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Aplicant(s)

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Uppfinningens benämning
Title of invention

"New compounds".

Härmed intygas att bifogade handlingar är tragna kopier av beskrivning och patentkrav samt annat material till patent- och registreringsverket den dag som angett på handlingarna.

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Ex Officio

M. Ström

Expeditionsavgift Kr 25:-
New compounds

Abstract of the disclosure

The present invention relates to new compounds having antihypertensive effect, which compounds are of the formula I

![Chemical structure](image)

wherein $R^1$ is selected from the group consisting of $-\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OC}_2\text{H}_5$, and $-(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_3$ and $R^2$ is selected from the group consisting of $-\text{C}_2\text{H}_5$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}(\text{CH}_3)\text{C}_2\text{H}_5$, $-\text{CH}_2\text{CH}_2\text{OCH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_3$, and $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{OCH}_3$, $R^3$ is selected from the group consisting of chloro, bromo, methyl and methoxy, and $R^4$ is selected from the group consisting of chloro, bromo, methyl, methoxy, ethoxy,
process for the preparation of said compounds, method for lowering the blood pressure in mammals including man, and pharmaceutical preparations containing said compounds.

The present invention relates to new compounds having valuable antihypertensive properties, process for their preparation, method for lowering blood pressure in mammals including man, and pharmaceutical preparations containing said compounds.

The object of the present invention is to obtain new antihypertensive agents, which lower blood pressure in the peripheral vessels in lower doses than they lower blood pressure in the heart vessels, by selective dilation of peripheral blood vessels.

Compounds of the formula

\[
\begin{align*}
\text{H}_3\text{COOC} & \quad \text{COOCH}_3 \\
\text{H}_3\text{C} & \quad \text{CH}_3
\end{align*}
\]

wherein R is nitro or trifluoromethyl in 2 or 3-position are known to possess cerebral vasodilating effect, effect against angina pectoris or blood pressure lowering effect.

Agents which relax vascular smooth muscle may be used for treatment of arterial hypertension since such patients suffer from elevated peripheral resistance to blood flow. Compounds which interfere with vascular smooth muscle activity have been used clinically for several years. However, their usefulness has often been limited due to insufficient efficacy and/or due to adverse effects. Side effects (outside the cardiovascular system) have often been connected with properties of the agent not relevant to the smooth muscle relaxant effect. Sometimes the vasodilating agents have also exerted a negative effect on the contractility of the heart.

It appears that the development of specific smooth muscle relaxants devoid of adverse effects, can offer a therapeutic advantage in arterial hypertension and for treatment of ischaemic heart disease and of the acutely failing heart. Furthermore, such agents can also be useful in treatment of other conditions with excessive activation of smooth muscle of the visceral type.
It has now surprisingly been shown that the compounds of the formula I

wherein \( R^1 \) is selected from the group consisting of \(-\text{CH}_3\), \(-\text{CH}_2\text{CH}_2\text{OCH}_3\), \(-\text{CH}_2\text{CH}_2\text{OC}_2\text{H}_5\) and \(-\{\text{CH}_2\text{CH}_2\text{O}\}_2\text{CH}_3\) and \( R^2 \) is selected from the group consisting of \(-\text{C}_2\text{H}_5\), \(-\text{CH(CH}_3)_2\), \(-\text{C(CH}_3)_3\), \(-\text{CH(CH}_3)_2\text{C}_2\text{H}_5\), \(-\text{CH}_2\text{CH}_2\text{OCH(CH}_3)_2\), \(-\text{CH(CH}_3)_2\text{CH}_2\text{OCH}_3\), and \(-\text{C(CH}_3)_2\text{CH}_2\text{OCH}_3\).

\( R^3 \) is selected from the group consisting of chloro, bromo, methyl and methoxy, and \( R^4 \) is selected from the group consisting of chloro, bromo, methyl, methoxy, ethoxy possesses a specific muscle relaxing effect related to the peripheral vascular system whereby the compounds are devoid of adverse effects.

Specific preferred compounds of the invention are:

1) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester;

2) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-ethylester-5-(2-methoxyethylster)

3) 2,6-dimethyl-4-(2-chloro-3-bromophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester

4) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-isopropylester

5) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(1-methylpropylster)

6) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methyl-5-tert.butylester

7) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(2-methoxy-1-methylethylester)

8) 2,6-dimethyl-4-(2-bromo-3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester
9) 2,6-dimethyl-4-(2,3-dibromophenyl)-1,4-dihydropyridine-
   -3,5-dicarboxylic acid-3-methylester-5-ethylester
10) 2,6-dimethyl-4-(2-methyl-3-chlorophenyl)-1,4-dihydropyridine-
    -3,5-dicarboxylic acid-3-methylester-5-isopropylester
11) 2,6-dimethyl-4-(2-methoxy-3-chlorophenyl)-1,4-dihydropyridine-
    -3,5-dicarboxylic acid-3-methylester-5-ethylester
12) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-
    -3,5-dicarboxylic acid-3-(2-methoxyethyl)ester-5-isopropylester
13) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-
    -3,5-dicarboxylic acid-3-(2-ethoxyethyl)ester-5-ethylester
14) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-
    -3,5-dicarboxylic acid-3-[2-(methoxyethoxy)ethyl]ester-5-
    -isopropylester
15) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-
    -3,5-dicarboxylic acid-3-methylester-5-(2-isopropoxy-
    -ethyl)ester
16) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-
    -3,5-dicarboxylic acid-3-methylester-5-(2-methoxy-1,1-
    -dimethylethyl)ester.

The substances are intended to be administered orally or
parenterally for acute and chronic treatment of above mentioned
cardiovascular disorders.

The biological effects of the new compounds have been tested,
and the different tests carried out will be shown and explained
below.

The new compounds are obtained according to methods known
per se.

Thus,

a) a compound of formula IIa

\( \text{IIa} \)

wherein \( R^1, R^3 \) and \( R^4 \) have the meanings given above is reacted with
a compound of formula IIIa
wherein $R^2$ has the meaning given above to give a compound of formula I, or

a\(^2\) a compound of formula IIb

wherein $R^2$, $R^3$ and $R^4$ have the meanings given above is reacted with a compound of formula IIIb

wherein $R^1$ has the meaning given above, to the formation of a compound of formula I; or

b\(^1\) a compound of formula IV

wherein $R^3$, and $R^4$ have the meanings given above is reacted with the compounds of formulas Va and IIIa

(Va)

(IIIa)
wherein R¹ and R² have the meanings given above to the formation of a compound of formula I, or
b²) a compound of formula IV above wherein R³, and R⁴ have the meanings given above is reacted with the compounds of formulas Vb and VIb

\[ \text{(Vb)} \]

\[ \text{(VIb)} \]

wherein R¹ and R² have the meanings given above, to the formation of a compound of formula I; or
c¹) a compound of formula IIa wherein R¹, R³ and R⁴ have the meanings given above is reacted with a compound of the formula VIa

\[ \text{(VIa)} \]

wherein R² has the meaning given above in the presence of ammonia, to the formation of a compound of the formula I, or
c²) a compound of formula IIb wherein R², R³, and R⁴ have the meanings given above is reacted with a compound of formula VIb

\[ \text{(VIb)} \]

wherein R¹ has the meaning given above, in the presence of ammonia, to the formation of a compound of the formula I; or
d) a compound of formula IV above, wherein R³, and R⁴ have the meanings given above, is reacted with the compounds of the formulas Va and Vb above, wherein R¹ and R² have the meanings given above, in the presence of ammonia, to the formation of a compound of the formula I.
The invention also relates to any embodiment of the process of which one starts from any compound obtained as an intermediate in any process step and one carries out the lacking process step, or one breaks off the process at any step, or at which one forms a starting material under the reaction conditions, or at which a reaction component possibly in the form of its salt is present.

The new compounds may, depending on the choice of starting materials and process, be present as optical antipodes or racemate, or, if they contain at least two asymmetric carbon atoms, be present as an isomer mixture (racemate mixture).

The isomer mixtures (racemate mixtures) obtained may, depending on physical-chemical differences of the component, be separated into the two stereoisomeric (diastereomeric) pure racemate e.g. by means of chromatography and/or fractional crystallization.

The racemates obtained can be separated according to known methods, e.g., by means of recrystallization from an optically active solvent, by means of microorganisms, or by a reaction with optically active acids forming salts of the compound, and separating the salts thus obtained, e.g. by means of the different solubility of the diastereomeric salts, from which the antipodes may be set free by the action of a suitable agent. Suitably useable optically active acids are e.g. the L- and D-forms of tartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulfonic acid or quinic acid. Preferably the more active part of the two antipodes is isolated.

Suitably such starting materials are used for carrying out the reactions of the invention, which material leads to groups of end products preferably desired and particularly to the specifically described and preferred end products.

The starting materials are known or may, if they are novel, be obtained according to processes known per se.

In clinical use the compounds of the invention are usually administered orally, rectally or by injection in the form of a pharmaceutical preparation, which contains the active component as free base in combination with a pharmaceutically acceptable carrier.
Thus the mentioning of the new compounds of the invention is here related to the free amine base even if the compounds are generally or specifically described, provided that the context in which such expressions are used, e.g., in the examples, with this broad meaning should not correspond. The carrier may be a solid, semisolid or liquid diluent or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1 and 99% by weight of the preparation, suitably between 0.5 and 20% by weight in preparations for injection and between 2 and 50% by weight in preparations for oral administration.

In the preparation of pharmaceutical preparations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, pulverulent carrier, as e.g., with lactose, saccharose, sorbitol, mannitol, starch, such as potatoe starch, corn starch, amylopectin, cellulose derivatives or gelatine, as well as with an antifriction agent such as magnesium stearate, calcium stearate, polyethylene-glycol waxes or the like, and be pressed into tablets. If coated tablets are wanted, the above prepared core may be coated with concentrated solution of sugar, which solution may contain, e.g., gum arabicum, gelatine, talc, titandioxide or the like. Furthermore, the tablets may be coated with a laquer dissoived in an easily volatile organic solvent or mixture of solvents. To this coating a dye may be added in order to easily distinguish between tablets with different active compounds or with different amounts of the active compound present.

In the preparation of soft gelatine capsules (pearl-shaped, closed capsules), which consist of gelatine and, e.g., glycerine, or in the preparation of similar closed capsules, the active compound is mixed with a vegetable oil. Hard gelatine capsules may contain granules of the active compound in combination with a solid, pulverulent carrier as lactose, saccharose, sorbitol, mannitol, starch (as, e.g., potatoe starch, corn starch or amylopectin), cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared in the form of suppositories, which contain the active substance in a mixture with a neutral fat base, or they may be prepared in the form of gelatine-rectal capsules which contain the active substance in a mixture with a vegetable oil or paraffin oil.
Liquid preparations for oral administration may be present in the form of sirups or suspensions, e.g. solutions containing from about 0.2 % by weight of about 20 % by weight of the active substance described, glycerol and propylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent.

Solutions for parenteral administration by injection may be prepared as an aqueous solution of a watersoluble pharmaceutically acceptable salt of the active compound, preferably in a concentration from about 0.5 % by weight to about 10 % by weight. These solutions may also contain stabilizing agents and/or buffering agents and may suitably be available in different dosage unit ampoules.

The preparation of pharmaceutical tablets for peroral use is carried out in accordance with the following method:

The solid substances included are ground or sieved to a certain particle size. The binding agent is homogenized and suspended in a certain amount of solvent. The therapeutic compound and necessary auxiliary agents are mixed with continuous and constant mixing with the binding agent solution and are moistened so that the solution is uniformly divided in the mass without overmoistening any parts. The amount of solvent is usually so adapted that the mass obtains a consistency reminding of wet snow. The moistening of the pulverulent mixture with the binding agent solution causes the particles to gather together slightly to aggregates and the real granulating process is carried out in such a way that the mass is pressed through a sieve in the form of a net of stainless steel having a mesh size of about 1 mm. The mass is then placed in thin layers on a tray to be dried in a drying cabinet. This drying takes place during 10 hours and has to be standardized carefully as the damp degree of the granulate is of outmost importance for the following process and for the feature of the tablets. Drying in a fluid bed may possibly be used. In this case the mass is not put on a tray but is poured into a container having a net bottom.

After the drying step the granules are sieved so that the particle size wanted is obtained. Under certain circumstances powder has to be removed.

To the so called final mixture, disintergrating, antifriction agents and antiadhesive agents are added. After this mixture the mass shall have its right composition for the tabletting step.
The cleaned tablet punching machine is provided with a certain set of punches and dies, whereupon the suitable adjustment for the weight of the tablets and the degree of compression is tested out. The weight of the tablet is decisive for the size of the dose in each tablet and is calculated starting from the amount of therapeutic agent in the granules. The degree of compression affects the size of the tablet, its strength and its ability of disintegrate in water. Especially with regard to the two later properties the choice of compression pressure (0.5 to 5 ton) means something of a compromise. When the right adjustment is set, the preparation of tablets is started and is carried out with a rate of 20,000 to 200,000 tablets per hour. The pressing of the tablets requires different times and depends on the size of the batch.

The tablets are freed from adhering pulver in a specific apparatus and are then stored in closed packages until they are delivered.

Many tablets, especially those which are rough or bitter, are coated with a coating. This means that they are coated with a layer of sugar or some other suitable coating.

The tablets are usually packed by machines having an electronic counting device. The different types of packages consist of glass or plastic gallipots but also boxes, tubes and specific dosage adapted packages.

The daily dose of the active substance varies and is dependent on the type of administration, but as a general rule it is 100 to 1000 mg/day of active substance at peroral administration and 5 to 1000 mg/day at intravenous administration.

The following illustrates the principle and the adaptation of invention, however, without being limited thereto. Temperature is given in degree Celsius.

**Example 1** (method a¹, a²)
Preparation of 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester.

2.87 g of 2,3-dichlorobenzylidene acetyl acetic acid-methylester and 1.3 g of 3-aminocrotonic acid ethylester were dissolved in 10 mls of t.-butanol. The reaction mixture was allowed to stand at ambient temperature for 4 days, whereupon the t.-butanol was evaporated and the residue was dissolved was stirred with a small amount of iso-
propylether, whereby the compound crystallized. After recrystallization from isopropylether pure 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-
dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester
was obtained. M.p. 145°C. Yield 75 %.

Example 2 (method b\textsuperscript{1}, b\textsuperscript{2})

Preparation of 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-
dicarboxylic acid-3-ethylester-5-(2-methoxyethyler)
ester

4.4 g of 2,3-dichlorobenzaldehyde, 3.2 g of 3-aminocrotonic acid ethylester, 4.0 g acetylacetic acid-2-methoxyethylester and
25 mls of ethanol were refluxed over night. The reaction mixture
poured out onto ice-water, whereby the compound crystallized. After
filtration recrystallization was carried out from ethanol, whereby
pure 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-
dicarboxylic acid-3-ethylester-5-(2-methoxyethyler)ester was obtained.
M.p. 139°C. Yield 36 %.

Examples 3-16

The compounds of table 1 below were prepared in accordance
with Examples 1 and 2 above.

<table>
<thead>
<tr>
<th>Ex No.</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>R\textsuperscript{4}</th>
<th>Prep acc to Ex</th>
<th>Mp °C</th>
<th>Yield %</th>
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<td>-C(CH\textsubscript{3})\textsubscript{3}</td>
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<td>Br</td>
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<td>62</td>
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<td>Cl</td>
<td>Cl</td>
<td></td>
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</table>
Example 17 (method c¹, c²)
5.74 g of 2,3-dichlorobenzylideneacetylacetate acid methyl ester, 2.6 g of ethylacetocetate and 2.8 mls of conc. NH₃ were dissolved in 25 mls tert.-butanol. The reaction mixture was allowed to stand at ambient temperature for 5 days, whereupon the tert.-butanol was evaporated and the residue was dissolved in isopropylether. After cooling the compound crystallized and after recrystallization from isopropylether pure 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester was obtained. M.p. 145°C. Yield 59 %.

Example 18 (method d)
10.7 g of 2-bromo-3-chlorobenzaldehyde, 6.3 g of ethylacetocetate, 5.7 g of methylacetocetate and 5 mls of conc. NH₃ were dissolved in 25 mls of ethanol. The reaction mixture was refluxed over night, whereupon it was poured out onto ice-water. Thereby the compound crystallized and after recrystallization from ethanol pure 2,6-dimethyl-4-(2-bromo-3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester was obtained. M.p. 159°C. Yield 48 %.

Biological tests
The antihypertensive effect of the compounds was tested in conscious, unrestrained spontaneously hypertensive rats (SHR) of the Okamoto strain. The animals had been prepared by prior implantation of indwelling catheters in the abdominal aorta via the femoral artery. Mean arterial blood pressure (MABP) and heart rate were continuously monitored. After a 2 hour control period the compound under study was administered by oral intubation at 2 hour intervals, suspended in methocel solution (5 ml/kg body weight). The cumulated doses were 1, 5 and 25 μmoles/kg bodyweight. The antihypertensive response, i.e., the BP reduction to each dose, was expressed as a percentage of the initial control BP level and plotted against the dose on a logarithmic scale. The dose which would give 20 per cent BP reduction was then determined by interpolation. The results are shown in table 2.

The specificity towards smooth muscle relaxation was examined as follows: The isolated portal vein preparation of Wistar rats was mounted in an organ bath together with a paced isolated papillary heart muscle preparation of the same animal. The integrated contractile
activity of the portal vein smooth muscle and the peak force amplitude of the papillary, myocardial, preparation were recorded. The respective activities during a 30 min control period were set as 100 per cent and the ensuing activities under the influence of an agent under study were expressed as a percentage thereof. The agent was administered at 10 min intervals and the potency for vasodilatation (-log ED$_{50}$ of portal vein) and that of myocardial depression (-log ED$_{50}$ of papillary muscle) were determined by interpolation from the concentration-effect relationships determined in each experiment. A "separation" value was determined for each compound by averaging the differences of the -log ED$_{50}$ values for vasodilatation and myocardial depression, respectively, obtained in the experiments. This logarithmic separation value was transformed into numeric format and entered into Table 2.

The compounds of the invention were compared with Nifedipin [2,6-dimethyl-4-(2-nitropheryl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3,5-dimethylester].

**Table 2**

<table>
<thead>
<tr>
<th>Compound according to Ex</th>
<th>SHR ED$_{20}$ μmoles/kg bodyweight</th>
<th>Ratio heart</th>
<th>vasc</th>
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<td>98</td>
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1. A compound of the formula I

\[ \text{I} \]

\[ \begin{array}{c}
\text{R}^4 \\
\text{R}^3 \\
\text{R}^1 \text{OOC} \\
\text{H}_3 \text{C} \\
\text{H} \\
\text{N} \\
\text{CH}_3 \\
\text{COOR}^2
\end{array} \]

wherein \( \text{R}^1 \) is selected from the group consisting of \(-\text{CH}_3\), \(-\text{CH}_2\text{CH}_2\text{OCH}_3\), \(-\text{CH}_2\text{CH}_2\text{OC}_2\text{H}_5\), and \(-(\text{CH}_2\text{CH}_2\text{O})_2\text{OCH}_3\); \( \text{R}^2 \) is selected from the group consisting of \(-\text{CH}_2\text{CH}_3\), \(-\text{CH}(\text{CH}_3)_2\), \(-\text{C}(\text{CH}_3)_3\), \(-\text{CH}(\text{CH}_3)_2\text{C}_2\text{H}_5\), \(-\text{CH}_2\text{CH}_2\text{OCH}(\text{CH}_3)_2\), \(-\text{CH}(\text{CH}_3)_2\text{OCH}_3\) and \(-\text{C}(\text{CH}_3)_2\text{CH}_2\text{OCH}_3\); \( \text{R}^3 \) is selected from the group consisting of chloro, bromo, methyl and methoxy, and \( \text{R}^4 \) is selected from the group consisting of chloro, bromo, methyl, methoxy and ethoxy.

2. A compound according to clause 1, wherein

1) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester;
2) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-ethylester-5-(2-methoxyethylester)
3) 2,6-dimethyl-4-(2-chloro-3-bromophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester
4) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-isopropylester
5) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(1-methylpropylester)
6) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methyl-5-tert.butylester
7) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(2-methoxy-1-methylethylester)
8) 2,6-dimethyl-4-(2-bromo-3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester
9) 2,6-dimethyl-4-(2,3-dibromophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester
10) 2,6-dimethyl-4-(2-methyl-3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-isopropylester
11) 2,6-dimethyl-4-(2-methoxy-3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester
12) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-(2-methoxyethyl)ester-5-isopropylester
13) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-(2-ethoxyethyl)ester-5-ethylester
14) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-[2-(2-methoxyethoxy)ethyl]ester-5-isopropylester
15) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(2-isopropoxyethyl)ester or
16) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(2-methoxy-1,1-dimethylethyl)ester is selected.

3. A process for preparing compounds of the formula I

```
   H3C       COOR2
      R4      R3

R1OOC

```

wherein \( R^1 \) is selected from the group consisting of \(-\text{CH}_3\), \(-\text{CH}_2\text{CH}_2\text{OCH}_3\), \(-\text{CH}_2\text{CH}_2\text{OC}_2\text{H}_5\), and \(-(\text{CH}_2\text{CH}_2\text{O})_2\text{OCH}_3\), \( R^2 \) is selected from the group consisting of \(-\text{CH}_2\text{CH}_3\), \(-\text{CH(CH}_3)_2\), \(-\text{C(CH}_3)_3\), \(-\text{CH(CH}_3)\text{C}_2\text{H}_5\), \(-\text{CH}_2\text{CH}_2\text{OCH(CH}_3)_2\), \(-\text{CH(CH}_3)\text{CH}_2\text{OCH}_3\) and \(-\text{C(CH}_3)_2\text{CH}_2\text{OCH}_3\), \( R^3 \) is selected from the group consisting of chloro, bromo, methyl and methoxy, and \( R^4 \) is selected from the group consisting of chloro, bromo, methyl, methoxy and ethoxy, characterized in that
1) a compound of formula IIa

\[
\begin{array}{c}
\text{IIa} \\
\text{R}^3 \\
\text{R}^4 \\
\text{CH} \\
\text{H}_3\text{CCC-COR}^1
\end{array}
\]

wherein \( \text{R}^1, \text{R}^3 \) and \( \text{R}^4 \) have the meanings given above is reacted with a compound of formula IIa

\[
\begin{array}{c}
\text{IIa} \\
\text{NH}_2 \\
\text{C=CH-C} \\
\text{CH}_3 \\
\text{OR}^2
\end{array}
\]

wherein \( \text{R}^2 \) has the meaning given above to the formation of a compound of the formula I;

2) a compound of formula IIb

\[
\begin{array}{c}
\text{IIb} \\
\text{R}^3 \\
\text{R}^4 \\
\text{CH} \\
\text{H}_3\text{CCC-C-COR}^2
\end{array}
\]

wherein \( \text{R}^2, \text{R}^3 \) and \( \text{R}^4 \) have the meanings given above is reacted with a compound of formula IIb

\[
\begin{array}{c}
\text{IIb} \\
\text{NH}_2 \\
\text{C=CH-C} \\
\text{CH}_3 \\
\text{OR}^1
\end{array}
\]

wherein \( \text{R}^1 \) has the meaning given above, to the formation of a compound of the formula I;

b1) a compound of formula IV

\[
\begin{array}{c}
\text{IV} \\
\text{R}^3 \\
\text{R}^4 \\
\text{H} \\
\text{C=O}
\end{array}
\]

\[60\]
wherein $R^3$, and $R^4$ have the meanings given above is reacted with the compounds of formulas Va and IIIa

\[ \text{Va} \]

\[ \text{IIIa} \]

wherein $R^1$, and $R^2$ have the meanings given above to the formation of a compound of formula I:

b) a compound of formula IV above wherein $R^3$, and $R^4$ have the meanings given above is reacted with the compounds of formulas Vb and IIIb

\[ \text{Vb} \]

\[ \text{IIIb} \]

wherein $R^1$ and $R^2$ have the meanings given above, to the formation of a compound of formula I;

c) a compound of formula IIa above, wherein $R^1$, $R^3$, and $R^4$ have the meanings given above, is reacted with a compound of formula VIA

\[ \text{VIA} \]

wherein $R^2$ has the meaning given above in the presence of ammonia, to the formation of a compound of the formula I,

c) a compound of formula IIb above, wherein $R^2$, $R^3$, and $R^4$ have the meanings given above, is reacted with a compound of formula VIB

\[ \text{VIB} \]

\[ \text{VIA} \]
wherein R¹ has the meaning given above in the presence of ammonia to the formation of a compound of the formula I; or
d) a compound of formula IV above, wherein R³ and R⁴ have the meanings given above, is reacted with the compounds of the formulas Va and Vb above, wherein R¹, and R² have the meanings given above in the presence of ammonia to the formation of a compound of the formula I.

4. A process according to clause 3, wherein 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester is prepared by reacting 2,3-dichlorobenzaldehyde, 3-aminocrotonic acid ethylester and acetylacetic acid methylester.

5. A process according to clause 3, wherein 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-ethylester-5-(2-methoxyethyl)ester is prepared from 2,3-dichlorobenzaldehyde, 3-aminocrotonic acid ethylester and acetylacetic acid-(2-methoxyethyl)ester.

6. A process according to clause 3, wherein 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-isopropylester is prepared from 2,3-dichlorobenzaldehyde, 3-aminocrotonic acid isopropylester and acetylacetic acid methylester.

7. A process according to clause 3, wherein 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(2-methoxy-1-methylethyl)ester is prepared from 2,3-dichlorobenzaldehyde, 3-aminocrotonic acid-(2-methoxy-1-methyl-ethyl)ester, and acetylacetic acid methylester.

8. A method for treating arterial hypertension by relaxing vascular smooth muscle in mammals, including man, by administering a therapeutic active amount of a compound of formula I
wherein $R^1$ is selected from the group consisting of $-\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OC}_2\text{H}_5$, and $-(\text{CH}_2\text{CH}_2\text{O})_2\text{OCH}_3$, $R^2$ is selected from the group consisting of $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}(\text{CH}_3)\text{C}_2\text{H}_5$, $-\text{CH}_2\text{CH}_2\text{OCH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_3$ and $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{OCH}_3$, $R^3$ is selected from the group consisting of chloro, bromo, methyl and methoxy, and $R^4$ is selected from the group consisting of chloro, bromo, methyl, methoxy and ethoxy.

9. A method according to clause 8, wherein 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester is administered.

10. A method according to clause 8, wherein 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-ethyl ester-5-(2-methoxyethyl)ester is administered.

11. A method according to clause 8, wherein 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methyl ester-5-isopropylester is administered.

12. A method according to clause 8, wherein 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methyl ester-5-(2-methoxy-1-methyl ethylester is administered.

13. Pharmaceutical preparation, which comprises as an active ingredient a therapeutically effective dose of at least one antihypertensive compound having vascular smooth muscle relaxing properties which compound has the formula I

\[
\begin{align*}
\text{R}^1 & \text{OOC} \\
\text{H}_3 \text{C} & \\
\text{N} & \\
\text{CH}_3
\end{align*}
\]

wherein $R^1$ is selected from the group consisting of $-\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OC}_2\text{H}_5$, and $-(\text{CH}_2\text{CH}_2\text{O})_2\text{OCH}_3$, $R^2$ is selected from the group consisting of $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}(\text{CH}_3)\text{C}_2\text{H}_5$, $-\text{CH}_2\text{CH}_2\text{OCH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_3$ and $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{OCH}_3$, $R^3$ is selected from the group consisting of chloro, bromo, methyl and methoxy, and $R^4$ is selected from the group consisting of chloro, bromo, methyl, methoxy and ethoxy in association with a pharmaceutically acceptable carrier.
14. A pharmaceutical preparation according to clause 13, wherein the active ingredient is a therapeutically effective dose of at least one of said compounds in racemic form.

15. A pharmaceutical preparation according to clause 13, wherein the active ingredient is a therapeutically effective dose of at least one of said compounds as the optically active, dextro-rotatory isomer.

16. A pharmaceutical preparation according to clause 13, wherein the active ingredient is a therapeutically effective dose of at least one of said compounds as the optically active, levo-rotatory isomer.

17. A pharmaceutical preparation according to clause 13, wherein the substituted 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid-diester compound comprises 0.1 to 99 % by weight of the preparation.

18. A pharmaceutical preparation according to clause 13 in a form suitable for administration by injection wherein the substituted 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid-diester compound comprises about 0.5 to about 20 % by weight of the preparation.

19. A pharmaceutical preparation according to clause 18, for parenteral application which comprises an aqueous solution of a water soluble salt of said substituted 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid-diester compound in an amount of about 0.5-10 % by weight of the preparation.

20. A pharmaceutical preparation according to clause 12 in a form suitable for oral administration wherein the substituted 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid-diester compound comprises about 0.2 % to about 50 % by weight of the preparation.

21. A pharmaceutical preparation according to clause 13, wherein the active ingredient is 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester.

22. A pharmaceutical preparation according to clause 13, wherein the active ingredient is 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-ethylester-5-(2-methoxyethylester).
23. A pharmaceutical preparation according to clause 13, wherein the active ingredient is 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-isopropyl-ester.

24. A pharmaceutical preparation according to clause 13, wherein the active ingredient is 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(2-methoxy-1-methylethyl)ester.

25. Compounds according to clauses 1 to 2 and substantially as described.

26. A process for preparing new compounds according to clauses 3 to 7 and substantially as described.

27. A method of treating arterial hypertension by relaxing vascular smooth muscle according to clauses 8 to 12 and substantially as described.

28. Pharmaceutical preparations according to clauses 13 to 24 and substantially as described.
1. A compound of the formula I

$$\text{R}^4$$

$$\text{R}^3$$

$$\text{R}^1\text{OOC}$$

$$\text{COOR}^2$$

$$\text{H}_3\text{C}$$

$$\text{N}$$

$$\text{CH}_3$$

wherein \( \text{R}^1 \) is selected from the group consisting of -CH\(_3\), -CH\(_2\)CH\(_2\)OCH\(_3\), -CH\(_2\)CH\(_2\)OC\(_2\)H\(_5\), and -(CH\(_2\)CH\(_2\))\(_2\)OCH\(_3\), \( \text{R}^2 \) is selected from the group consisting of -CH\(_2\)CH\(_3\), -CH(CH\(_3\))\(_2\), -C(CH\(_3\))\(_3\), -CH(CH\(_3\))C\(_2\)H\(_5\), -CH\(_2\)CH\(_2\)OCH(CH\(_3\))\(_2\), -CH(CH\(_3\))CH\(_2\)OCH\(_3\), and -C(CH\(_3\))\(_2\)CH\(_2\)OCH\(_3\), \( \text{R}^3 \) is selected from the group consisting of chloro, bromo, methyl and methoxy, and \( \text{R}^4 \) is selected from the group consisting of chloro, bromo, methyl, methoxy and ethoxy.

2. A compound according to claim 1, wherein

1) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester;
2) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-ethylester-5-(2-methoxyethylester)
3) 2,6-dimethyl-4-(2-chloro-3-bromophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester
4) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-isopropylester
5) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(1-methylpropylester)
6) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methyl-5-tert.butylester
7) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(2-methoxy-1-methylethylester)
8) 2,6-dimethyl-4-(2-bromo-3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester
9) 2,6-dimethyl-4-(2,3-dibromophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester
10) 2,6-dimethyl-4-(2-methyl-3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-isopropylester
11) 2,6-dimethyl-4-(2-methoxy-3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester
12) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-(2-methoxyethyl)ester-5-isopropylester
13) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-(2-ethoxyethyl)ester-5-ethylester
14) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-[2-(2-methoxyethoxy)ethyl]ester-5-isopropylester
15) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(2-isopropyloxyethyl)ester or
16) 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(2-methoxy-1,1-dimethylethyl)ester is selected.

3. A process for preparing compounds of the formula I

\[
\text{(I)}
\]

wherein \( R^1 \) is selected from the group consisting of \(-\text{CH}_3, -\text{CH}_2\text{OCH}_3, -\text{CH}_2\text{CH}_2\text{OC}_2\text{H}_5, \) and \(-\text{(CH}_2\text{CH}_2\text{O})_2\text{OCH}_3\), \( R^2 \) is selected from the group consisting of \(-\text{CH}_2\text{CH}_3, -\text{CH(CH}_3)_2, -\text{C(CH}_3)_3, -\text{CH(CH}_3\text{)}_2\text{C}_2\text{H}_5, -\text{CH}_2\text{CH}_2\text{OCH(CH}_3)_2, -\text{CH(CH}_3\text{)}_2\text{CH}_2\text{OCH}_3 \) and \(-\text{C(CH}_3\text{)}_2\text{CH}_2\text{OCH}_3\), \( R^3 \) is selected from the group consisting of chloro, bromo, methyl and methoxy, and \( R^4 \) is selected from the group consisting of chloro, bromo, methyl, methoxy and ethoxy, characterized in that
1) a compound of formula IIa

\[
\begin{align*}
\text{CH} & \text{NH}_2 \\
\text{H}_3\text{C} & \text{CH} \quad \text{C} \quad \text{OR}_2 \\
\text{R}^3 & \\
\end{align*}
\]

wherein \( R^1, R^3 \) and \( R^4 \) have the meanings given above is reacted with a compound of formula IIIa

\[
\begin{align*}
\text{NH}_2 & \\
\text{C} & \text{=CH} - \\
\text{CH}_3 & \\
\end{align*}
\]

wherein \( R^2 \) has the meaning given above to the formation of a compound of the formula I;

2) a compound of formula IIb

\[
\begin{align*}
\text{CH} & \\
\text{H}_3\text{C} & \text{C} \quad \text{COR}_2 \\
\text{R}^3 & \\
\text{R}^4 & \\
\end{align*}
\]

wherein \( R^2, R^3 \) and \( R^4 \) have the meanings given above is reacted with a compound of formula IIIb

\[
\begin{align*}
\text{NH}_2 & \\
\text{C} & \text{=CH} - \\
\text{CH}_3 & \\
\end{align*}
\]

wherein \( R^1 \) has the meaning given above, to the formation of a compound of the formula I;

3) a compound of formula IV

\[
\begin{align*}
\text{R}^4 & \\
\text{R}^3 & \\
\end{align*}
\]
wherein $R^3$, and $R^4$ have the meanings given above is reacted with the compounds of formulas Va and IIIa

\[
\begin{align*}
&\text{Va} \\
&\begin{array}{c}
\text{OR}^1 \\
\text{CH}_3 \\
\text{OR}^2 \\
\text{NH}_2 \\
\text{C=CH-C} \\
\text{OR}^1 \\
\text{CH}_3 \\
\text{OR}^2 \\
\text{NH}_2 \\
\text{C=CH-C} \\
\text{OR}^1 \\
\text{CH}_3 \\
\text{OR}^2 \\
\text{NH}_2 \\
\text{C=CH-C} \\
\text{OR}^1 \\
\text{CH}_3 \\
\end{array}
\end{align*}
\]

(wherein $R^1$, and $R^2$ have the meanings given above to the formation of a compound of formula I)

b) a compound of formula IV above wherein $R^3$, and $R^4$ have the meanings given above is reacted with the compounds of formulas Vb and IIIb

wherein $R^1$ and $R^2$ have the meanings given above, to the formation of a compound of formula I;

c) a compound of formula IIa above, wherein $R^1$, $R^3$, and $R^4$ have the meanings given above, is reacted with a compound of formula VIa

wherein $R^2$ has the meaning given above in the presence of ammonia, to the formation of a compound of the formula I,

c) a compound of formula IIb above, wherein $R^2$, $R^3$, and $R^4$ have the meanings given above, is reacted with a compound of formula VIb
wherein $R^1$ has the meaning given above in the presence of ammonia to the formation of a compound of the formula I; or

d) a compound of formula IV above, wherein $R^3$ and $R^4$ have the meanings given above, is reacted with the compounds of the formulas Va and Vb above, wherein $R^1$, and $R^2$ have the meanings given above in the presence of ammonia to the formation of a compound of the formula I.

4. A method for treating arterial hypertension by relaxing vascular smooth muscle in mammals, including man, by administering a therapeutic active amount of a compound of formula I

\[
\begin{align*}
\text{R}^1 & \text{OOC} \\
\text{H}_3 & \text{C} \\
\text{H} & \text{N} \\
\text{CH}_3 & \\
\text{COOR}^2
\end{align*}
\]

wherein $R^1$ is selected from the group consisting of $-\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OC}_2\text{H}_5$, and $-(\text{CH}_2\text{CH}_2\text{O})_2\text{OCH}_3$, $R^2$ is selected from the group consisting of $-\text{CH}_2\text{CH}_3$, $-\text{CH}($CH$_3)_2$, $-\text{C}($CH$_3)_3$, $-\text{CH}($CH$_3)$C$_2$H$_5$, $-\text{CH}_2\text{CH}_2\text{OCH}($CH$_3)_2$, $-\text{CH}($CH$_3)$CH$_2\text{OCH}_3$ and $-\text{C}($CH$_3)_2\text{CH}_2\text{OCH}_3$, $R^3$ is selected from the group consisting of chloro, bromo, methyl and methoxy, and $R^4$ is selected from the group consisting of chloro, bromo, methyl, methoxy and ethoxy.

5. Pharmaceutical preparation, which comprises as an active ingredient a therapeutically effective dose of at least one antihypertensive compound having vascular smooth muscle relaxing properties which compound has the formula I

\[
\begin{align*}
\text{R}^1 & \text{OOC} \\
\text{H}_3 & \text{C} \\
\text{H} & \text{N} \\
\text{CH}_3 & \\
\text{COOR}^2
\end{align*}
\]
wherein $R^1$ is selected from the group consisting of -CH$_3$, -CH$_2$CH$_2$OCH$_3$, -CH$_2$CH$_2$OC$_2$H$_5$, and -(CH$_2$CH$_2$O)$_2$OCH$_3$, $R^2$ is selected from the group consisting of -CH$_2$CH$_3$, -CH(CH$_3$)$_2$, -C(CH$_3$)$_3$, -CH(CH$_3$)C$_2$H$_5$, -CH$_2$CH$_2$OCH(CH$_3$)$_2$, -CH(CH$_3$)CH$_2$OCH$_3$ and -C(CH$_3$)$_2$-CH$_2$OCH$_3$, $R^3$ is selected from the group consisting of chloro, bromo, methyl and methoxy, and $R^4$ is selected from the group consisting of chloro, bromo, methyl, methoxy and ethoxy in association with a pharmaceutically acceptable carrier.

6. A pharmaceutical preparation according to claim 5, wherein the substituted 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid-diester compound comprises 0.1 to 99 % by weight of the preparation.

7. Compounds according to claims 1 to 2 and substantially as described.

8. A process for preparing new compounds according to claim 3 and substantially as described.

9. A method of treating arterial hypertension by relaxing vascular smooth muscle according to claim 4 and substantially as described.

10. Pharmaceutical preparations according to claims 5 to 6 and substantially as described.