO$_4$ and concentrated. The corresponding imine was recrystallized from ligroin (38 g; 88% yield; mp = 127-128°C).

The imine (30 g, 89 mmol) and diethylphosphite (15.4 g, 111.3 mmol) were refluxed in 80 ml of toluene for 5 hours. The mixture was evaporated to dryness. HPLC assay of the residue showed that one of the diastereomers is formed predominantly (84% vs 3% of the reaction mixture). The major diastereomer of diethyl $\alpha$-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(1-phenyl-ethyl)-aminomethylphosphonate was isolated by successive crystallizations (10g): $[\alpha]_D^{27} + 8.33^\circ$ (c=1.649, CHCl$_3$); mp = 105-106°C).

(+)-Diethyl $\alpha$-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(1-phenyl-ethyl)-aminomethylphosphonate (9.5 g, 20 mmol) was hydrogenated in ethanol in the presence of 2.5 g of 10% Pd on charcoal to give (-)-diethyl $\alpha$-(3,5-di-tert-butyl-4-hydroxyphenyl)-aminomethylphosphonate (5.6 g; 76% yield; mp = 143-145°C (recrystallized from ligroin/CH$_2$Cl$_2$); $[\alpha]_D^{21}$ -12.12^\circ$ (c=1.650, CHCl$_3$).
(-)-Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-aminomethylphosphonate (11 g, 29.6 mmol) and pyridine-4-carboxaldehyde (6.3 g, 59.3 mmol) were dissolved in 125 ml of MeOH. The mixture was acidified with concentrated HCl (blue bromophenol indicator). After half an hour of stirring at room temperature, NaBH₃CN (5.6 g, 89 mmol) dissolved in 30 ml MeOH was added and the pH was adjusted again with HCl. The reaction mixture was stirred at room temperature for 4 hours then evaporated to dryness and extracted with CH₂Cl₂ and water. The organic phase was dried over MgSO₄ and evaporated. The residue was separated by column chromatography (silicagel, 95/5 CHCl₃/MeOH to give (-)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(4-picolyl)-aminomethylphosphonate [(11 g; 80% yield; mp = 66-69°C; [α]D²⁻44.05° (c=1.992, CHCl₃)].

b) 3,5-Di-tert-butyl-4-hydroxybenzaldehyde (30 g, 123.5 mmol) and (S)-(−)-1-phenyl-ethylamine (15.7 g, 129.7 mmol) were stirred in 100 ml of THF for one day to give the corresponding imine (36.5 g; 88% yield; mp = 127-128°C).

The imine (20 g, 59.3 mmol) and diethylphosphite (10.2 g, 74.2 mmol) were refluxed in 60 ml of toluene for 7 hours. The mixture was evaporated to dryness. HPLC assay of the residue indicated the diastereomeric ratio to be 60 to 40% in addition to starting materials. The latter were stripped off by column chromatography on silicagel (98/2 CH₂Cl₂/MeOH). The fractions containing the mixture of diastereomers were evaporated to dryness and recrystallized three times from ligroin/MTBE to yield the major diastereomer of diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(1-phenyl-ethyl)-aminomethylphosphonate [12 g; mp = 104-105°C; [α]D²⁻10.53° (c=1.643, CHCl₃)].

(-)-Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(1-phenyl-ethyl)-aminomethylphosphonate (42 g, 88.4 mmol) was hydrogenated in ethanol in the presence of 6 g of 10% Pd on charcoal to give (+)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-aminomethylphosphonate (24.5 g; 75% yield; mp = 143-144°C (recrystallized from ligroin/MTBE); [α]D²⁺11.04° (c=1.714, CHCl₃)).

(+)-Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-aminomethylphosphonate (11 g, 29.6 mmol) and pyridine-4-carboxaldehyde (6.35 g, 59.3 mmol) in 125 ml of MeOH were reacted with NaBH₃CN (5.6 g, 89 mmol) in the same manner as described for the (-) enantiomer. Column chromatography on silicagel (95/5 CHCl₃ / MeOH) gave (+)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(4-picolyl)-aminomethylphosphonate (12 g, 87% yield; mp = 67-70°C; [α]D²⁺43.03° (c=1.984, CHCl₃)].
Example 17 - Enantiomers of diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-picolyl)-aminomethylphosphonate

\[
(+)/(-) \quad \begin{array}{c}
\text{HO} \\
t-\text{Bu}
\end{array} \quad \begin{array}{c}
\text{t-Bu} \\
\text{CH}
\end{array} \quad \text{PO}_{2} \text{Et}_{2}
\]

a) In the same manner as described in example 16, (+)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-aminomethylphosphonate (1 g, 2.7 mmol) and pyridine-3-carboxaldehyde (0.43 g, 4 mmol) were reacted with NaBH₃CN (0.34 g, 5.4 mmol) in MeOH for 5 hours at room temperature to yield after trituration in petroleum ether (+)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-picolyl)-aminomethylphosphonate (1 g, 80% yield; mp = 116-119°C; \([\alpha]_D^{25} +42.88°\) (c=1.614, CHCl₃)).
b) respectively,
(-)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-aminomethylphosphonate (1 g, 2.7 mmol) and pyridine-3-carboxaldehyde (0.43 g, 4 mmol) were reacted with NaBH₃CN (0.34 g, 5.4 mmol) in MeOH to give (-)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-picolyl)-aminomethylphosphonate (0.7 g, 56%; mp = 118-120°C).

Example 18 - Enantiomers of diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate

\[
(+)/(-) \quad \begin{array}{c}
\text{OMe} \\
\text{OMe}
\end{array} \quad \begin{array}{c}
\text{HO} \\
\text{OMe}
\end{array} \quad \text{CH} \quad \text{PO}_{2} \text{Et}_{2}
\]

The enantiomers of a racemic mixture were separated by preparative HPLC on Chiralcel OD and isocratic elution with hexane/ethanol (9:1), UV detection at 254 nm. Baseline separation was achieved, and the contents of both peaks were evaporated to white solids in which none of the other isomer could be detected by analytical HPLC.
First peak: retention time 18 min, \([\alpha]_D^{20} -7.4°\) (c = 0.244% w/v, EtOH)

Second peak: retention time 34 min, \([\alpha]_D^{20} + 8.3°\) (c = 0.255% w/v, EtOH)
The structures of both enantiomers were confirmed by NMR and MS spectroscopies and elemental analysis.

Elemental analysis: C_{18}H_{25}N_{2}O_{6}P

% Calc.  C 54.54  H 6.36  N 7.07

% Found  C 53.85  H 6.22  N 6.81

(+)-Enantiomer:
mp : 153-157°

mp : 155-158°

(-)-Enantiomer:

% Found  C 54.25  H 6.24  N 6.94

Example 19 - Enantiomers of diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-phenylpropyl)-aminomethylphosphonate

\[
\begin{array}{c}
\text{PO}_3\text{Et}_2 \\
\text{HO} \\
\text{NH-(CH}_2)_3
\end{array}
\]

\text{t-Bu}
\text{C-H}
\text{t-Bu}

\text{t-Bu}

a) (-)-Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-aminomethylphosphonate (1.7 g, 4.5 mmol) and 3-phenylpropionaldehyde (0.6 g, 4.5 mmol) in 20 ml of absolute methanol were stirred under nitrogen, at room temperature for 30 min. NaBH₃CN (0.3 g, 4.5 mmol) dissolved in 10 ml of methanol was added and the mixture was allowed to react at room temperature for another hour. The reaction mixture was evaporated to dryness and the residue dissolved in CH₂Cl₂. The organic phase was washed with water, then dried over MgSO₄. Column chromatography with 98/2 CHCl₃/MeOH as eluent gave (-)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-phenylpropyl)-aminomethylphosphonate [1.2 g; 56% yield; [α]₀^20 +33.1° (c=2.055, CHCl₃)].

b) (+) Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-aminomethylphosphonate (1.2 g, 3.2 mmol) and 3-phenylpropionaldehyde (0.4 g, 3.2 mmol) in 20 ml of absolute methanol were reacted in the same manner with NaBH₃CN (0.2 g, 3.2 mmol) in 10 ml of methanol to yield after column chromatography, (+) diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-phenylpropyl)-aminomethylphosphonate [0.94 g; 61% yield; [α]₀^20 +31.1° (c=1.930, CHCl₃)].

c) - The structures of both enantiomers were confirmed by IR, NMR and MS. They were separated by analytical HPLC on Chiralpak AD and isocratic elution with hexane/2-propanol (9:1/v:v).
Example 20 - Diisopropyl o-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-amino-methylphosphonate

Diisopropyl phosphite (3.3 g, 20 mmol) was added to 2.58 g (10 mmol) of 3,5-dimethoxy-4-hydroxybenzaldehyde N-(3-pyridyl) imine dissolved in 15 ml toluene and the mixture was refluxed for 17 h. The solvent and the excess of diisopropyl phosphite were evaporated and the residue was purified by column chromatography (9/1 CH2Cl2/MeOH) and recrystallisation from a mixture of EtOH/AcOEt to give 1.56 g (37%) of a white solid, mp = 157-160°.

MS (m/e) = 424: M⁺, 259 (100%): M⁺ - PO3iPr2
NMR (CDCl3): δ =8.08, 7.96, 7.03 and 6.84 (4m, 1H each): aromatic H, 3-pyridyl, 6.69 (d, J = 2Hz, 2H): aromatic H, substituted phenyl, 5.8 (broad, 1H): OMe, 4.82 (d x d, 1H, J=7 and 10Hz): N-H, 4.55 (d xd, 1H, J=7 and 23Hz): CH-PO3iPr2, 4.75-4.65 and 4.55-4.45 (2m, 2H total): P-O-CH-(CH3)2, 3.86 (s, 6H): OCH3, 1.34, 1.28, 1.24 and 0.9: (4d, J=7Hz): P-O-CH-(CH3)2

Example 21 - Diisopropyl o-(4-hydroxy-3-methoxy-5-methylphenyl)-N-(3-pyridyl)-amino-methylphosphonate

A mixture of 1.9 g (11 mmol) of 4-hydroxy-3-methoxy-5-methylbenzaldehyde (mp= 98-100°) and 1.08 g (11 mmol) of 3-aminopyridine dissolved in 15 ml toluene and a catalytic amount of p-toluenesulfonic acid (ca. 5 mg) contained in a flask connected to a Dean Stark apparatus was refluxed for 15 h. The solution was evaporated to dryness to give 2.7 g (100%) of the crude imine.

Diisopropyl phosphite (5.48 g, 33 mmol) was added to 2.77 g (11 mmol) of the above imine dissolved in 20 ml THF and the mixture was refluxed for 24 h. The solvent and the excess of diisopropyl phosphite were evaporated and the residue was purified by column chromatography (95/5 CHCl3/MeOH) and recrystallisation from a
mixture of petroleum ether/CH₂Cl₂ to yield 1.9 g (43%) of a white solid, mp = 123-124°.
MS (m/e) = 408: M⁺, 243 (100%): M⁺ - PO₃iPr₂
NMR (CDCl₃): δ = 8.07, 7.95, 7.02 and 6.84 (4m, 1H each): aromatic H, 3-pyridyl,
6.83-6.81: (m, 2H): aromatic H, substituted phenyl, 5.8 (s, 1H): OH, 4.78 (d x d,
1H, J=7.5 and 10Hz): N-H, 4.30 (d x d, 1H, J=7.5 and 23Hz): CH-PO₃iPr₂, 4.73-4.65
and 4.48-4.40 (2m, 2H total): P-O-CH-(CH₃)₂, 3.85 (s, 3H): OCH₃, 2.22 (s, 3H):
CH₃, 1.33, 1.26, 1.24 and 0.96: (4d, J=7Hz): P-O-CH-(CH₃)₂

Example 22 - Diisopropyl α-(3-n-butyl-4-hydroxy-5-methoxyphenyl)-N-(3-pyridyl)-
amino-methylphosphonate

A mixture of 6.1 g (30 mmol) of 3-n-butyl-4-hydroxy-5-methoxybenzaldehyde and
2.76 g (30 mmol) of 3-aminopyrididine dissolved in 50 ml toluene and a catalytic
amount of p-toluenesulfonic acid (ca. 5 mg) contained in a flask connected to a Dean
Stark apparatus was refluxed for 16 h. The solution was evaporated to dryness to
give 7.8 g (94%) of the crude imine.
Diisopropyl phosphite (4.20 g, 25 mmol) was added to 2.4 g (8 mmol) of
the above imine dissolved in 30 ml THF and the mixture was refluxed for 24 h. The
solvent and the excess of diisopropyl phosphite were evaporated and the residue was
purified by column chromatography (95/5 CHCl₃/MeOH) and recrystallisation from a
mixture of petroleum ether/CH₂Cl₂ to yield 1.9 g (43%) of a white solid, mp = 142-144°.
MS (m/e) = 450: M⁺, 285 (100%): M⁺ - PO₃iPr₂
NMR (CDCl₃): δ = 8.07, 7.95, 7.0 and 6.84 (4m, 1H each): aromatic H, 3-pyridyl,
6.83-6.80: (m, 2H): aromatic H, substituted phenyl, 5.8 (s, 1H): OH, 4.74 (d x d,
1H, J=7.5 and 10Hz): N-H, 4.54 (d x d, 1H, J=7.5 and 23Hz): CH-PO₃iPr₂, 4.75-4.65
and 4.50-4.40 (2m, 2H total): P-O-CH-(CH₃)₂, 3.85 (s, 3H): OCH₃, 2.60 (t, 2H), 1.5
(m, 2H), 1.31 (m, 2H) and 0.90 (t, 3H): n-Bu, 1.33, 1.26, 1.24 and 0.94: (4d, J=7Hz):
P-O-CH-(CH₃)₂

Example 23 - Diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-methyl-
N-(3-picolyt)-aminomethylphosphonate
A mixture of 3.0 g (16.5 mmol) of syringaldehyde, 2.03 g (16.6 mmol) of N-methyl-3-picolyamine and 2.3 g (16.6 mmol) diethyl phosphite dissolved in 15 ml toluene and a catalytic amount of p-toluenesulfonic acid (ca. 5 mg) contained in a flask connected to a Dean Stark apparatus was refluxed for 2 h. The solution was evaporated and the residue was purified by column chromatography (95/5 CHCl3/Methanol) to yield 3.2 g (46%) of a yellow oil.

**Example 24 - Diisopropyl α-(4-hydroxy-3-methoxy-5-methylphenyl)-N-methyl-N-(3-picolyl)-aminomethylphosphonate**

A mixture of 2.0 g (12 mmol) of 4-hydroxy-3-methoxy-5-methylbenzaldehyde, 1.8 g (13.2 mmol) of N-methyl-3-picolyamine and 2.2 g (13.2 mmol) diisopropyl phosphite dissolved in 15 ml toluene and a catalytic amount of p-toluenesulfonic acid (ca. 2 mg) contained in a flask connected to a Dean Stark apparatus was refluxed for 2 h. The solution was evaporated and the residue was purified by column chromatography (95/5 CHCl3/Methanol) to yield 2.1 g (40%) of a yellow oil.

**NMR (CDCl3):** δ = 8.54, 8.50, 7.72 and 7.24 (4m, 1H each): aromatic H, 3-picolyl, 6.97 and 6.77 (2m, 2H): aromatic H, substituted phenyl, 5.75 (broad, 1H): OH, 4.86-4.78 and 4.51-4.42 (2m, 2H total): P-O-CH(CH3)2, 3.84 (d, J = 24Hz, 1H): CH2-PO3iPr2, 3.97 and 3.34 (2d, J = 13.5 Hz, 2H): N(CH3)-CH2-Py, 3.91 (s, 3H):
OCH₃, 2.36 (s, 3H): CH₃, 2.26 (s, 3H): N(CH₃)-CH₂-Py, 1.39, 1.37, 1.21 and 0.83 (4d, J = 7 Hz, 12 H): P-O-CH(CH₃)₂

The following compounds may also be obtained in an analogous manner to Examples 1 to 24:

- Diethyl α-(4-hydroxy-3-methoxy-5-n-propylphenyl)-N-(3-pyridyl)-aminomethylphosphonate;
- Diisopropyl α-(4-hydroxy-3-methoxy-5-n-propylphenyl)-N-(3-pyridyl)-aminomethylphosphonate;
- Diethyl α-(3-i-butyl-4-hydroxy-5-methoxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate; and
- Diisopropyl α-(3-i-butyl-4-hydroxy-5-methoxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate.

Table 1 lists the physicochemical data of compounds of formula (I) that were prepared by the methods illustrated by examples 1-24 of this application. These methods are disclosed in EP 0 559 079A (corresponding to the US Patent 5 424 303).
### Table 1 - Aminophosphonates of formula (I)

![Chemical Structure](image.png)

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<td>3-(2-methylpyridyl)</td>
<td>Et</td>
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<td>C&lt;sub&gt;19&lt;/sub&gt;H&lt;sub&gt;27&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;6&lt;/sub&gt;P</td>
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* : Identified by NMR and MS spectroscopies

** : (+)Enantiomer of Compound 20

*** : (-)Enantiomer of Compound 20
Table 1 - Aminophosphonates of formula (I), (cont.)

![Chemical Structure]

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<th>X¹</th>
<th>X²</th>
<th>X³</th>
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<th>Z</th>
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<td>C₂₀H₂₉N₂O₆P</td>
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*: Identified by NMR and MS spectroscopies

**Biological Data**

*In vitro Data* - The compounds of formula (I) were tested for lowering the production of Lp(a) in primary cultures of Cynomolgus hepatocytes according to the assays described below. Two incubation times were used: 4 h for Assay 1 and 24 h for Assay 2.


The viability of cells was determined by Trypan blue staining. The cells were then seeded at a density of 1.5-2.10⁵ viable cells per 2cm² in 24 well tissue culture plates in a volume of 500µl per well of Williams E tissue culture medium containing 10% fetal calf serum. Cells were incubated for 4-6 hours at 37°C in a CO₂ incubator (5% CO₂) in the presence of 20µM of the test compounds dissolved in ethanol. Four wells were used for each compound. Nicotinic acid and steroid hormones were used as references to validate the assay system since they are known to decrease Lp(a) in man. Control cells were incubated in the presence of ethanol only.

The amount of Lp(a) secreted in culture medium was directly assayed by ELISA using a commercially available kit. Cells were washed and lysed as described by A.L. White et al, Journal of Lipid Research vol 34, p. 509-517, (1993) and the cellular content of Lp(a) was assayed as described above.
Changes in Lp(a) concentration in culture medium are given as the percentage of value measured for the control plates at 4 h (Assay 1) or 24 h (Assay 2).

**Results - Assay 1:** compounds 2, 7, 11, 15, 16, 18 and 20 were found to change the concentrations of Lp(a) in the culture medium in the range from -12 to -34%.

**Assay 2:** compounds 1, 2, 3, 5, 7, 11, 13, 15, 17, 19, 20, 21, 26 to 29, 32, 34 to 52, 57 to 60, 65 and 66 were found to change the concentrations of Lp(a) in the culture medium in the range from -7 to -37%.

**In Vivo Data - Study Protocol:** Male cynomolgus monkeys weighing between 3 and 7 kg were divided into groups of 3 to 4 animals each. Prior to treatment their plasma Lp(a) levels were followed over a two month period to ascertain a constant baseline value. Test compounds were given orally by gavage at the dose of 25 mg/kg/day for 4 weeks and Lp(a) was measured at day 28. At the end of the dosing period, animals were maintained for a treatment free period of 4 weeks, whereupon their plasma Lp(a) levels returned to pretreatment levels. This control provided proof that the decrease in Lp(a) measured was caused by the pharmacological activity of the test compounds.

**Results - At Days -7 and 28,** after an overnight fast, blood samples were collected on EDTA and Lp(a) was measured by the highly sensitive and specific ELISA test. Results (mean of 3-4 values of each group) were expressed as % of predose (Day -7).

Selected compounds of formula (I) were tested under the experimental conditions to investigate their pharmacological activity in vivo.

The compounds No 1, 2, 3, 7, 15, 17, 19, 20, 21, 27, 28, 32, 39, 44 and 52 lower plasma Lp(a) in the range of -13% to -51% (value measured at Day 28, % change from predose at Day -7).

The compounds of Formula (I) have therefore a therapeutic potential for the treatment of the following diseases where Lp(a) is associated with accelerated atherosclerosis, abnormal proliferation smooth muscle cells and increased thrombogenesis: coronary heart disease, peripheral artery disease: intermittent claudication, extracranial carotid atherosclerosis, stroke, restenosis after angioplasty and atherosclerosis occuring after heart transplant. The primary indications of these compounds would be the treatment of the diseases mentioned above.
Claims

1. The use of a compound of formula (I):

\[
\begin{align*}
\text{X}^1, \text{X}^2, \text{identical or different, are H, a straight or branched alkyl or alkoxy group} \\
\text{having from 1 to 8 carbon atoms, a hydroxy group or a nitro group,} \\
\text{X}^3 \text{ is H, an alkyl group from 1 to 4 carbon atoms, X}^3\text{O and one of the two other} \\
\text{substituents X}^1 \text{ or X}^2 \text{ may form an alkylidene dioxy ring having from 1 to 4 carbon} \\
\text{atoms,} \\
\text{R}^1, \text{R}^2, \text{identical or different, are H, a straight or branched alkyl group having from} \\
\text{1 to 6 carbon atoms,} \\
\text{B is CH}_2, \text{CH}_2-\text{CH}_2 \text{ or CH}=\text{CH,} \\
\text{n is zero or 1,} \\
\text{Z is H, a straight or branched alkyl group having from 1 to 8 carbon atoms, an acyl} \\
\text{group R}^3\text{-CO where R}^3 \text{ is an alkyl group from 1 to 4 carbon atoms, a perfluoroalkyl} \\
\text{group from 1 to 4 carbon atoms,} \\
\text{A is H, CH}_2-\text{CH}=\text{CH}_2, \text{a straight, branched or cyclic alkyl group having from 1 to 8} \\
\text{carbon atoms, or is selected from the following groups:}
\end{align*}
\]
where:

- k is an integer from 2 to 4,
- m is 0 or an integer from 1 to 5,
- $X^4$, $X^5$, $X^6$ are identical or different, with values H, a straight or branched alkyl or alkoxy group from 1 to 8 carbon atoms, a hydroxy, trifluoromethyl, nitro, amino, dimethylamino, diethylamino group, or a halogen atom (F, Cl, Br, I).
- $X^7$ is H or CH$_3$.
- R is a straight or branched alkyl group.
- $X^4$ and $X^5$ may form an alkylidenedioxy ring having from 1 to 4 carbon atoms.
having from 1 to 6 carbon atoms, an aryl or arylalkyl group from 6 to 9 carbon atoms, or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for use in decreasing plasma and tissue lipoprotein(a) levels.

2. A use according to claim 1 for the manufacture of a medicament for the treatment of thrombosis by decreasing plasma lipoprotein(a) levels.

3. A use according to claim 1 for the manufacture of a medicament for the treatment of restenosis following angioplasty by decreasing plasma lipoprotein(a) levels.

4. A use according to claim 1 for the manufacture of a medicament for the treatment of atherosclerosis by decreasing plasma lipoprotein(a) levels.

5. A use according to any one of claims 1 to 4 wherein the compound of formula (I) is selected from:

- diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(4-picolyl)-aminomethylphosphonate,
- diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(2-picolyl)-aminomethylphosphonate,
- diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-picolyl)-aminomethylphosphonate,
- diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-[2-(2-pyridyl)ethyl]-aminomethylphosphonate,
- diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
- dimethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
- diisopropyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
- diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(2-pyridyl)-aminomethylphosphonate,
- diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(4-pyridyl)-aminomethylphosphonate,
- diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-[5-(2-chloropyridyl)]-aminomethylphosphonate.
diethyl α-(4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diethyl α-(3,4-methylenedioxyphenyl)-N-(3-pyridyl)-aminophosphonate,
diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
dimethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diisopropyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(2-pyridyl)-aminomethylphosphonate,
diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(4-pyridyl)-aminomethylphosphonate,
diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-picolyl)-aminomethylphosphonate,
diethyl α-(4-hydroxy-3-methoxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diethyl α-(3-ethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diethyl α-(3,4,5-trimethoxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diethyl α-(3,5-dimethyl-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
(+)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(4-picolyl)-aminomethylphosphonate,
(-)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(4-picolyl)-aminomethylphosphonate,
(+)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-picolyl)-aminomethylphosphonate,
(-)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-picolyl)-aminomethylphosphonate,
(+)-diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
(-)-diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
(+)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-phenylpropyl)-aminomethylphosphonate,
(-)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-phenylpropyl)-aminomethylphosphonate,
diisopropyl α-(3,5-di-methoxy-4-hydroxyphenyl)-N-[5-(2-methylpyridyl)]-aminomethylphosphonate,
diethyl α-(3-tert-butyl-4-hydroxy-5-methylphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diethyl α-(4-hydroxy-3-methoxy-5-methylphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diisopropyl α-(4-hydroxy-3-methoxy-5-methylphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
5 diethyl α-(3-n-butyl-4-hydroxy-5-methoxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diisopropyl α-(3-n-butyl-4-hydroxy-5-methoxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diethyl α-(4-hydroxy-3-methoxy-5-n-propylphenyl)-N-(3-pyridyl)-aminomethylphosphonate;
diisopropyl α-(4-hydroxy-3-methoxy-5-n-propylphenyl)-N-(3-pyridyl)-aminomethylphosphonate;
diethyl α-(3-i-butyl-4-hydroxy-5-methoxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate;
diisopropyl α-(3-i-butyl-4-hydroxy-5-methoxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-pyridyl)
aminomethylphosphonate;
Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(2-picoly)
aminomethylphosphonate;
20 diaminomethylphosphonate;
Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-picoly)
aminomethylphosphonate;
Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-methyl-N-(3-picoly)
aminomethylphosphonate;
25 Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(2-pyridylethyl)
aminomethylphosphonate; and
Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(2-picoly)
aminomethylphosphonate.

6. A use as claimed in any one of claims 1 to 4 in which the compound of formula (I) is represented by the sub-formula (Ia):

![Chemical Structure](image)

(Ia)
or a pharmaceutically acceptable salt thereof.

7. A use as claimed in claim 6 in which:
X₁ is H, C₁₋₈ alkyl or C₁₋₈ alkoxy;
X₂ is C₁₋₈ alkyl or C₁₋₈ alkoxy;
X₃ is H, C₁₋₄ alkyl, or X₃O and one of the two other substituents X₁ or X₂ may
form an alkyldiene dioxy ring having from 1 to 4 carbon atoms;
R¹, R², which may be identical or different, are H or C₁₋₆ alkyl;
B is CH₂CH₂, CH=CH, or CH₂;
n is zero or 1;
Z is H or a C₁₋₈ alkyl group;
m is 0 or an integer from 1 to 5;
X₄ is H, or C₁₋₈ alkyl, C₁₋₈ alkoxy or halo;
and the pyridyl ring is attached by the ring carbon α- or β- to the nitrogen (2- or 3-
pyridyl);
or a salt, preferably a pharmaceutically acceptable salt, thereof.

8. A use as claimed in claim 7 in which, in the compound of formula (Ia), X₁ is H,
C₁₋₄ alkyl or C₁₋₄ alkoxy.

9. A use as claimed in claim 8 in which, in the compound of formula (Ia), X₁ is
hydrogen, methyl or methoxy.

10. A use as claimed in any one of claims 7 to 9 in which, in the compound of
formula (Ia), X₂ is C₁₋₄ alkyl or C₁₋₄ alkoxy.

11. A use as claimed claim 10 in which, in the compound of formula (Ia), X₂ is
methyl or methoxy.

12. A use as claimed in claim 7 in which, in the compound of formula (Ia), X₁ and
X₂ are both alkoxy or one of X₁ and X₂ is alkyl and the other is alkoxy, or one of X₁
and X₂ is C₁₋₄ alkyl and the other of X₁ and X₂ is C₁₋₃ alkyl.

13. A use as claimed in claim 12 in which, in the compound of formula (Ia), X₁ and
X₂ are methoxy and methoxy, methoxy and methyl, n-propyl or iso-butyl, or methyl
and methyl or t-butyl, respectively.

14. A use as claimed in any one of claims 7 to 13 in which, in the compound of
formula (Ia), X₃ is hydrogen.

15. A use as claimed in any one of claims 7 to 14 in which, in the compound of
formula (Ia), (B)ₙ is a direct bond.
16. A use as claimed in any one of claims 7 to 15 in which, in the compound of
formula (Ia), R¹ and R² is each a straight or branched C(1-3)alkyl group.

17. A use as claimed in claim 16 in which, in the compound of formula (Ia), R¹ and
R² is each a C₂ or C₃ alkyl group.

18. A use as claimed in any one of claims 7 to 17 in which, in the compound of
formula (Ia), Z is hydrogen.

19. A use as claimed in any one of claims 7 to 18 in which, in the compound of
formula (Ia), X⁴ is hydrogen or methyl which is preferably on the ring carbon
adjacent to N.

20. A use as claimed in any one of claims 7 to 19 in which, in the compound of
formula (Ia), the pyridyl ring is attached by the ring carbon β- to the nitrogen (3-
pyridyl).

21. A compound of formula (Ia) as defined in any one of claims 7 to 20 and
excluding:
   Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-pyridyl)
aminomethylphosphonate;
   Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(2-picolylo)
aminomethylphosphonate;
   Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-picolylo)
aminomethylphosphonate;
   Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-methyl-N-(3-picolylo)
aminomethylphosphonate;
   Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(2-pyridylethyl)
aminomethylphosphonate; and
   Diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(2-picolylo)
aminomethylphosphonate.

22. A compound of formula (Ia) as defined in claim 21 selected from:
dimethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-pyridyl-
aminomethylphosphonate,
diisopropyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-pyridyl-
aminomethylphosphonate,
diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(2-pyridyl-
aminomethylphosphonate,
diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(4-pyridyl)-
aminomethylphosphonate,
diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-[5-(2-chloropyridyl)]-
aminomethylphosphonate.

diethyl α-(4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diethyl α-(3,4-methylenedioxyphenyl)-N-(3-pyridyl)-aminophosphonate,
diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
dimethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-
aminomethylphosphonate,
diisopropyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-
aminomethylphosphonate,
diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(2-pyridyl)-aminomethylphosphonate,
diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(4-pyridyl)-aminomethylphosphonate,
diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(2-picoly)-aminomethylphosphonate,
diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-picolyl)-aminomethylphosphonate,
diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(4-picoly)-aminomethylphosphonate,
diethyl α-(4-hydroxy-3-methoxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diethyl α-(3-ethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diethyl α-(3,4,5-trimethoxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
diethyl α-(3,5-dimethyl-4-hydroxyphenyl)-N-(3-pyridyl)-aminomethylphosphonate,
(+)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(4-picoly)-
aminomethylphosphonate,
(-)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(4-picoly)-
aminomethylphosphonate,

(+)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-picoly)-
aminomethylphosphonate,
(-)-diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(3-picoly)-
aminomethylphosphonate,
(+)-diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-
aminomethylphosphonate,
(-)-diethyl α-(3,5-dimethoxy-4-hydroxyphenyl)-N-(3-pyridyl)-
aminomethylphosphonate.

diisopropyl α-(3,5-di-methoxy-4-hydroxyphenyl)-N-[5-(2methyl-pyridyl)]-
aminomethylphosphonate,
diethyl α-(3-tert-butyl-4-hydroxy-5-methylphenyl)-N-(3-pyridyl)-
aminomethylphosphonate,
diethyl α-(4-hydroxy-3-methoxy-5-methylphenyl)-N-(3-pyridyl)-amino-
methylphosphonate,
diisopropyl α-(4-hydroxy-3-methoxy-5-methylphenyl)-N-(3-pyridyl)-amino-
methylphosphonate,

5
diethyl α-(3-n-butyl-4-hydroxy-5-methoxyphenyl)-N-(3-pyridyl)-amino-
methylphosphonate,
diisopropyl α-(3-n-butyl-4-hydroxy-5-methoxyphenyl)-N-(3-pyridyl)-amino-
methylphosphonate,
diethyl α-(4-hydroxy-3-methoxy-5-n-propylphenyl)-N-(3-pyridyl)-
aminomethylphosphonate;
diisopropyl α-(4-hydroxy-3-methoxy-5-n-propylphenyl)-N-(3-pyridyl)-
aminomethylphosphonate;
diethyl α-(3-i-butyl-4-hydroxy-5-methoxyphenyl)-N-(3-pyridyl)-
aminomethylphosphonate; and

diisopropyl α-(3-i-butyl-4-hydroxy-5-methoxyphenyl)-N-(3-pyridyl)-
aminomethylphosphonate.

23. A pharmaceutical composition comprising a compound of formula (Ia) as defined
in claim 21 and a pharmaceutically acceptable carrier or excipient.

24. A compound of formula (Ia) as defined in claim 21 for use in therapy.

25. A process for preparing a compound of formula (Ia) as defined in claim 21 which
process comprises

(a) when Z is hydrogen, treating an imine of formula (II):

\[
\begin{align*}
\text{(II)}
\end{align*}
\]

in which B, X^1, X^2, X^3 and n are as defined in claim 21;

30 with a phosphite compound of formula (III):

\[
\text{HPO(OR^1)(OR^2)}
\]

(III)
in which $R^1$ and $R^2$ are as defined in claim 21; or a trialkyl silyl derivative or metal salt thereof;
in the presence or absence of a catalyst, optionally in a solvent;

(b) for compounds of formula (Ia) in which $Z$ is not hydrogen, treating equimolar amounts of an aldehyde of formula (V):

\[
\begin{array}{c}
\text{X}^1 \\
\text{X}^2 \\
\text{X}^3 \\
\text{(B)}_n\text{C} \\
\text{X}^4
\end{array}
\]

(V)

in which $B$, $X^1$, $X^2$, $X^3$ and $n$ are as defined in claim 21;
with a secondary amine of formula (VII):

HNZA

(VII)

(c) in compounds of formula (I) in which $m$ is not zero, treating a compound of formula (VIII):

\[
\begin{array}{c}
\text{X}^1 \\
\text{X}^2 \\
\text{X}^3 \\
\text{(B)}_n\text{C} \\
\text{OR}^1 \\
\text{OR}^2 \\
\text{NH}_2
\end{array}
\]

(VIII)

in which $B$, $R^1$, $R^2$, $X^1$, $X^2$, $X^3$ and $n$ are as defined in claim 21;
an aldehyde of formula (IX):

\[
\begin{array}{c}
\text{X}^4 \\
\text{(CH}_2\text{)}_{(m-1)}\text{C} \\
\text{X}^5
\end{array}
\]

(IX)
in which $m$ is an integer form 1 to 5 and $X^4$ is as hereinbefore defined under reductive amination conditions.
26. A process for preparing an individual enantiomer of an aminophosphonate of formula (I) which process comprises treating either of the (+) or (-) enantiomer of the \( \alpha \)-substituted aminomethylphosphonate of formula (X):

\[
\begin{align*}
X^1 & \\
X^2 & \\
X^3 & \\
\text{(B)} & \\
n & \\
\text{OR}^1 & \\
\text{OR}^2 & \\
\text{NH}_2 & \\
\text{OP} &
\end{align*}
\]  

\( (X) \)

in which \( B, R^1, R^2, X^1, X^2, X^3 \) and \( n \) are as defined in claim 1; with an aldehyde of formula (XI):

\[
R^3-\text{CHO} 
\]  

\( (XI) \)

in which \( R^3 \) is as defined in claim 1; under reductive amination conditions.

27. A process as claimed in claim 26 in which the reaction is carried out in the presence of sodium cyanoborohydride in an alcoholic solvent, preferably methanol, at a pH between 3 to 6 and at a temperature between 0°C and 25°C.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/66 A61K31/675

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbol)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category *</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>EP,A,0 703 239 (HOECHST AKTIENGESELLSCHAFT) 27 March 1996 see the whole document ---</td>
<td>21-27</td>
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier document but published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referring to an oral discussion, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search:

23 September 1996

Date of mailing of the international search report:

5.10.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016

Authorized officer:

Theuns, H

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INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. [x] Claims Nos.: 1, 5–20 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

   The expression "decreasing plasma and tissue lipoprotein (a) levels" is not a proper description of a therapeutic application, because it is not immediately clear which disorders may be treated as a result of such.

3. [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (I)) (July 1992)
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