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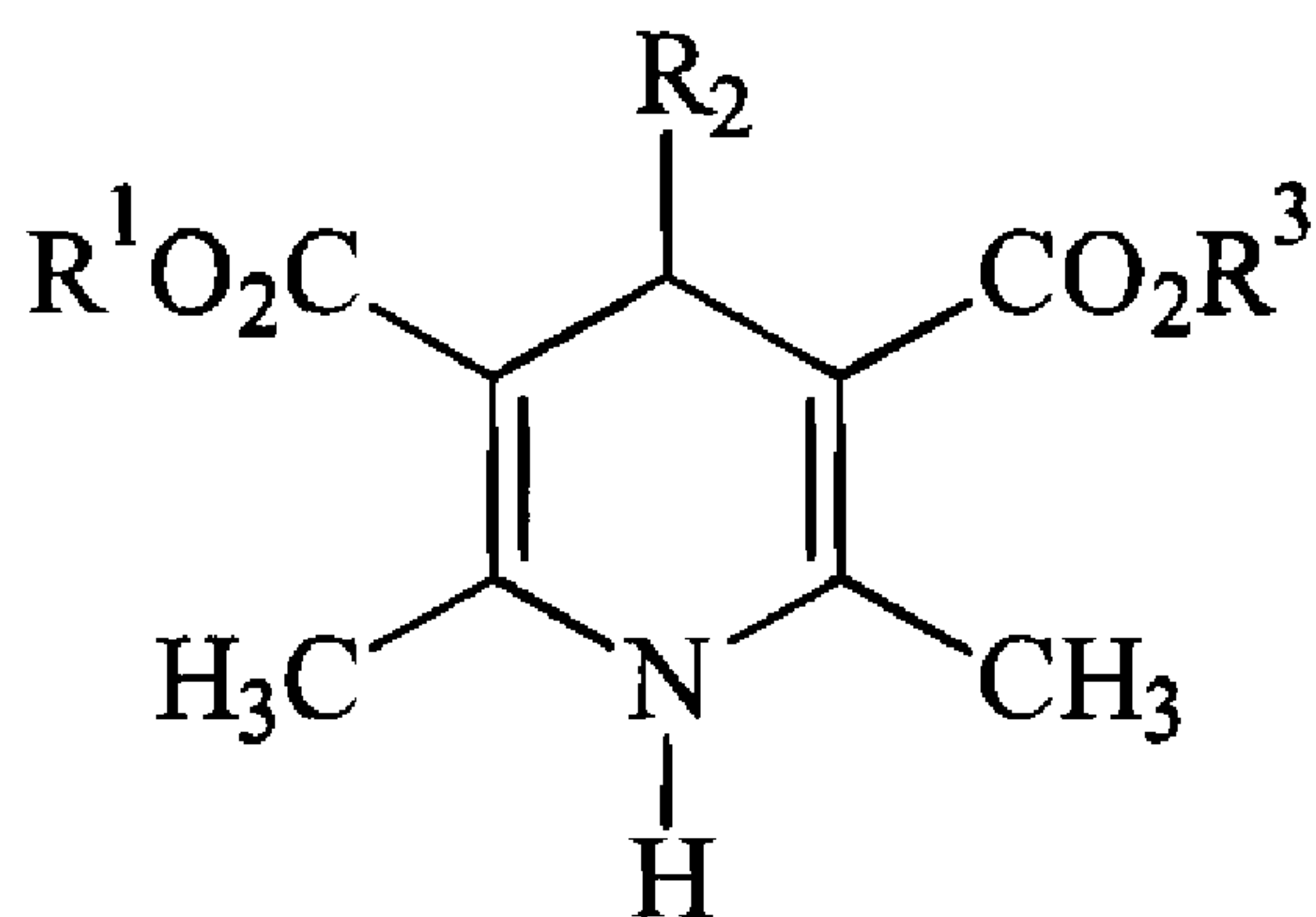
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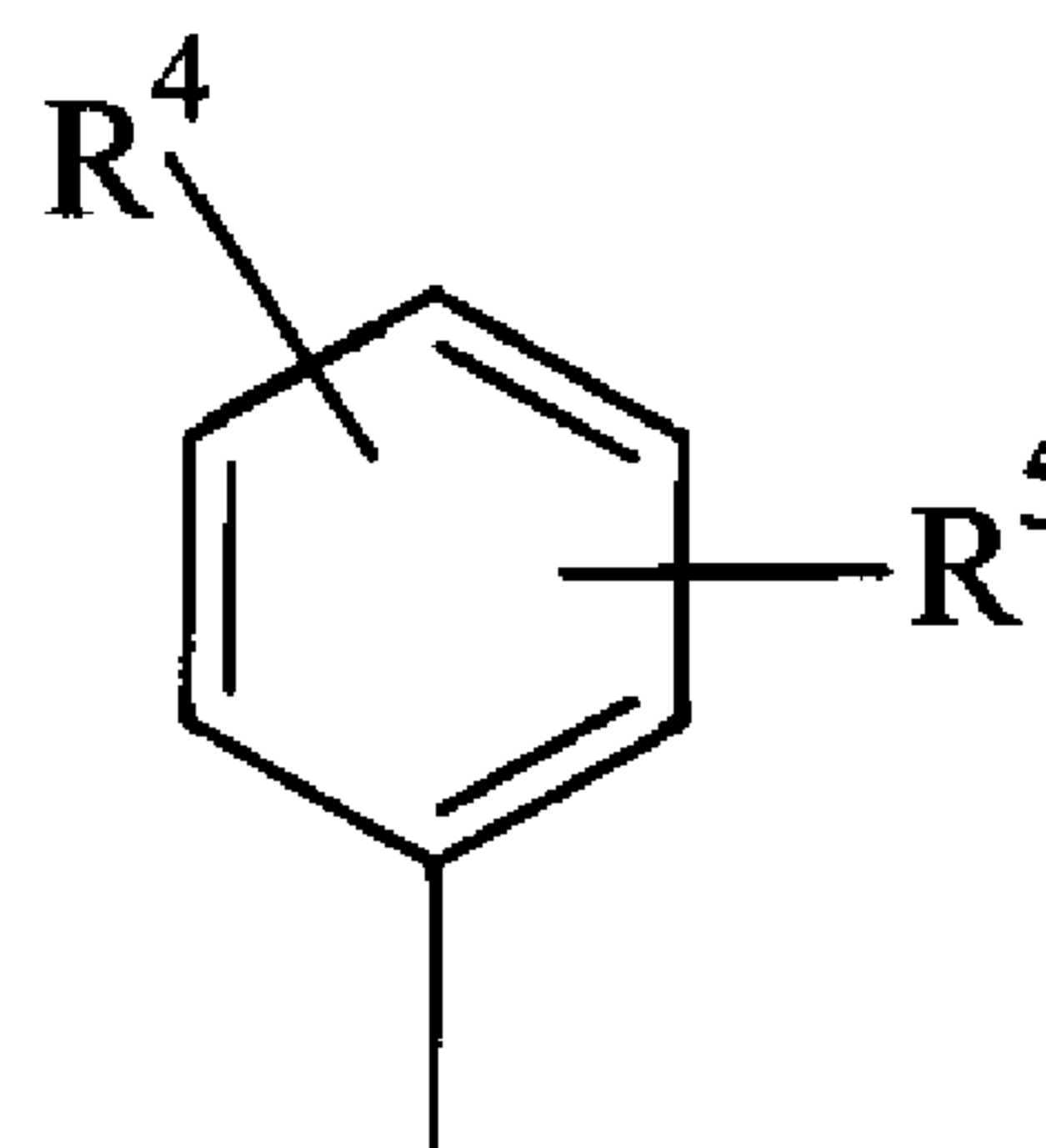
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(54) Titre : DERIVES DE SUBSTITUTION PHENYLIQUES DE 1,4-DIHYDROPYRIDINES

(54) Title: PHENYL-SUBSTITUTED 1,4-DIHYDROPYRIDINES



(I)



(II)

(57) Abrégé/Abstract:

The invention provides compositions, uses and commercial packages for the treatment of a dementia or depression. The compounds of the invention have the general formula: (see formula I) wherein: R¹ and R³ are identical or different and represent: (i) straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by straight-chain or branched alkoxy having up to 6 carbon atoms or hydroxyl, or (ii) cycloalkyl having 3 to 7 carbon atoms; and R² represents the radical: (see formula II) wherein: R⁴ and R⁵ are identical or different and represent a halogen atom, cyano, ethinyl, trifluoromethoxy, methyl, methylthio, trifluoromethyl, straight-chain or branched alkoxy having up to 4 carbon atoms or a hydrogen atom, with the proviso that R⁴ and R⁵ are not a hydrogen atom simultaneously; or a physiologically acceptable salt thereof.

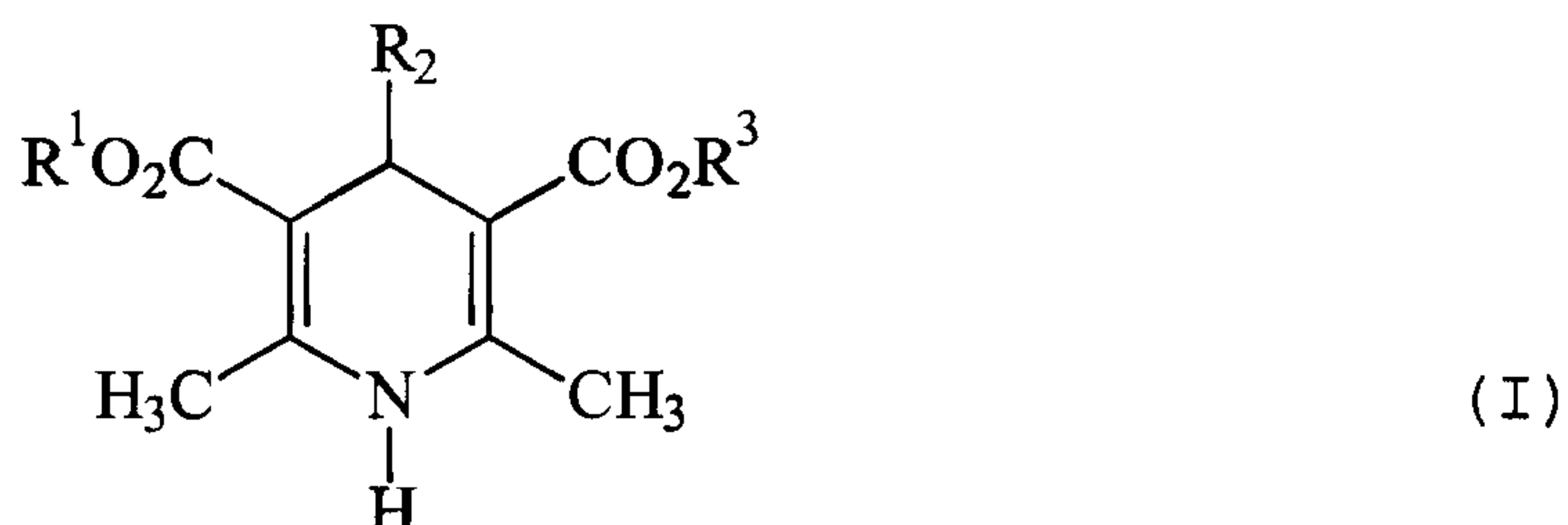


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Phenyl-substituted 1,4-dihydropyridines

Abstract

The invention provides compositions, uses and commercial packages for the treatment of a dementia or depression. The compounds of the invention have the general formula:



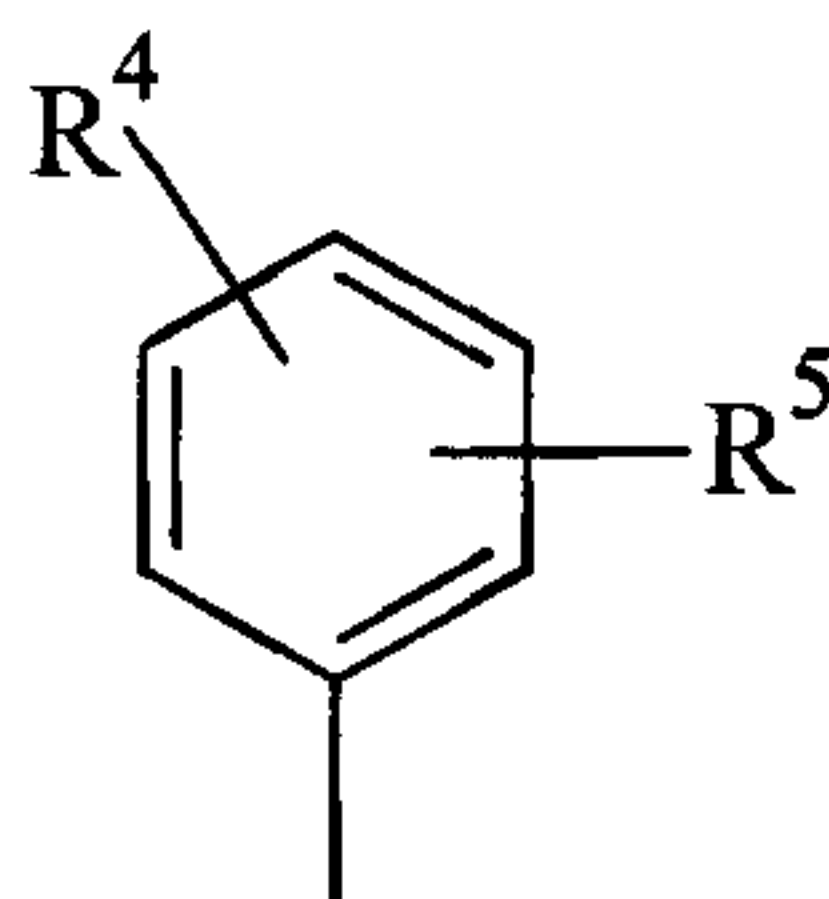
wherein:

10 R^1 and R^3 are identical or different and represent:

(i) straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by straight-chain or branched alkoxy having up to 6 carbon atoms or hydroxyl, or

15 (ii) cycloalkyl having 3 to 7 carbon atoms; and

R^2 represents the radical:



wherein:

20 R^4 and R^5 are identical or different and represent a halogen atom, cyano, ethynyl, trifluoromethoxy, methyl, methylthio, trifluoromethyl, straight-chain or branched alkoxy having up to 4 carbon atoms or a hydrogen atom, with the proviso that R^4 and R^5 are not a hydrogen atom

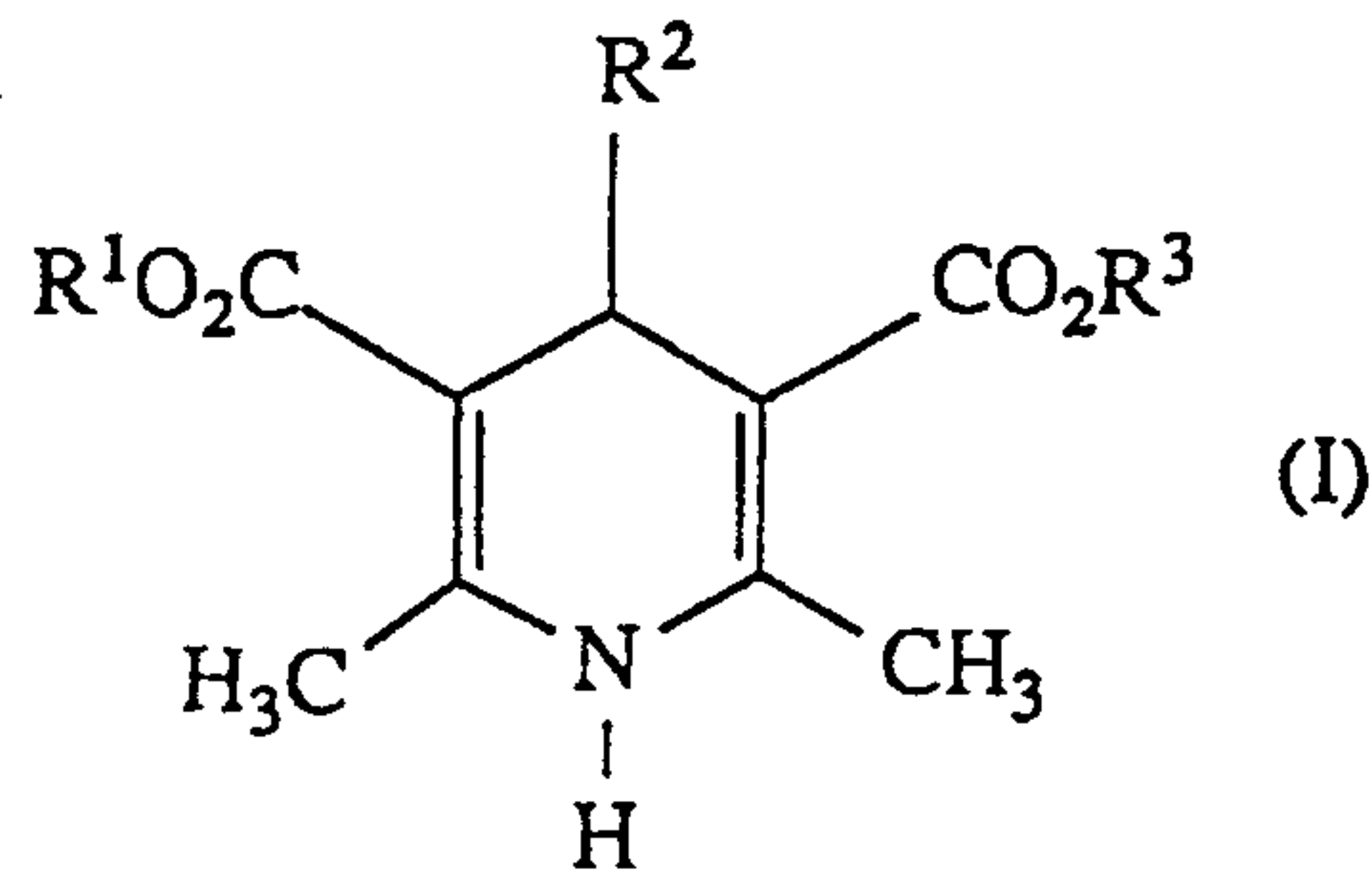
25 simultaneously; or

a physiologically acceptable salt thereof.

The invention relates to novel phenyl-substituted 1,4-dihydropyridines, processes for their preparation and their use in medicaments, in particular as cerebrally active agents.

5 It has been disclosed that some dihydropyridines, such as e.g. nimodipine, have cerebral activity [cf. German Offenlegungsschrift 28 15 578]. Dihydropyridines having circulatory activity have also been disclosed which in
 10 the 4-position carry a phenyl ring which is substituted by halogen, CN or CF₃ [cf. German Offenlegungsschrift 1 963 188, German Offenlegungsschrift 2 117 572, German Offenlegungsschrift 2 117 573 and EP 007 293).

The present invention relates to selected new 4-phenyl-substituted 1,4-dihydropyridines of the general formula
 15 (I)



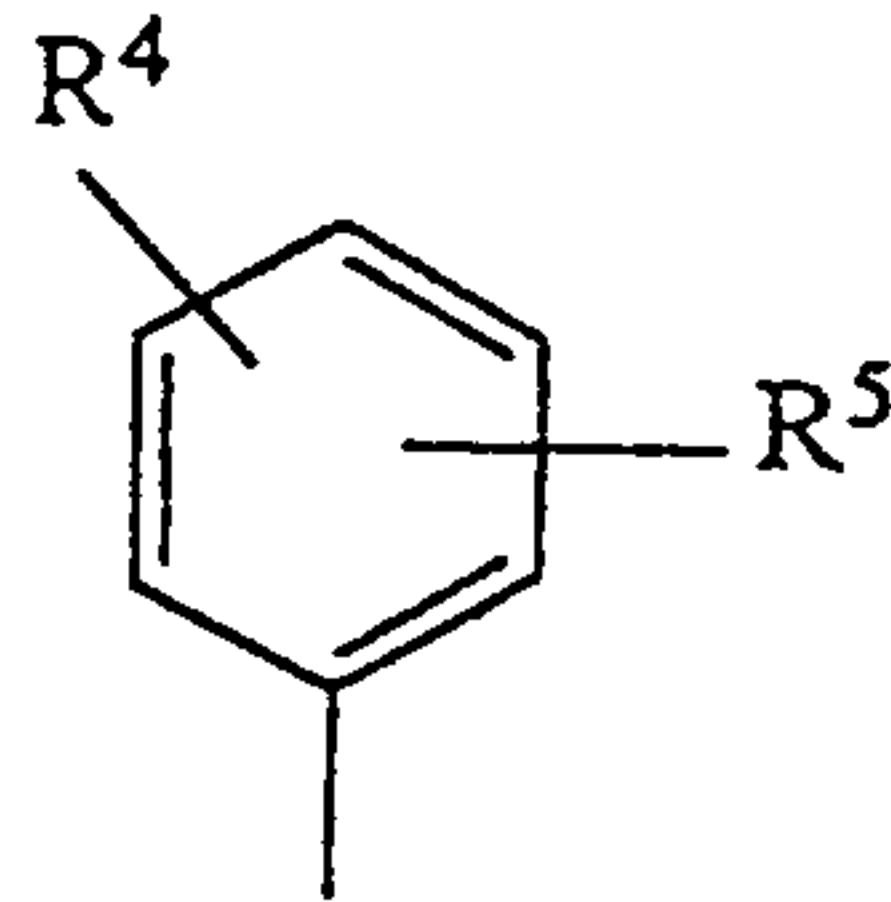
in which

R¹ and R³ are identical or different and represent

straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by straight-chain or branched alkoxy having up to 6 carbon atoms or hydroxyl, or

5 represent cycloalkyl having 3 to 7 carbon atoms,

and R² represents the radical



in which

R⁴ and R⁵ are identical or different and represent halo-
gen, cyano, ethinyl, trifluoromethoxy, methyl,
10 methylthio, trifluoromethyl, straight-chain or
branched alkoxy having up to 4 carbon atoms or
hydrogen, with the proviso that R⁴ and R⁵ are not
hydrogen simultaneously,

15 and their salts, in particular the new compounds of
exemplary embodiments 1-124 coming under the formula (I).

Physiologically acceptable salts are salts of the com-
pounds according to the invention with inorganic or
organic acids. Preferred salts are those with inorganic

acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonic acids such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, lactic acid, benzoic acid, or methanesulphonic acid, ethanesulphonic acid, phenylsulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid.

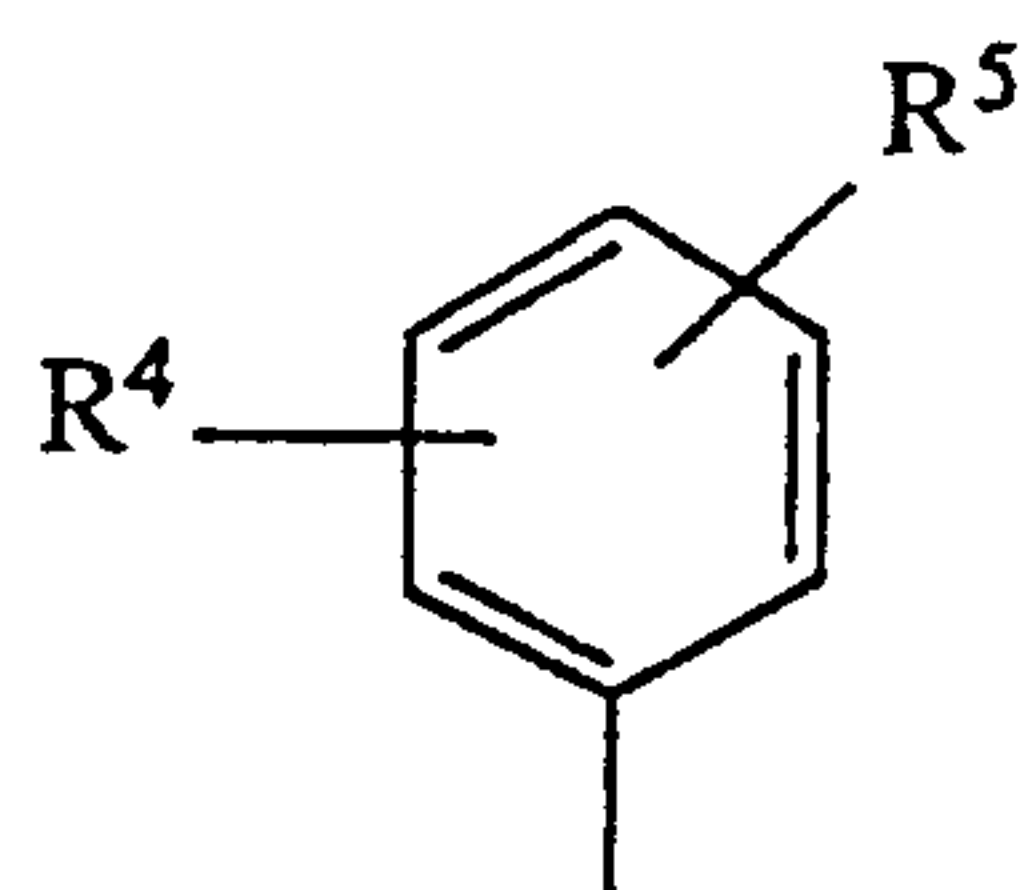
The compounds according to the invention exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the antipodes and to the racemic forms as well as the diastereomer mixtures. Like the diastereomers, the racemic forms can also be separated in a known manner into the stereoisomerically uniform constituents.

Preferred compounds are those of the general formula (I)

in which

R^1 and R^3 are identical or different and represent straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by straight-chain or branched alkoxy having up to 5 carbon atoms or hydroxyl, or represent cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl,

and R^2 represents the radical



in which

R^4 and R^5 are identical or different and represent fluorine, bromine, chlorine, cyano, ethinyl, trifluoromethoxy, methyl, methylthio, trifluoromethyl or straight-chain or branched alkoxy having up to 3 carbon atoms, or

R^4 or R^5 represents hydrogen

and their salts.

Particularly to be emphasized are new compounds of the general formula I, in which R^3 represents the radical $-(CH_2)_n-OR^6$, in which n represents a number from 2 to 4 and R^6 represents hydrogen or alkyl having 1 to 4 C atoms, in particular compounds of the formula I in which R^3 represents the radical $-CH_2-CH_2-OCH_3$, and R^1 is identical to or different from R^3 and represents straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by hydroxyl or alkoxy having 1 to 4 C atoms, or represents cyclopropyl, cyclopentyl,

cyclohexyl or cycloheptyl.

Of particular interest are compounds of the general formula I in which R² represents a cyanophenyl radical which as a second phenyl substituent carries fluorine, chlorine or CF₃. Of particular interest are also those compounds of the general formula I which in the 2- and 3-position of the phenyl radical R² are substituted by substituents from the group consisting of chlorine, fluorine, cyano and CF₃, the 2,3-dichlorophenyl radical being excluded.

Very particularly preferred compounds of the general formula (I) are the following:

- (±) isopropyl 2-methoxyethyl 4-(2-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (+) isopropyl 2-methoxyethyl 4-(2-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (-) isopropyl 2-methoxyethyl 4-(2-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (±) isopropyl 2-methoxyethyl 4-(2,3-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (+) isopropyl 2-methoxyethyl 4-(2,3-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (-) isopropyl 2-methoxyethyl 4-(2,3-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (±) isopropyl 2-methoxyethyl 4-(2,5-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (+) isopropyl 2-methoxyethyl 4-(2,5-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate

- (-) isopropyl 2-methoxyethyl 4-(2,5-difluorophenyl)-
1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (±) isopropyl 2-methoxyethyl 4-(2,6-difluorophenyl)-
1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 5 (+) isopropyl 2-methoxyethyl 4-(2,6-difluorophenyl)-
1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (-) isopropyl 2-methoxyethyl 4-(2,6-difluorophenyl)-
1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (±) isopropyl 2-methoxyethyl 4-(2,5-dichlorophenyl)-
10 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (+) isopropyl 2-methoxyethyl 4-(2,5-dichlorophenyl)-
1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (-) isopropyl 2-methoxyethyl 4-(2,5-dichlorophenyl)-
1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 15 (±) isopropyl 2-methoxyethyl 4-(2-chloro-6-fluoro-
phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxy-
late
- (+) isopropyl 2-methoxyethyl 4-(2-chloro-6-fluoro-
phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxy-
20 late
- (-) isopropyl 2-methoxyethyl 4-(2-chloro-6-fluoro-
phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxy-
late
- (±) isopropyl 2-methoxyethyl 4-(2-fluoro-3-trifluoro-
25 methylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-
dicarboxylate
- (+) isopropyl 2-methoxyethyl 4-(2-fluoro-3-trifluoro-
methylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-
dicarboxylate

- (-) isopropyl 2-methoxyethyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 5 (+) isopropyl 2-methoxyethyl 4-(3-chloro-2-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (+) isopropyl 2-methoxyethyl 4-(3-chloro-2-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 10 (-) isopropyl 2-methoxyethyl 4-(3-chloro-2-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (±) isopropyl 2-methoxyethyl 4-(2-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 15 (+) isopropyl 2-methoxyethyl 4-(2-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (-) isopropyl 2-methoxyethyl 4-(2-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (±) tert-butyl 2-methoxyethyl 4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 20 (+) tert-butyl 2-methoxyethyl 4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (-) tert-butyl 2-methoxyethyl 4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 25 (±) cycloheptyl 2-methoxyethyl 4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (+) cycloheptyl 2-methoxyethyl 4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (-) cycloheptyl 2-methoxyethyl 4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 30

- (±) cyclopentyl 2-methoxyethyl 4-(2-chloro-3-cyano-phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 5 (+) cyclopentyl 2-methoxyethyl 4-(2-chloro-3-cyano-phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (-) cyclopentyl 2-methoxyethyl 4-(2-chloro-3-cyano-phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 10 (±) cyclopentyl 2-methoxyethyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (+) cyclopentyl 2-methoxyethyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 15 (-) cyclopentyl 2-methoxyethyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (±) 2-methoxyethyl methyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 20 (+) 2-methoxyethyl methyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 25 (-) 2-methoxyethyl methyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- (±) cyclopentyl 2-methoxyethyl 4-(2-cyano-3-chloro-phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
- 30

(+) cyclopentyl 2-methoxyethyl 4-(2-cyano-3-chloro-phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate

5 (-) cyclopentyl 2-methoxyethyl 4-(2-cyano-3-chloro-phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

The invention also relates to processes for the preparation of the compounds of the general formula (I) according to the invention, characterized in that

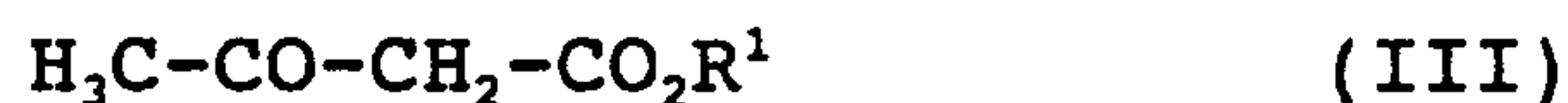
10 [A] aldehydes of the general formula (II)



in which

R^2 has the meaning indicated,

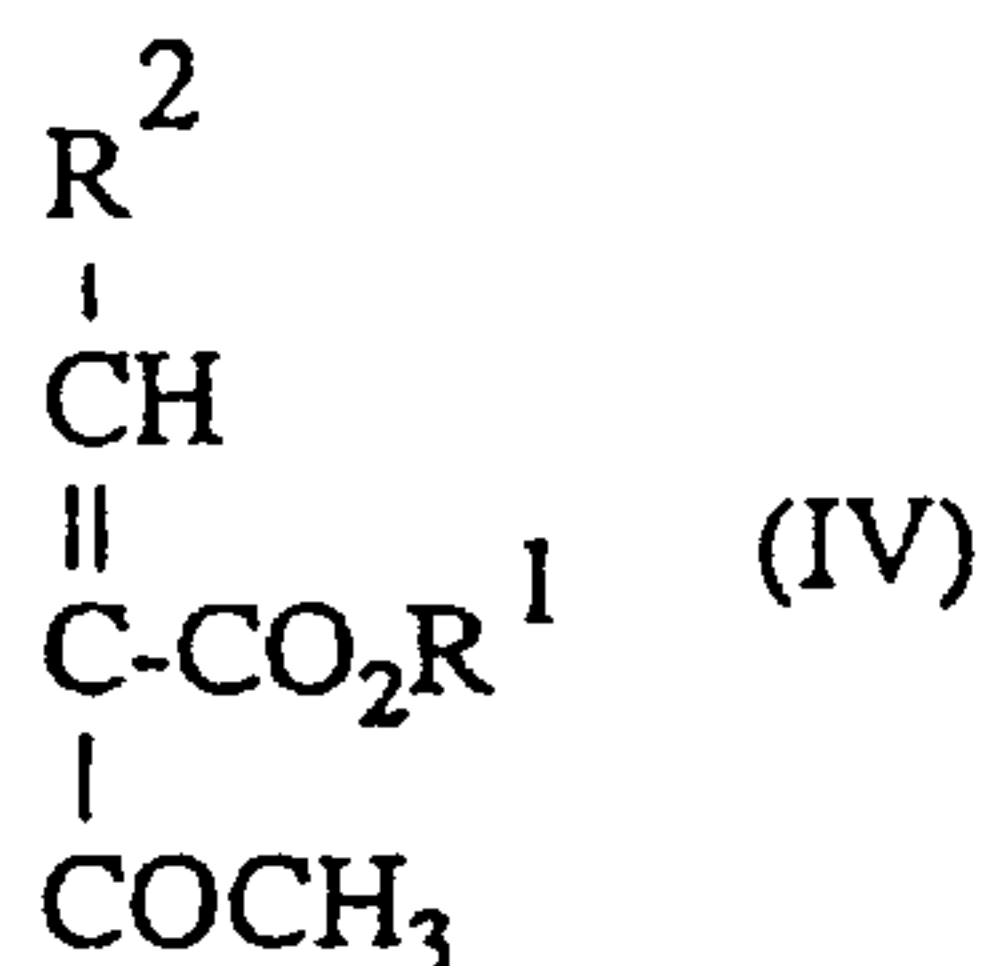
15 are reacted first with acetoacetic esters of the general formula (III)



in which

R^1 has the meaning indicated,

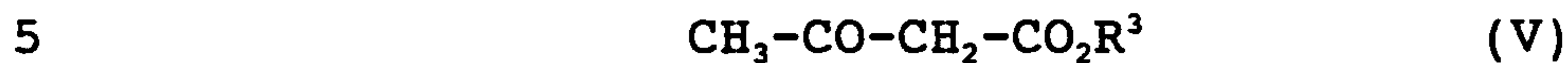
20 if appropriate with isolation of the corresponding ylidene compounds of the general formula (IV)



in which

R^1 and R^2 have the meaning indicated,

and these are then reacted either with compounds of the general formula (V)

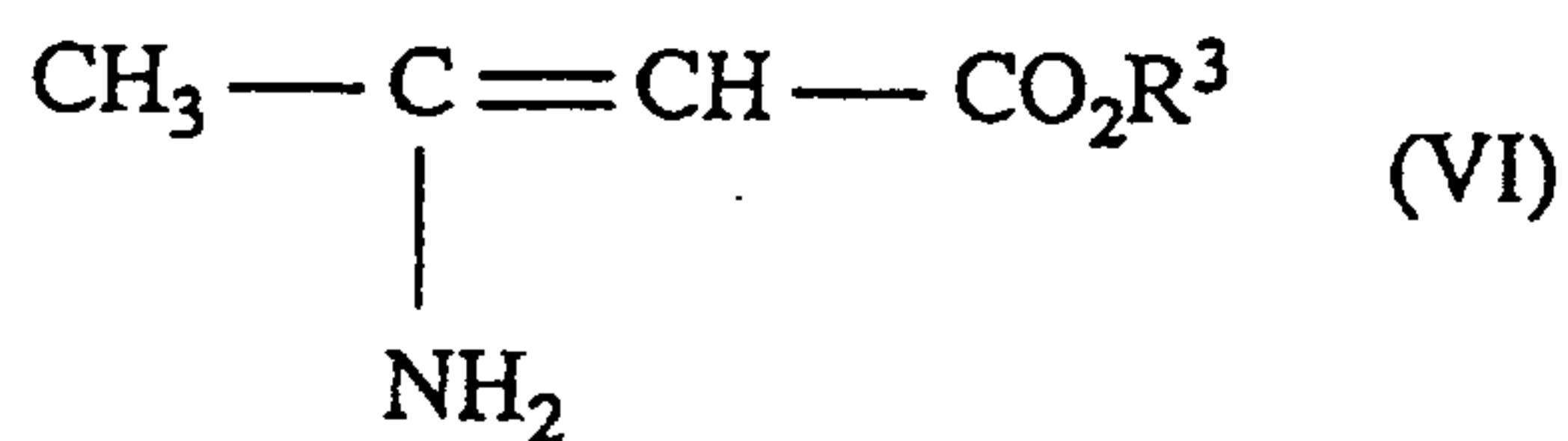


in which

R^3 has the meaning indicated,

in inert solvents, in the presence of ammonia or ammonium salts,

10 or directly with enamino derivatives of the general formula (VI)

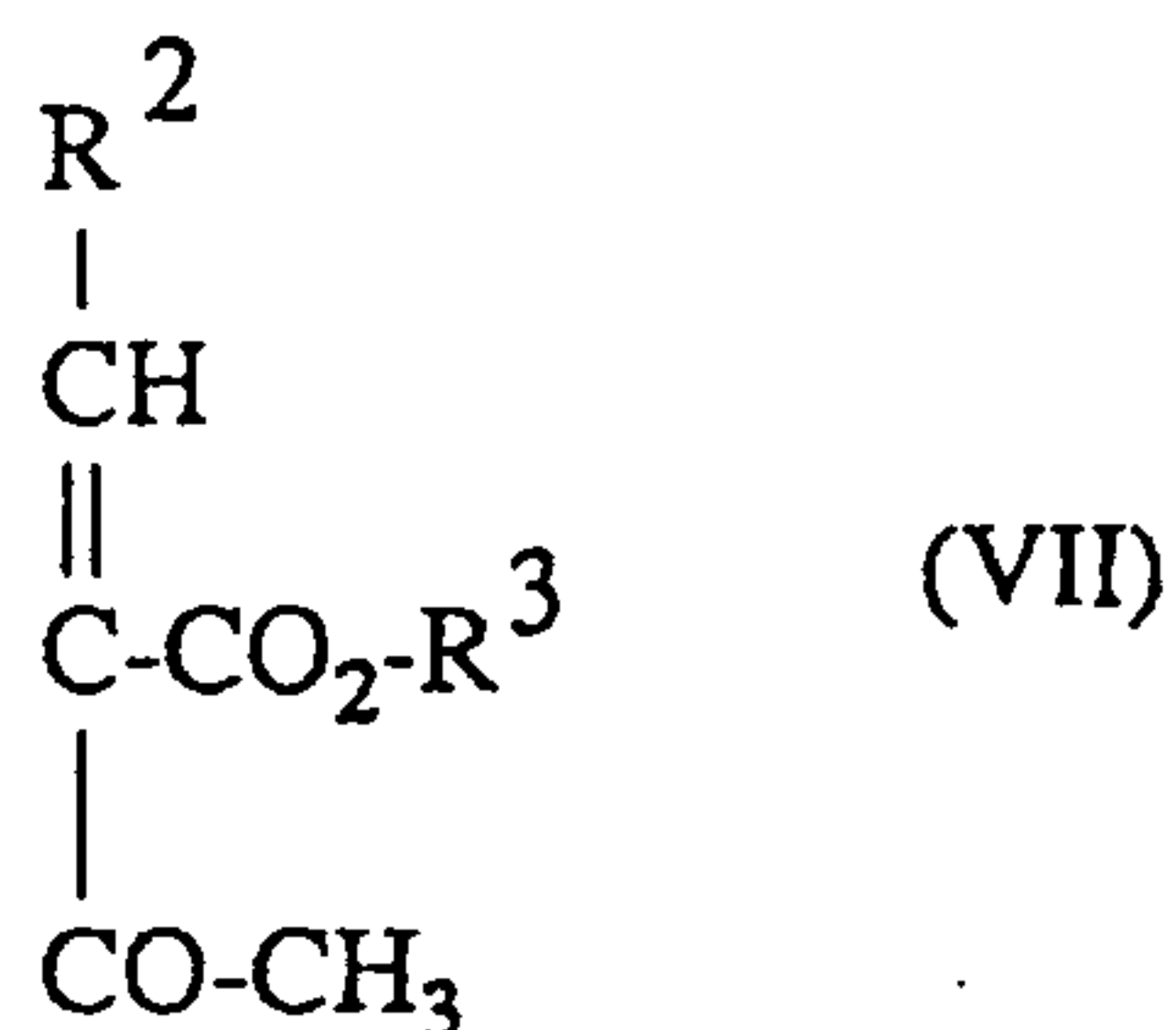


in which

R³ has the meaning indicated,

or

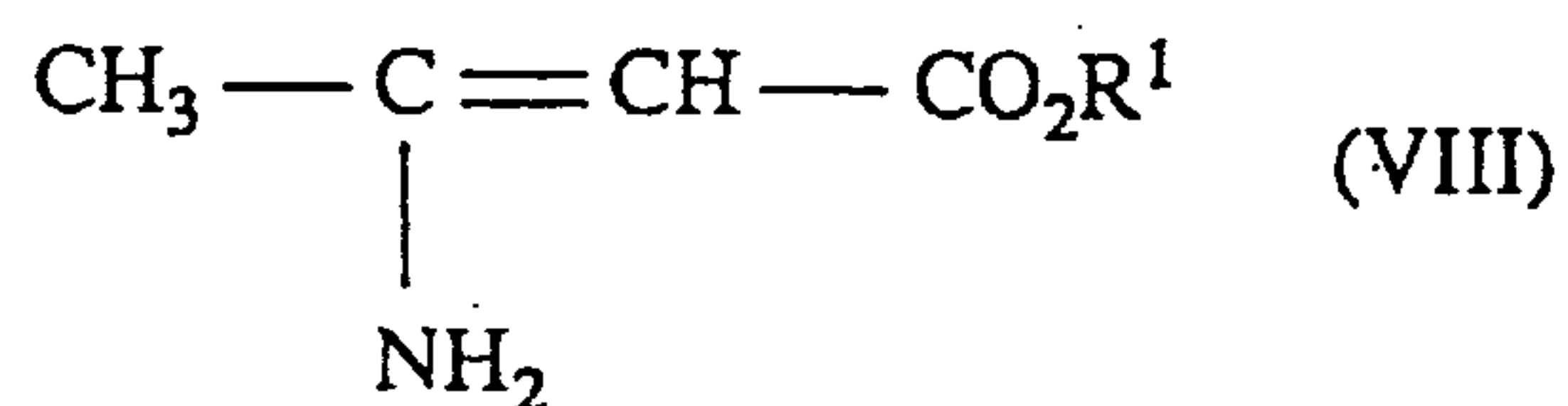
[B] the aldehydes of the general formula (II) are reacted first with the compounds of the general formula (V), if appropriate with isolation of the ylidene compounds of the general formula (VII)



in which

R² and R³ have the meaning indicated,

and these are reacted in a next step with the compounds of the general formula (III) in inert solvents, in the presence of ammonia or ammonium salts or directly with enamino-carboxylic acid derivatives of the general formula (VIII)

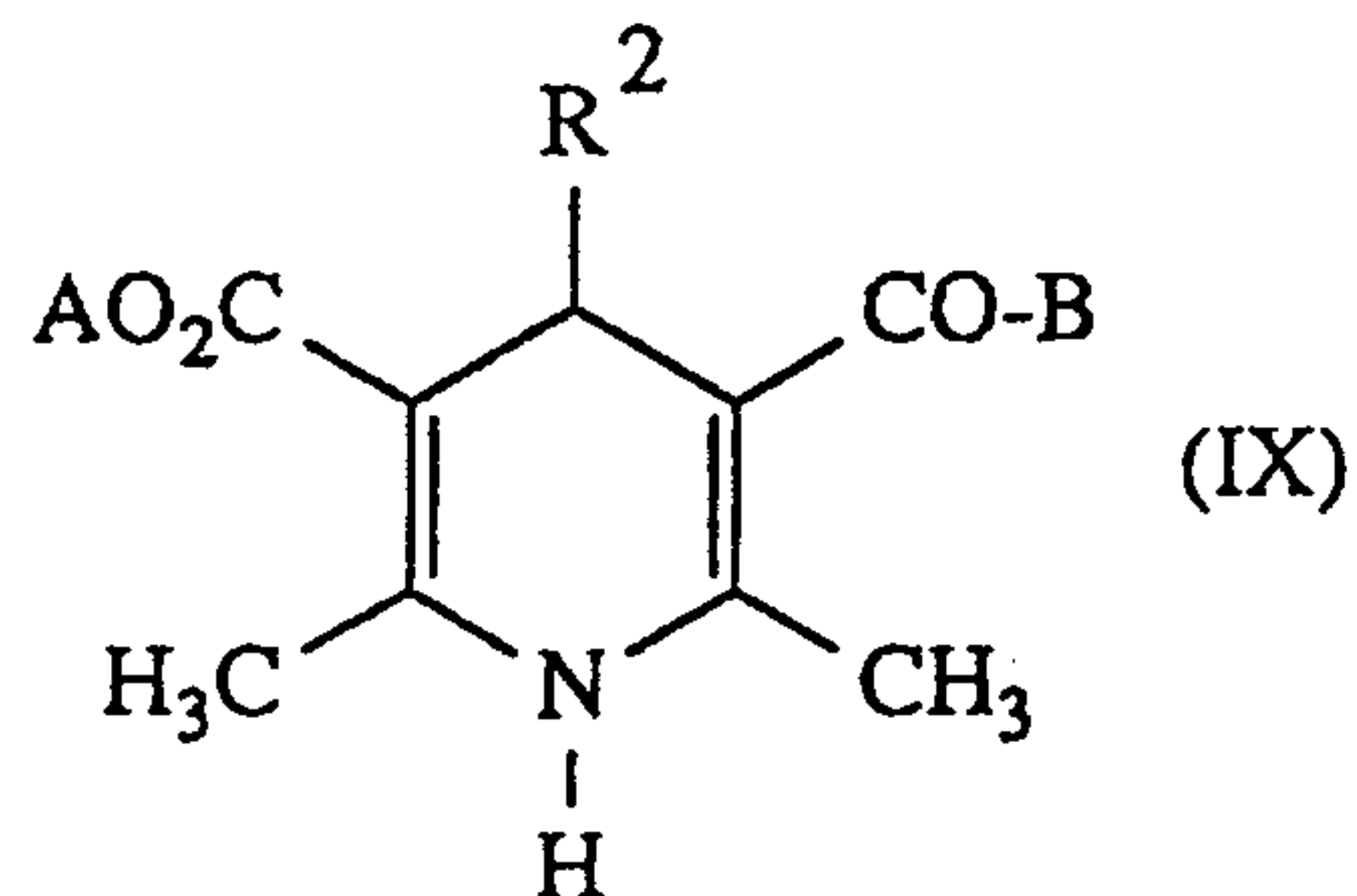


in which

R¹ has the meaning indicated,

or

[C] compounds of the general formula (IX)



in which

5 R² has the meaning indicated above,

A has the meaning of R¹ or R³ indicated above

and

B together with the -CO- group forms a reactive carboxylic acid derivative,

10 are reacted in inert solvents, in the presence of a base,

with compounds of the general formula (X)



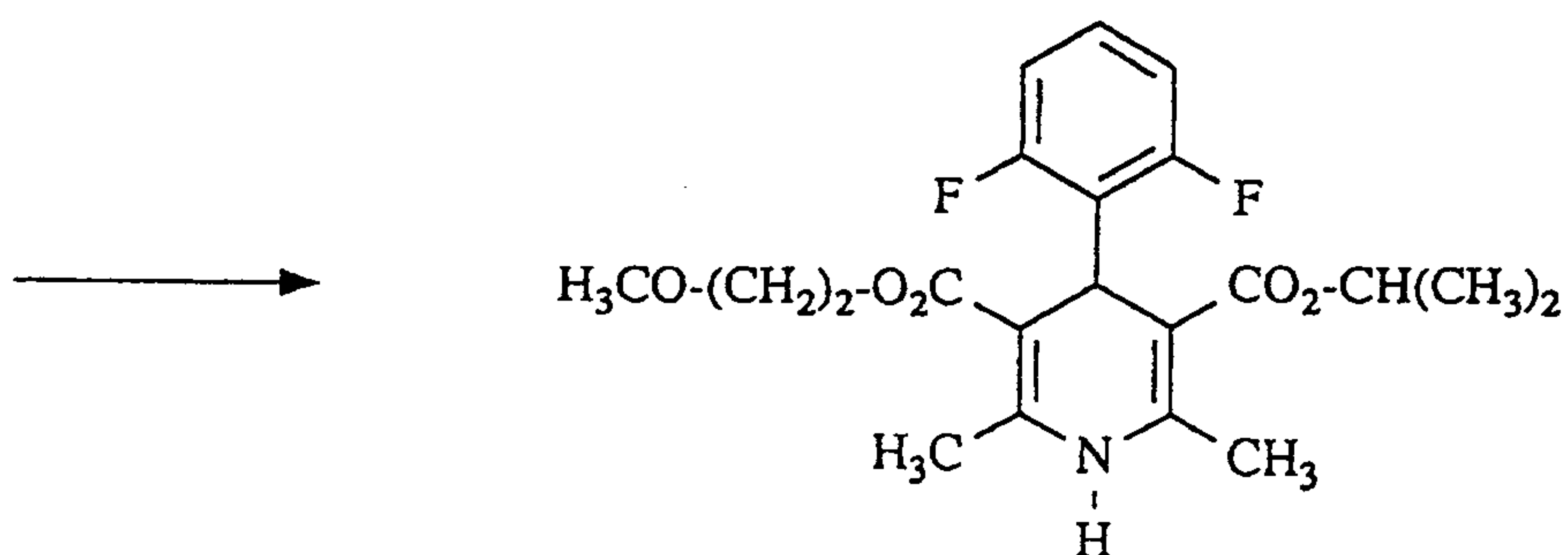
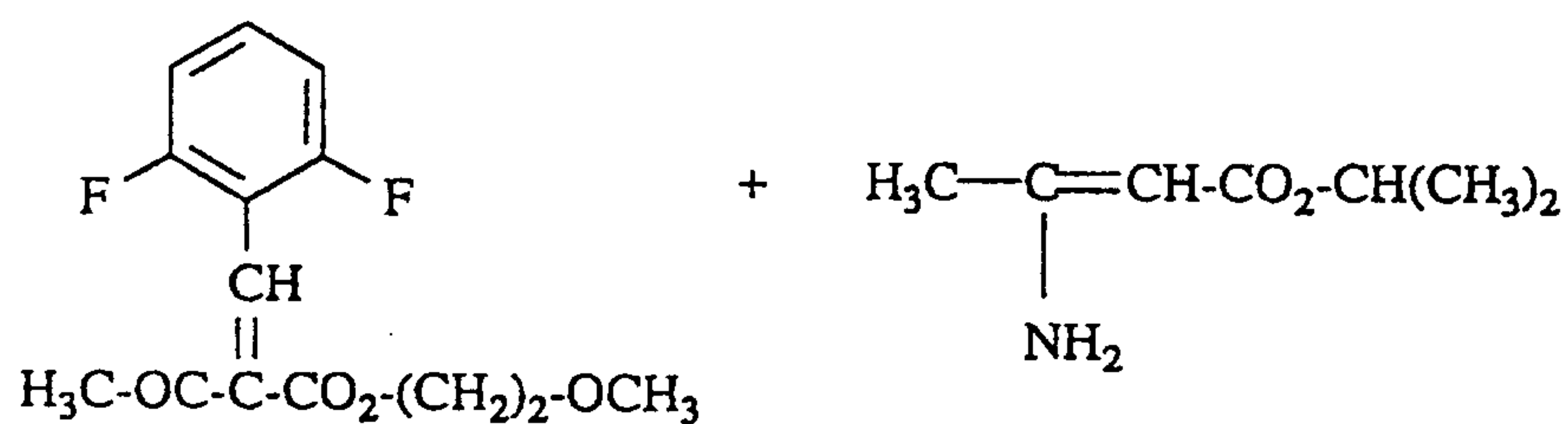
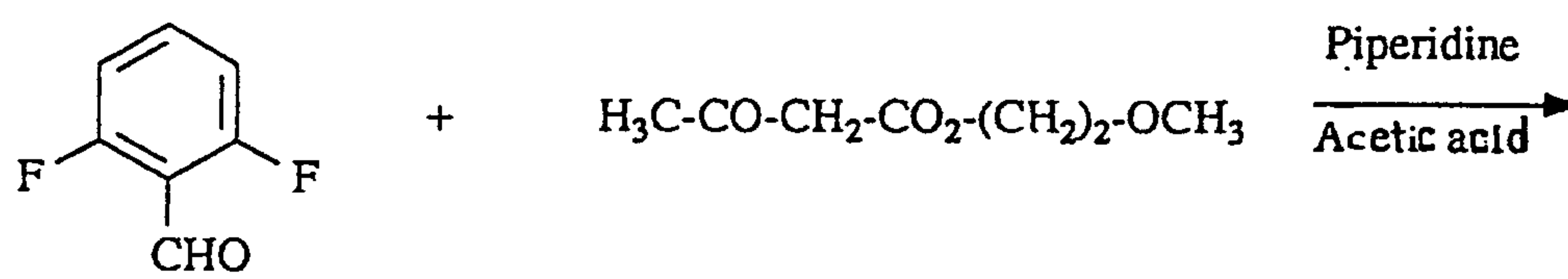
in which

R⁶ has the meaning of R¹ or R³ indicated,

and in the case of the pure ester enantiomers, the enantiomerically pure carboxylic acids are reacted, if appropriate first via the stage of a reactive acid derivative, with the corresponding alcohols.

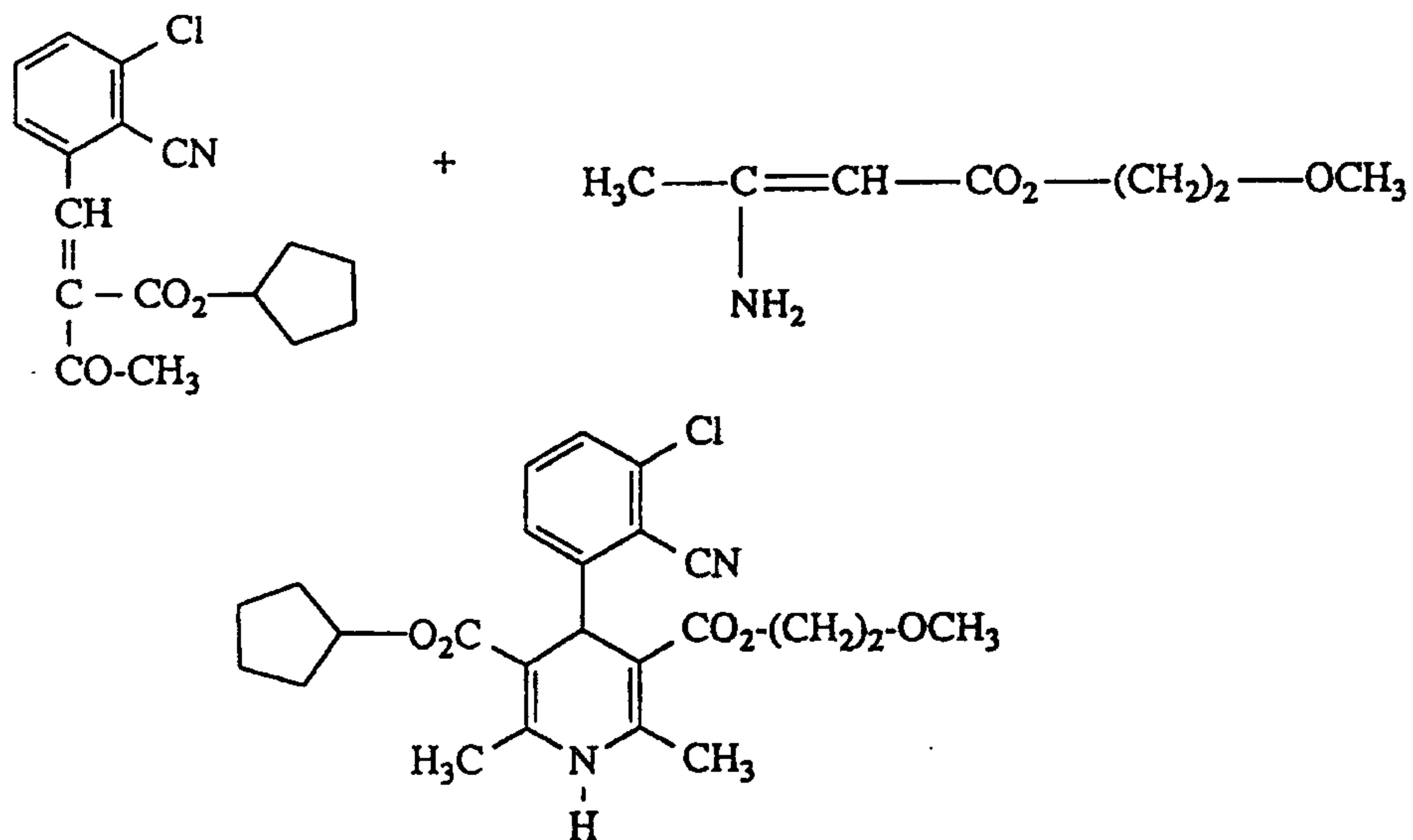
The process according to the invention can be illustrated by way of example by the following reaction scheme:

[A]

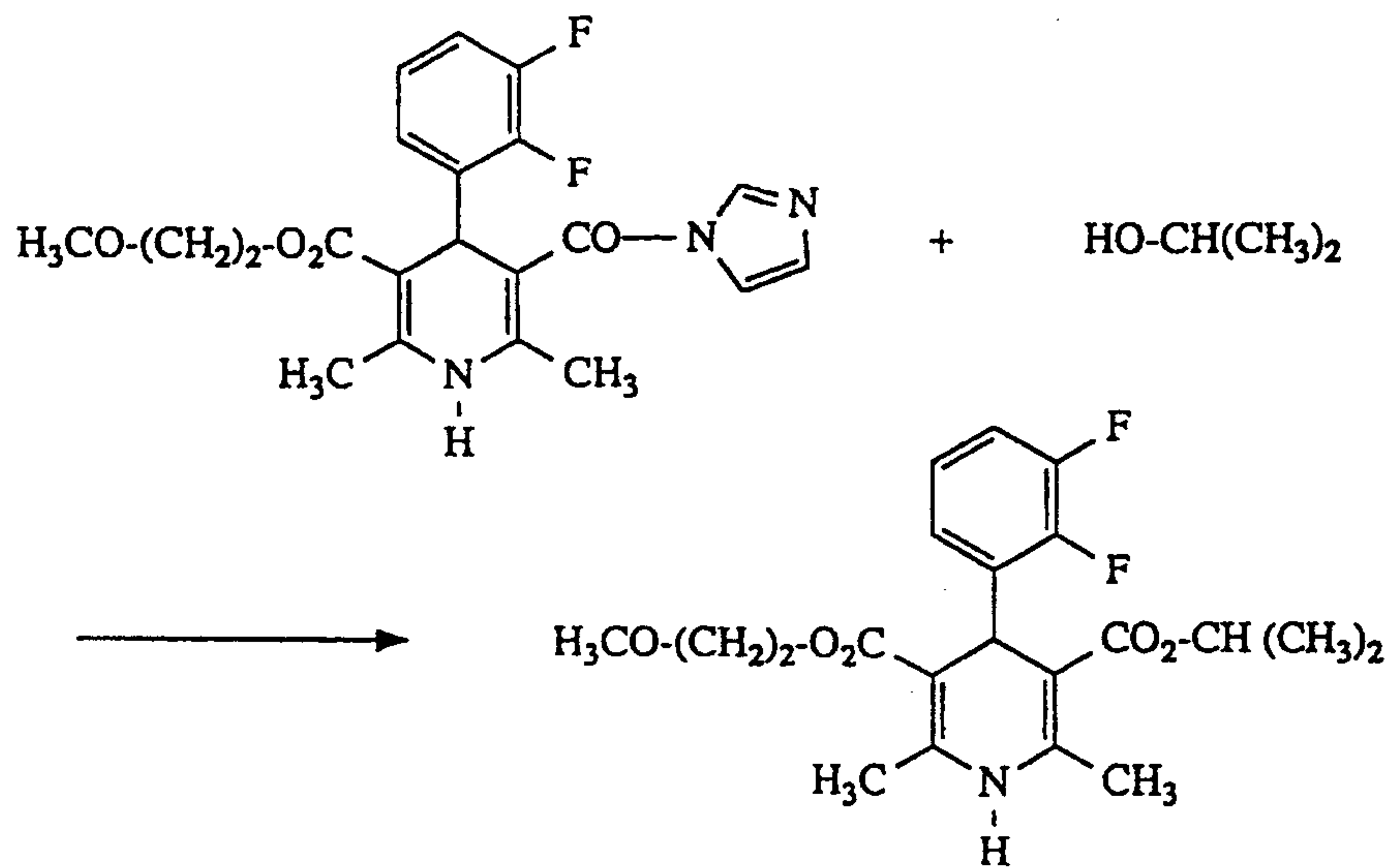


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[B]



[C]



Suitable solvents for processes [A] and [B] in this case are all inert organic solvents which do not change under the reaction conditions. These preferably include alcohols such as methanol, ethanol, propanol or isopropanol, 5 or ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether, or diethylene glycol dimethyl ether, acetonitrile, or amides such as hexamethylphosphoramide or dimethylformamide, or acetic acid or halogenated hydrocarbons such as methylene chloride, 10 carbon tetrachloride or hydrocarbons such as benzene or toluene. It is also possible to use mixtures of the solvents mentioned. Isopropanol, tetrahydrofuran, methanol, dioxane and dimethylformamide are preferred.

Suitable solvents for process [C] are the abovementioned 15 solvents with the exception of the alcohols and acetic acid.

Suitable bases are in general cyclic amines, such as, for example, piperidine, C₁-C₃-tri- and dialkylamines, such as, for example, di- and triethylamine or pyridine or 20 dimethylaminopyridine. Depending on the particular reaction steps, piperidine, dimethylaminopyridine and pyridine are preferred.

The auxiliaries employed are preferably condensing agents which can also be bases. The customary condensing agents 25 are preferred here such as carbodiimides e.g. N,N'-diethyl-, N,N'-dipropyl-, N,N'-diisopropyl- and N,N'-dicyclohexylcarbodiimide,

N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride, or carbonyl compounds such as carbonyldiimidazole, or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium-3-sulphonate or 2-tert-butyl-5-methylisoxazolium perchlorate, or acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or propanephosphonic anhydride, or isobutyl chloroformate, or benzotriazolyloxy-tris(dimethylamino)phosphonium hexafluorophosphate. N,N'-Dicyclohexylcarbodiimide and carbonyldiimidazole are preferred.

Suitable bases for the activation of the carboxylic acids are in general alkali metal carbonates such as, for example, sodium carbonate or potassium carbonate, or organic bases such as trialkylamines, e.g. triethylamine, N-ethylmorpholine, N-methylpiperidine or diisopropylethylamine, or dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). Dimethylaminopyridine is preferred.

The base is in general employed in an amount from 0.01 mol to 1 mol, preferably from 0.05 mol to 0.1 mol, in each case relative to 1 mol of the compounds of the general formulae (II) and (IX).

The auxiliaries are in general employed in an amount from 1 mol to 3 mol, preferably from 1 mol to 1.5 mol, in each case relative to 1 mol of the compounds of the general formulae (II) and (IX).

The reaction temperatures for processes [A] and [B] can be varied within a relatively wide range. In general, the reaction is carried out in a range from -20°C to 200°C, preferably from 0°C to 110°C.

- 5 The processes can be carried out at normal pressure, elevated pressure or reduced pressure (for example from 0.5 to 5 bar), preferably at normal pressure.

10 When carrying out the processes according to the invention, any desired ratio of the substances participating in the reaction can be used. In general, however, the reaction is carried out with molar amounts of the reactants.

15 Reagents suitable for the activation of the carboxylic acid are the customary reagents such as inorganic halides, for example thionyl chloride, phosphorus trichloride or phosphorus pentachloride, or carbonyl-diimidazole, carbodiimides such as cyclohexylcarbodiimide or 1-cyclohexyl-3-[2-(N-methylmorpholino)ethyl]-carbodiimide p-toluenesulphonate or N-hydroxyphthalimide or
20 N-hydroxy-benzotriazole.

25 Enantiomerically pure forms are obtained e.g. additionally by separating diastereomer mixtures of the compounds of the general formula (I) in which R¹ or R³ represents an enantiomerically pure chiral alcohol radical, according to a customary method, subsequently preparing the enantiomerically pure carboxylic acids and then optionally

converting into the enantiomerically pure dihydro-
pyridines by esterification with appropriate alcohols.

5 Suitable chiral ester radicals are all esters of enantio-
merically pure alcohols such as, for example, 1-phenyl-
ethanol, lactic acid, lactic acid esters, mandelic acid,
mandelic acid esters, 2-aminoalcohols, sugar derivatives
and many other enantiomerically pure alcohols.

10 The separation of the diastereomers is in general carried
out either by fractional crystallization, by column
chromatography or by countercurrent distribution. Which
is the optimum process must be decided from case to case;
sometimes it is also expedient to utilize combinations of
the individual processes.

15 The esterification of the enantiomerically pure dihydro-
pyridines is preferably carried out in ethers such as
diethyl ether or tetrahydrofuran, in dimethylformamide,
methylene chloride, chloroform, acetonitrile or toluene.

The aldehydes of the general formula (II) are known per
se or can be prepared by customary methods.

20 The acetoacetic esters of the general formulae (III) and
(V) and the enamino derivatives of the general formulae
(VI) and (VIII) are also known.

The reactive acid derivatives of the general formula (IX)
are known in some cases or are new and can then be

prepared by customary methods.

The compounds of the general formula (X) are known.

The compounds of the general formulae (IV) and (VII) are mostly known or can be prepared by customary methods.

5 The above preparation processes are only given for clarification. The preparation of the compounds of the general formula (I) is not restricted to these processes, but any modification of these processes is applicable in the same manner for the preparation of the compounds
10 according to the invention.

The compounds according to the invention show an unforeseeable, useful spectrum of pharmacological activity.

The compounds according to the invention are calcium channel ligands with selectivity for L-type calcium
15 channels of the central nervous system. This selectivity can be seen, for example, by comparison of the binding affinities to DHP binding sites in rats' brains and rats' hearts.

The compounds positively affect learning and memory
20 performance, as their performance-enhancing effect on rats in typical learning and memory models such as the water maze, Morris maze, passive avoidance and memory tests in automated Skinner boxes demonstrates. They have an antidepressant potential, as their activity in the rat

swimming tests according to Porsolt confirms.

Calcium flux

To determine the calcium flux, a suspension of cultured PC 12 cells is used. The cells are incubated at 37°C in
5 a customary culture medium together with the active compound to be investigated. To depolarize the cells, an activation medium having a high potassium concentration is added which at the same time contains radioactive calcium ($^{45}\text{Ca}^{2+}$). After a specific time interval, a medium
10 cooled to 0°C is added in order to stop the influx of radioactive calcium into the cells. The radioactivity in the harvested and dried cells is then determined. To determine the 0% limit of the inhibitory value, dimethyl sulphoxide (DMSO) is employed and the 100% inhibitory
15 value is determined using 10^{-6} mol/l pimozide.

Binding assays:

The binding affinities to PN 200-110 binding sites in rats' brains or rats' hearts are determined according to Rampe, D.R., Rutledge, A., Janis, R.A., Triggle, D.J.:
20 Can. Journ. Physiol. Pharmacol. 65, (1987) 1452.

Water maze:

Old Wistar rats (24 months) are placed in the starting position in a plastic tank (120x50x40 cm) filled with cold (14-15°) water and subdivided by vertical barriers.
25 In order to reach a ladder which enables the animals to escape from the water, they must swim around these barriers. The time which is required for finding the exit

and the number of errors on the way there are recorded. In this case, an error is defined as swimming up a blind alley or swimming over the boundary of imaginary squares into which the tank is subdivided in the direction away from the exit.

The rats remain in the maze until finding the exit, but at longest 300 sec. They are then taken out, dried and warmed under a red light. They then return to their home cages.

In a typical experiment, two equivalent animal groups (placebo, test substance each $n = 15$) are determined by means of a preliminary test. The animals then go through 6 test sessions, two per day. Test substances or placebo are administered orally 30 min before the experiments.

The measures of the learning- and memory-enhancing effect of the test substances in comparison to placebo are reduction of the time until reaching the exit, reduction of the number of errors and increase in the number of animals which find the exit at all.

Rat swimming test according to Porsolt

During a preliminary test, young rats are placed in a glass cylinder (40 cm high, 20 cm diameter) which is filled 17 cm high with water at 25°C. After 20 min in the water, the animals are taken out and warmed under a lamp for 30 min. In this preliminary test, all rats attempt to get out of the cylinder until after about 15 min they remain immobile ("behavioural despair", giving-up behaviour). 24 h later, the test session starts in which the rats are placed in the glass cylinder as on the

previous day, but this time for only 5 min. The lengths of time for which the rats remain immobile during these 5 min are recorded. In this case, a rat is regarded as immobile which, floating upright in the water, only carries out minimal movements in order to keep its head above water. Placebo or test substances (0.25, 0.5, 1, 5, 10 mg/kg; n = 6 per group) are administered orally three times; 23, 5 and 1 h before the test session (1, 19, 23 h after the preliminary test). The antidepressant effect of the test substances is seen in the reduction of the period of immobility in comparison to the placebo values.

As a result of their pharmacological properties, the compounds according to the invention can be employed for the preparation of medicaments for the treatment of central degenerative disorders, as, for example, occur in dementias (multi-infarct dementia, MID, primary degenerative dementia PDD, pre- and senile Alzheimer's disease, HIV dementia and other forms of dementia), Parkinson's disease or amyotrophic lateral sclerosis.

The active compounds are furthermore suitable for the treatment of cerebral function disorders in old age, of organic brain syndrome (OBS) and of age-associated memory impairment (AAMI).

They are useful for the prophylaxis and for the control of the sequelae of cerebral circulatory disorders such as cerebral ischaemias, strokes and of subarachnoid haemorrhages and for the treatment of brain traumas.

They are suitable for the treatment of depressions and of mania. Further areas of application are the treatment of migraine, of neuropathies which are caused e.g. by traumas, metabolic disorders such as diabetes mellitus, intoxications, microorganisms or autoimmune disorders, of addictive disorders and withdrawal symptoms.

The compounds according to the invention are Ca^{2+} antagonists with selectivity for L-type Ca^{2+} channels of the central nervous system.

This selectivity exceeds that of the known cerebrally active Ca^{2+} -antagonistic dihydropyridines nimodipine and nicardipine. This is seen e.g. in the comparison of the binding affinities to DHP (PN-200 110) binding sites in rats' brain and rats' heart [cf. Rampe, D.R., Rutledge, A., Janis, R.A., Triggle, D.J., Can. Journ. Physiol. Pharmacol. 65 (1987), 1452].

Ex. No.	K_i (Brain)[nM]	K_i (Heart)[nM]	Selectivity
	2.4	4.6	1.9
	32	14	0.44

12	7.2	72	10
15	2.0	11.3	5.7
18	8.2	28	3.4
25	1.7	8.0	4.7
33	3.6	7.9	2.2

The present invention also includes pharmaceutical

preparations which, in addition to inert, non-toxic, pharmaceutically suitable auxiliaries and excipients, contain one or more compounds of the general formula (I), or which consist of one or more active compounds of the formula (I), and processes for the production of these preparations.

The active compounds of the formula (I) should be present in these preparations in a concentration of 0.1 to 99.5% by weight, preferably of 0.5 to 95% by weight of the total mixture.

In addition to the active compounds of the formula (I), the pharmaceutical preparations can also contain other pharmaceutical active compounds.

The abovementioned pharmaceutical preparations can be prepared in a customary manner by known methods, for example using the excipient(s) or auxiliary(-ies).

In general, it has proven advantageous to administer the active compound(s) of the formula (I) in total amounts of about 0.01 to about 100 mg/kg, preferably in total amounts of about 0.1 mg/kg to 20 mg/kg of body weight every 24 hours, if appropriate in the form of several individual doses, to achieve the desired result.

However, it may sometimes be advantageous to deviate from the amounts mentioned, namely depending on the type and the body weight of the subject treated, on individual

behaviour towards the medicament, the nature and severity of the disorder, the type of preparation and administration, and the time and interval at which administration takes place.

- 5 The R_f values shown in each case were determined - if not stated otherwise - by thin layer chromatography on silica gel (aluminium foil, silica gel 60 F 254, E. Merck). The substance spots were visualized by observation under UV light and/or by spraying with 1% strength potassium permanganate solution or with molybdophosphoric acid solution.
- 10

- Flash chromatography was carried out on silica gel 60, 0.040 - 0.064 mm, E. Merck (see Still et al., J. Org. Chem. 43, 2923, 1978; for simpler separation problems see Aldrichimica Acta 18. 25. 1985). Elution with solvent gradients means: starting with the pure, non-polar solvent mixture component, the polar eluent component is admixed to an increasing extent until the desired product is eluted (TLC checking).
- 15

- 20 In the case of all products, the solvent was finally distilled off at about 0.1 mm tlg.

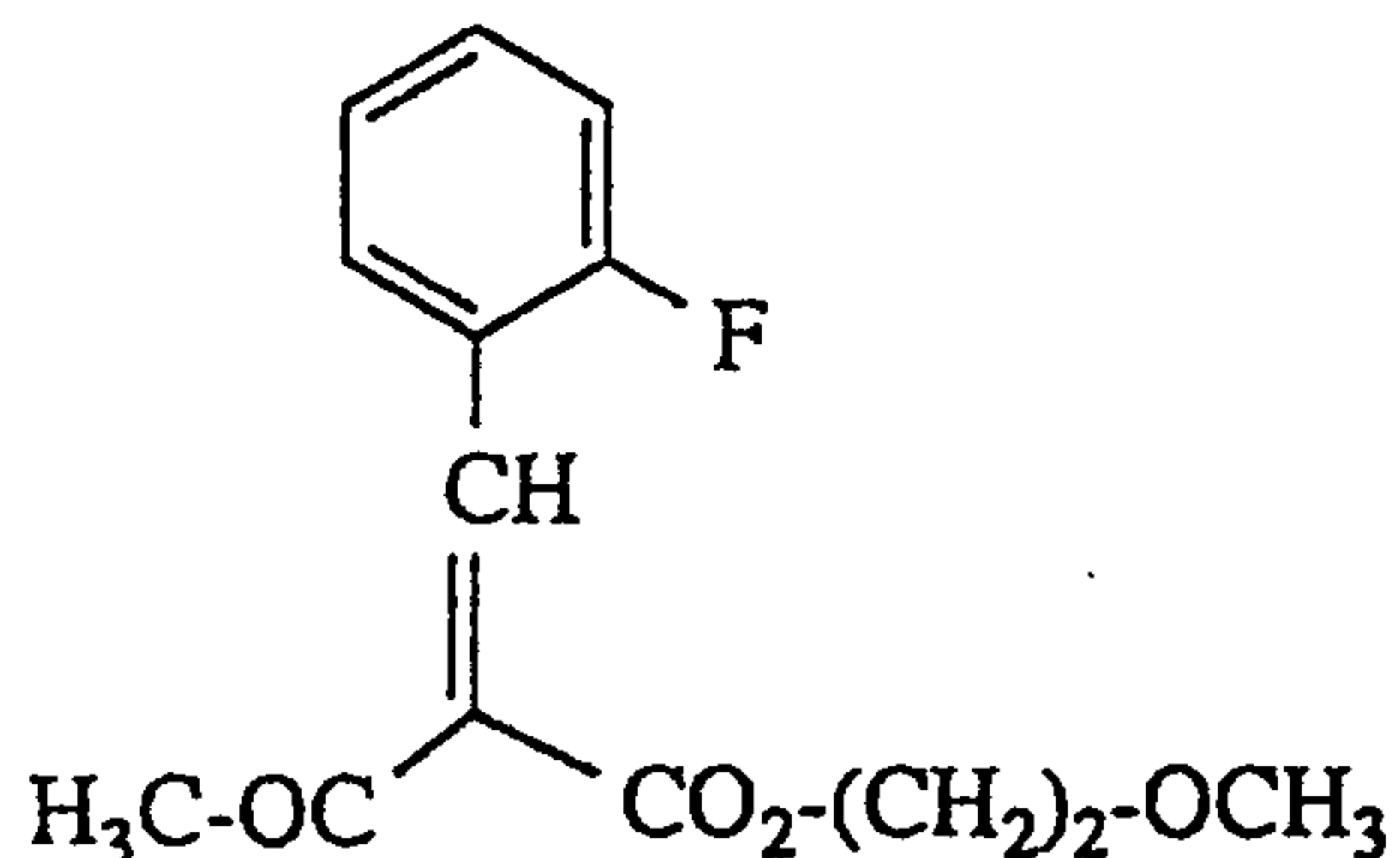
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The invention also provides uses of the compounds and compositions of the invention for the treatment of a dementia or depression and for the preparation of a medicament for the treatment of a dementia or depression.

5 Further, the invention provides a commercial package comprising a compound or composition of the invention and associated therewith instructions for the use thereof for treating a dementia or depression.

Starting compoundsExample I

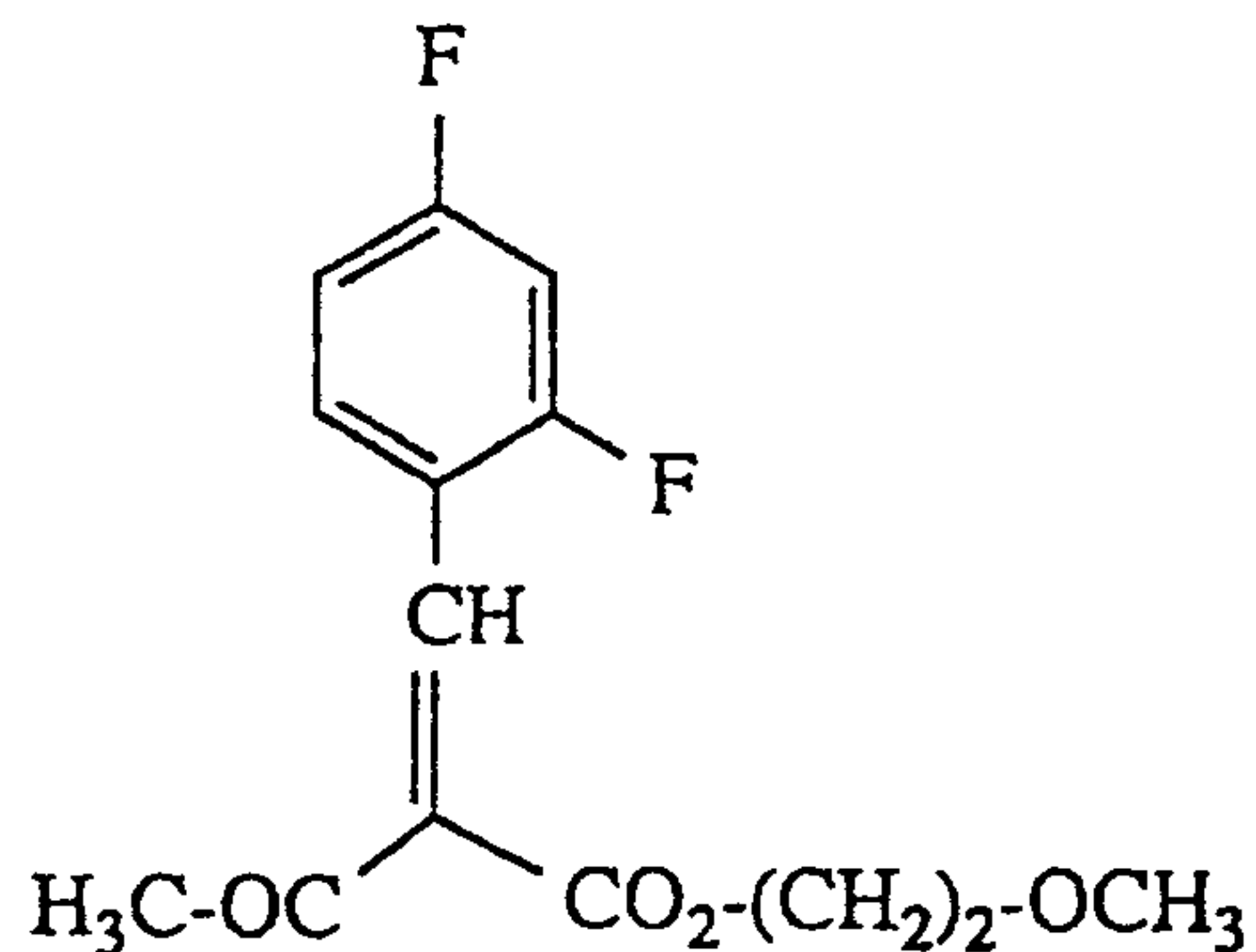
2-Methoxyethyl 2-acetyl-3-(2-fluorophenyl)-2-propenoate



10 g (80 mmol) of 2-fluorobenzaldehyde are dissolved in
5 200 ml of isopropanol with 13 g (80 mmol) of 2-methoxy-
ethyl acetoacetate. A freshly prepared solution of 1.0 ml
of piperidine and 0.5 ml of glacial acetic acid in 10 ml
of isopropanol is added to this solution and it is
stirred overnight at 40°C. The mixture is concentrated,
10 the residue is taken up in toluene, the solution is
concentrated again and the residue is purified by filtra-
tion on 300 ml of silica gel (eluent: toluene/ethyl
acetate 100:1 - 10:1) to give 15 g of the target compound
as a yellow oil which is immediately reacted further.

Example II

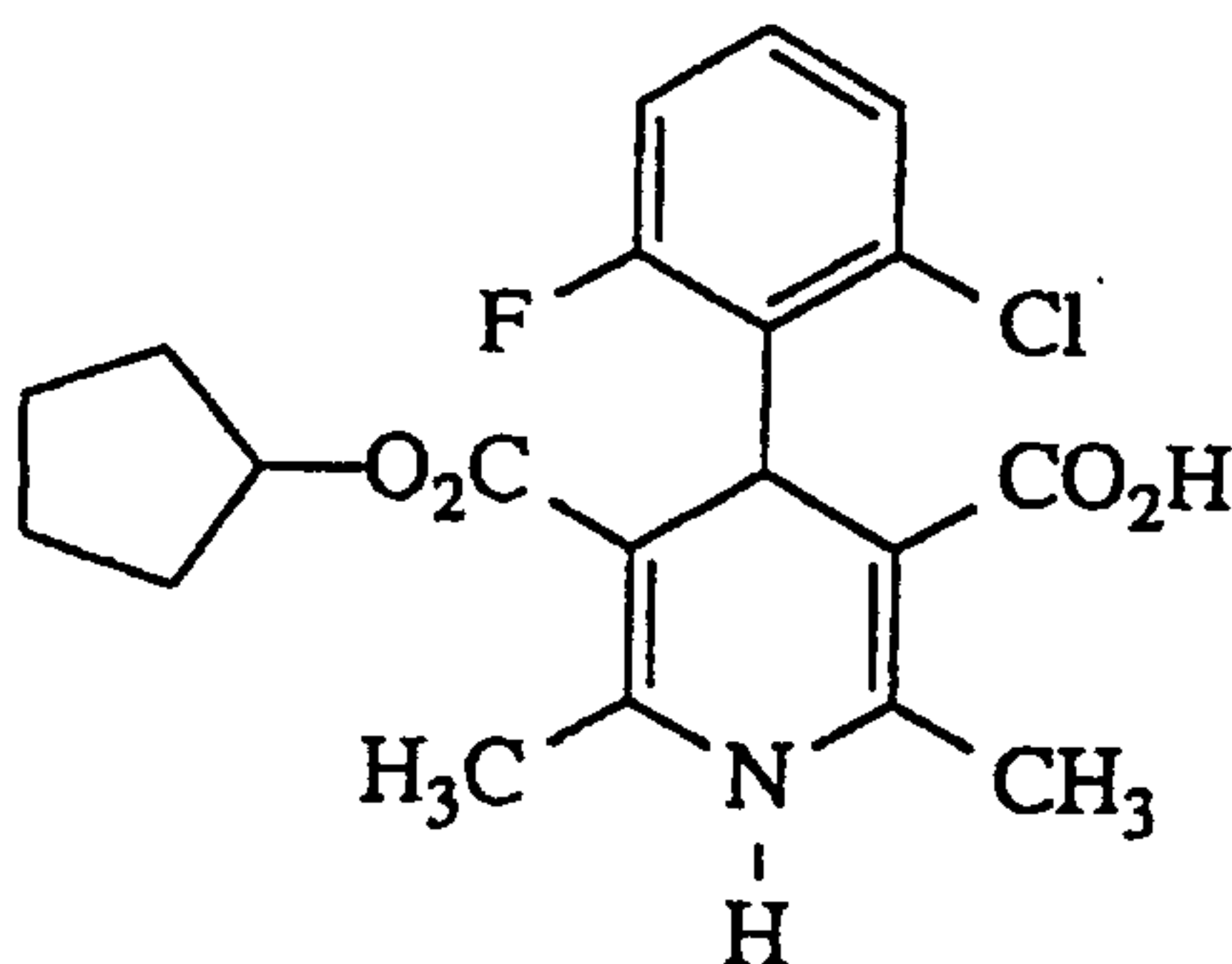
2-Methoxyethyl 2-acetyl-3-(2,4-difluorophenyl)-2-propenoate



5.0 g (35 mmol) of 2,4-difluorobenzaldehyde are dissolved
 5 in 100 ml of isopropanol with 5.7 g (35 mmol) of
 2-methoxyethyl acetoacetate. A freshly prepared solution
 of 1.0 ml of piperidine and 0.5 ml of glacial acetic acid
 in 5 ml of isopropanol is added to this solution and it
 is stirred overnight at 40°C. The mixture is concen-
 10 trated, the residue is taken up in toluene, the solution
 is concentrated again and the residue is purified by
 filtration on 100 ml of silica gel (eluent: toluene/ethyl
 acetate 100:1) to give 5 g of the target compound as a
 yellow oil which is immediately reacted further.

Example III

4-(2-Chloro-6-fluorophenyl)-3-cyclopentyloxycarbonyl-1,4-dihydro-2,6-dimethylpyridine-5-carboxylic acid

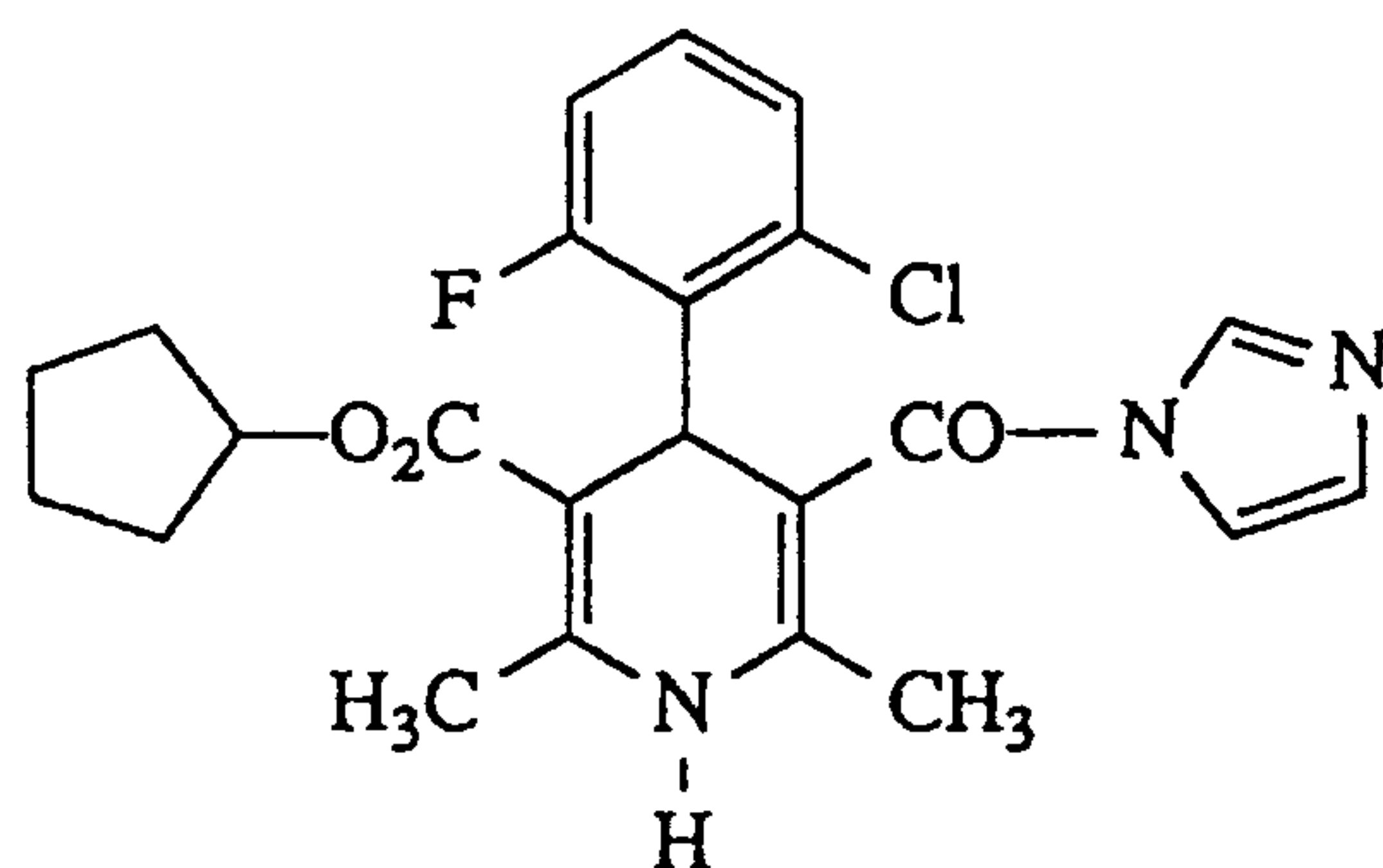


98 g (0.22 mol) of 4-(2-chloro-6-fluorophenyl)-3-(2-cyanoethyl)-cyclopentyloxycarbonyl-1,4-dihydro-2,6-dimethylpyridine-5-carboxylic acid are dissolved in 400 ml of 1,2-dimethoxyethane and the mixture is stirred at room temperature overnight with 400 ml of 1 N sodium hydroxide solution. The solvent volume is reduced to about half, the solution is washed with dichloromethane and the aqueous phase is acidified with 2 N hydrochloric acid (pH = 2). Extraction twice with dichloromethane, washing of the organic phase with water, drying over sodium sulphate, concentration and crystallization from ether yields 42 g of the target compound as a solid of melting point about 120°C (dec.).

Example IV

Cyclopentyl 4-(2-chloro-6-fluorophenyl)-1,4-dihydro-5-(1-imidazolylcarbonyl)-2,6-dimethylpyridine-3-carboxylate

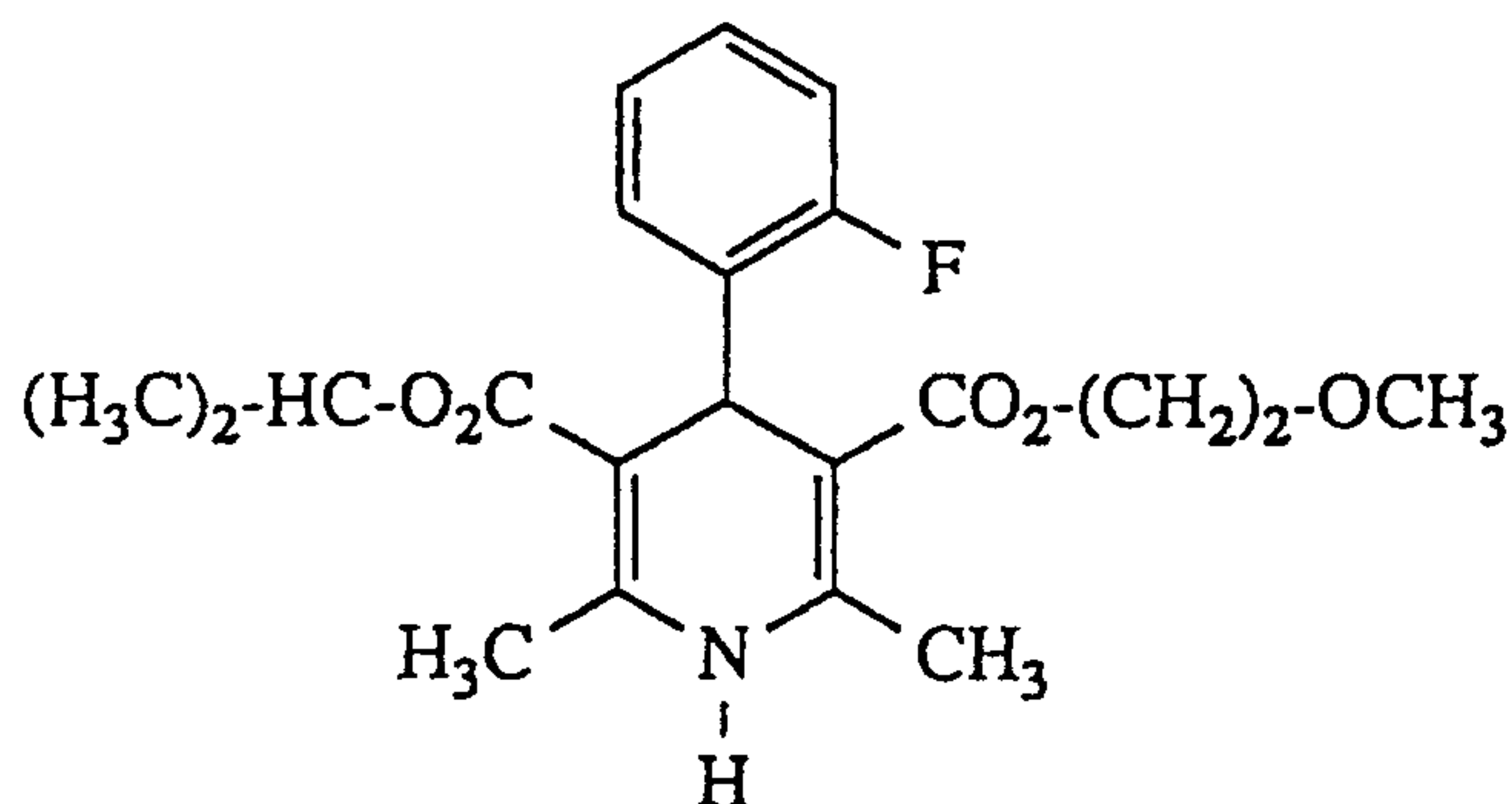
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13.6 g (83 mmol) of carbonyldiimidazole are added to
33.0 g (83 mmol) of 4-(2-chloro-6-fluorophenyl)-3-cyclo-
pentyloxycarbonyl-1,4-dihydro-2,6-dimethylpyridine-5-
5 mixture is heated to reflux for 3 h. Thin-layer chromato-
graphic checking (silica gel, toluene/ethyl acetate 1:1)
shows complete reaction, after which the reaction mixture
is concentrated, the residue is taken up in ethyl ace-
tate, and the solution is washed twice with water, dried
10 over sodium sulphate and concentrated again. The target
compound precipitates from ether in the form of white
crystals of m.p. 150°C.
Yield: 29.7 g

Preparation ExamplesExample 1

Isopropyl 2-methoxyethyl 4-(2-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate



5 4.0 g (about 15 mmol) of the compound from Example I are heated to reflux overnight in 100 ml of isopropanol with 2.2 g (15 mmol) of isopropyl 3-amino-2-butenate. After thin-layer chromatographic checking (SiO₂, toluene/ethyl acetate 5:1) shows complete conversion, the reaction

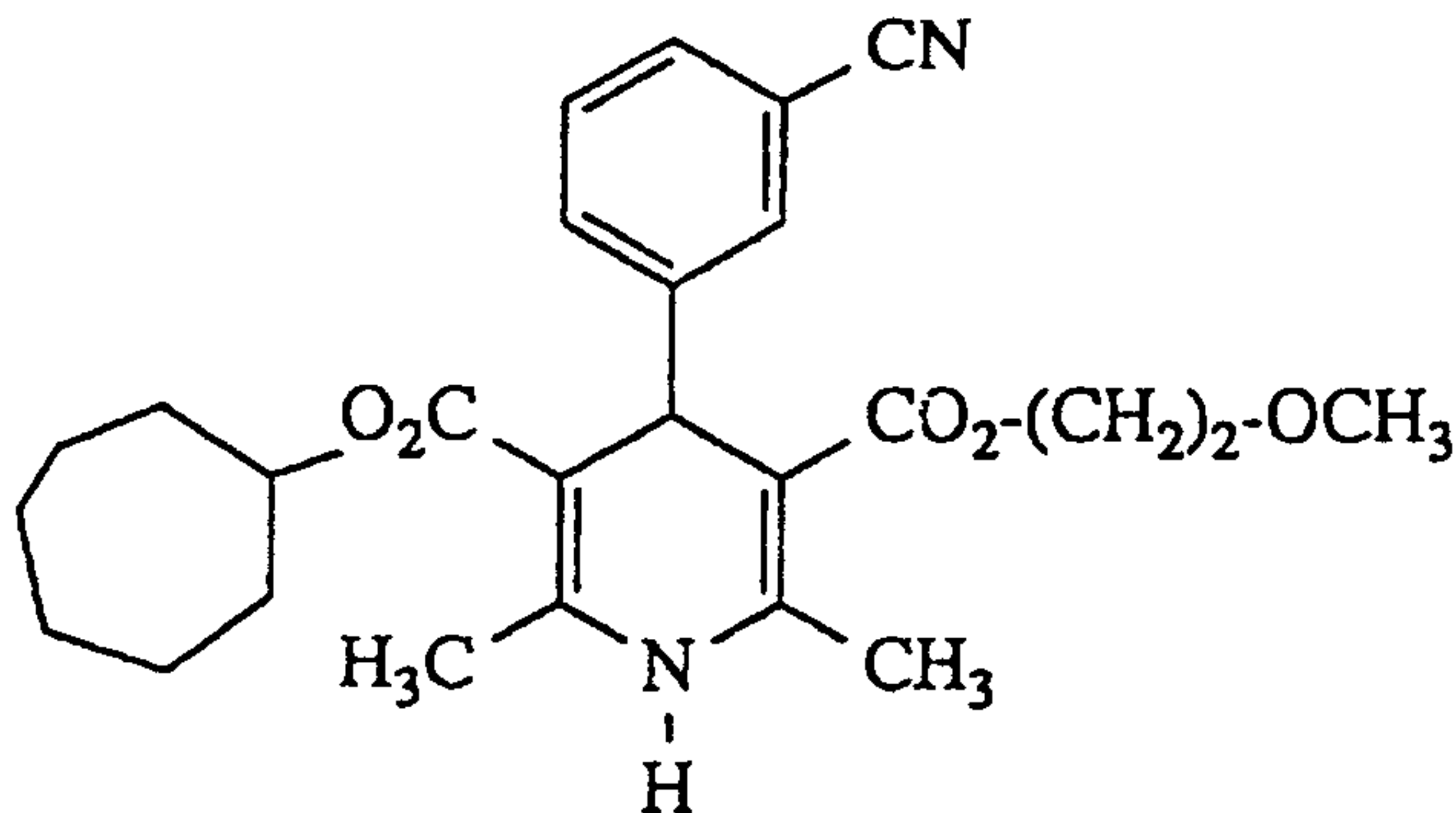
10 mixture is concentrated, the residue is taken up with toluene, the solution is concentrated again and the residue is then purified by filtration on silica gel (eluent: toluene/ethyl acetate 100:1 - 5:1). A crystallizing yellow oil is obtained, which is recrystallized

15 from methanol at about -15°C. 2.8 g (48%) of the target compound are obtained.

M.p.: 99-100°C.

Example 2

(-)-Cycloheptyl 2-methoxyethyl 4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate



5.0 g (14 mmol) of (-)-4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethyl-3-(2-methoxy)ethoxycarbonylpyridine-5-carboxylic acid [obtainable by chromatographic separation of the racemic monocarboxylic acid on chiral stationary phases] are stirred over molecular sieve (4 A) for 30 min in 50 ml of tetrahydrofuran. 2.3 g (14 mmol) of carbonyl-diimidazole are then added and the mixture is heated to reflux for 1 h, the molecular sieve is filtered off and the filtrate is concentrated. The residue is taken up in 30 ml of cycloheptanol and heated at 100°C for 6 h after addition of a spatula-tipful of N,N-dimethyl-4-aminopyridine. Repeated chromatography on silica gel in toluene/ethyl acetate, dichloromethane/isopropanol and cyclohexane/ethyl acetate mixtures and crystallization from diisopropyl ether/cyclohexane yields 1.0 g (16%) of the target compound as white crystals.

M.p.: 98-99°C

$[\alpha]_D^{20} = -24.2^\circ$ (c=0.9, CHCl₃)

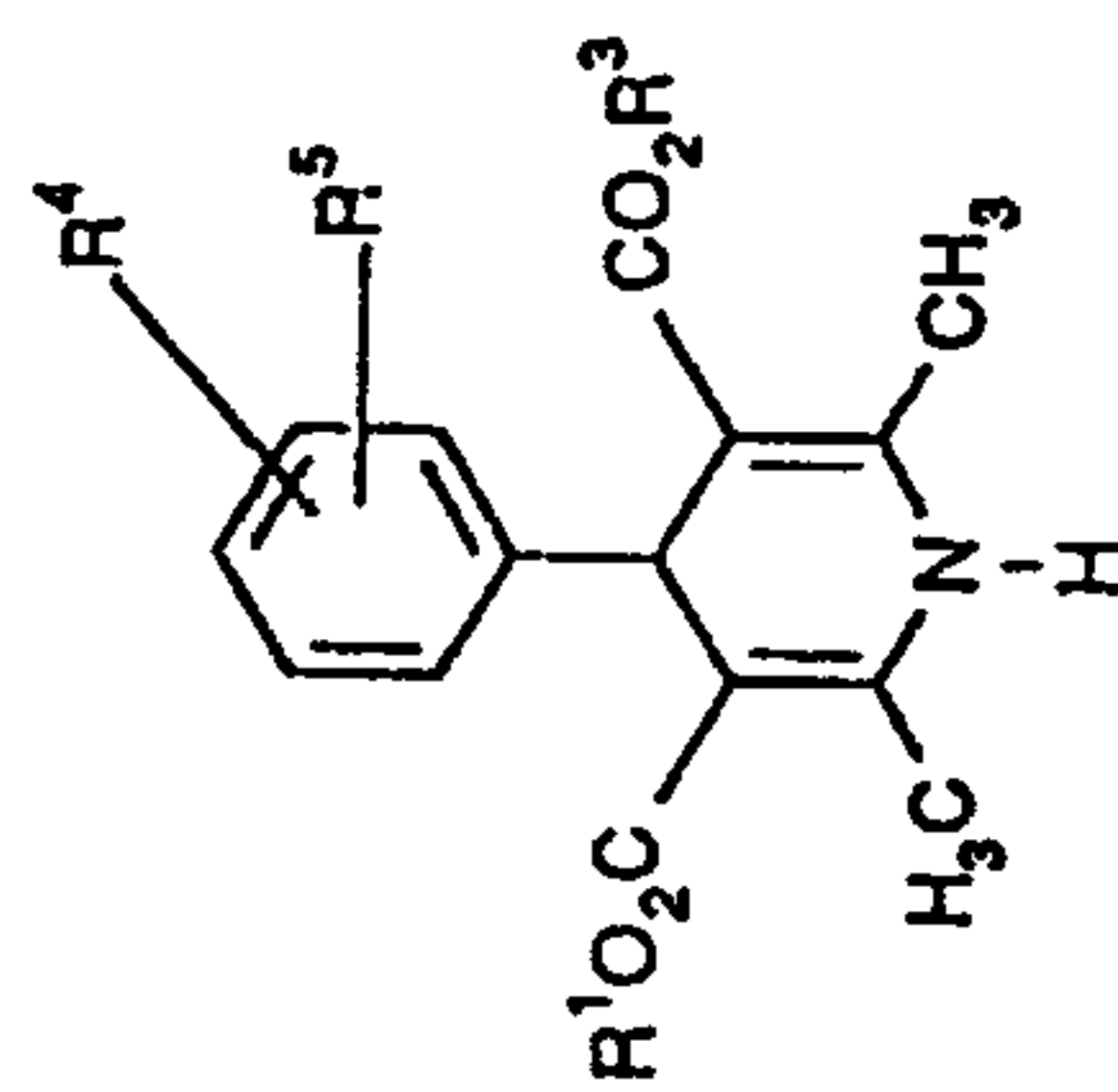
30725-25

The compounds shown in Table 1 are obtained in analogy to Examples 1 and 2, or by subjecting the racemic products to chromatographic separation into the enantiomerically pure target compounds on chiral stationary phases (Chiralcel[™] and Chiralpak[™], Daicel):

5

Table 1:

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Ex. No.	R ¹	R ⁴	R ⁵	R ³	Racemate/ enantiomer	M.p. (°C)	[α] _D ²⁰
3	H ₃ C-O-(CH ₂) ₂ -	2-Cl	6-F	-CH(CH ₃) ₂	racemate	57-59	
4	H ₃ C-O-(CH ₂) ₂ -	2-Cl	6-F	-CH(CH ₃) ₂	(+)-enantiomer		
5	H ₃ C-O-(CH ₂) ₂ -	2-Cl	6-F	-CH(CH ₃) ₂	(-)-enantiomer		
6	H ₃ C-O-(CH ₂) ₂	2-F	6-F	-CH(CH ₃) ₂	racemate	119-120	
7	H ₃ C-O-(CH ₂) ₂	2-F	6-F	-CH(CH ₃) ₂	(+)-enantiomer		+17.8 (c=0.5; CH ₂ Cl ₂)
8	H ₃ C-O-(CH ₂) ₂	2-F	6-F	-CH(CH ₃) ₂	(-)-enantiomer		-27 (c=0.73; CH ₂ Cl ₂)
9	H ₃ C-O-(CH ₂) ₂	2-F	3-F	-CH(CH ₃) ₂	racemate	135-136	
10	H ₃ C-O-(CH ₂) ₂	2-F	3-F	-CH(CH ₃) ₂	(+)-enantiomer		
11	H ₃ C-O-(CH ₂) ₂	2-F	3-F	-CH(CH ₃) ₂	(-)-enantiomer		
12	H ₃ C-O-(CH ₂) ₂	2-Cl	5-Cl	-CH(CH ₃) ₂	racemate	79-89	
13	H ₃ C-O-(CH ₂) ₂	2-Cl	5-Cl	-CH(CH ₃) ₂	(+)-enantiomer		+24.6 (c=1.51; CHCl ₃)
14	H ₃ C-O-(CH ₂) ₂	2-Cl	5-Cl	-CH(CH ₃) ₂	(-)-enantiomer		-24.9 (c=1.44; CHCl ₃)

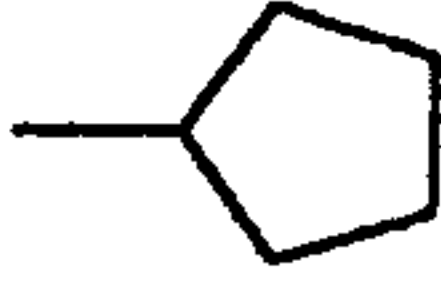
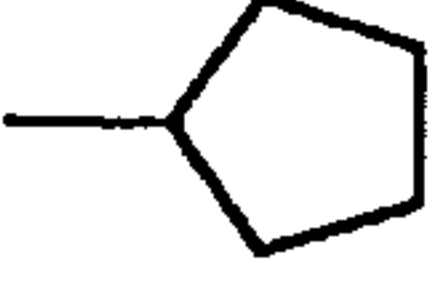
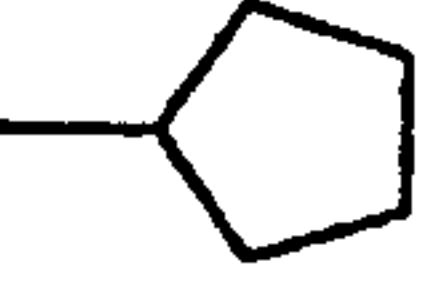
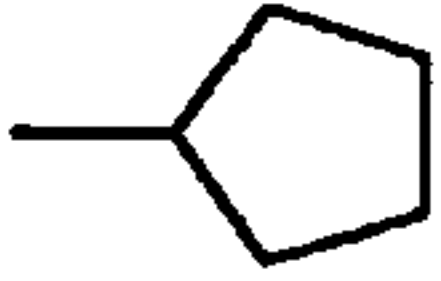
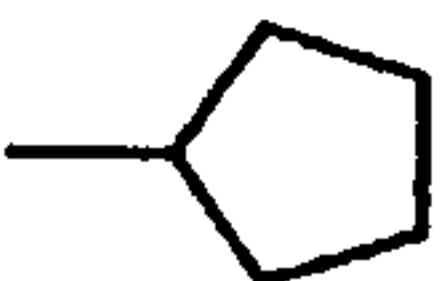
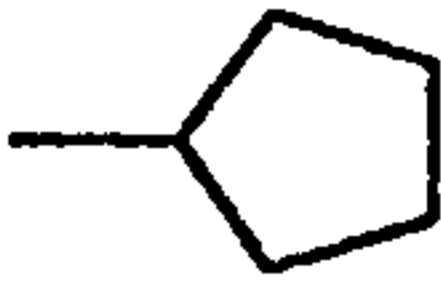
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Continuation of Table 1:

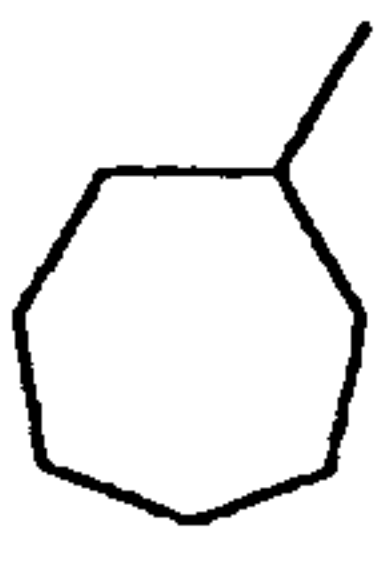
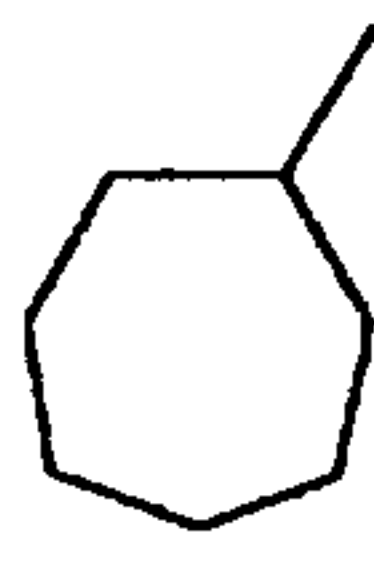

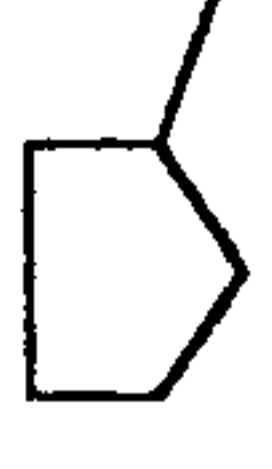

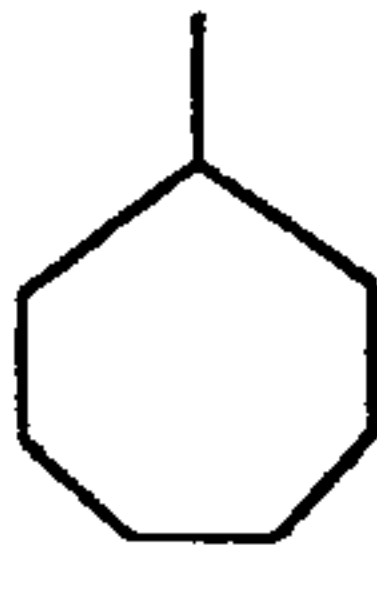
Ex. No.	R ¹	R ⁴	R ⁵	R ³	Racemate/ enantiomer	M.p. (°C)	[α] _D ²⁰
15	-CH(CH ₃) ₂	2-CN	3-Cl	-(CH ₂) ₂ -OCH ₃	racemate	151-152	
16	-CH(CH ₃) ₂	2-CN	3-Cl	-(CH ₂) ₂ -OCH ₃	(+)-enantiomer	149-151	+10.9(c=1.0; CHCl ₃)
17	-CH(CH ₃) ₂	2-CN	3-Cl	-(CH ₂) ₂ -OCH ₃	(-)-enantiomer	149-150	-12.7(c=1.0; CHCl ₃)
18	H ₃ C-O-(CH ₂) ₂ -	3-F	4-F	-CH(CH ₃) ₂	racemate	78	
19	H ₃ C-O-(CH ₂) ₂ -	3-F	4-F	-CH(CH ₃) ₂	(+)-enantiomer		
20	H ₃ C-O-(CH ₂) ₂ -	3-F	4-F	-CH(CH ₃) ₂	(-)-enantiomer		
21	H ₃ C-O-(CH ₂) ₂ -	2-F	5-F	-CH(CH ₃) ₂	racemate	104-106	
22	H ₃ C-O-(CH ₂) ₂ -	2-F	5-F	-CH(CH ₃) ₂	(+)-enantiomer	113	
23	H ₃ C-O-(CH ₂) ₂ -	2-F	5-F	-CH(CH ₃) ₂	(-)-enantiomer	113	-22.8(c=0.96; CHCl ₃)
24	-CH(CH ₃) ₂	2-CN	H	-(CH ₂) ₂ -OCH ₃	racemate	123-125	
25	-CH(CH ₃) ₂	2-CN	H	-(CH ₂) ₂ -OCH ₃	(+)-enantiomer	124-125	+5.5(c=0.9; CHCl ₃)
26	-CH(CH ₃) ₂	2-CN	H	-(CH ₂) ₂ -OCH ₃	(-)-enantiomer	122-123	-8.2(c=1.0; CHCl ₃)
27	H ₃ C-O-(CH ₂) ₂ -	2-F	3-CF ₃	-CH(CH ₃) ₂	racemate	140-142	
28	H ₃ C-O-(CH ₂) ₂ -	2-F	3-CF ₃	-CH(CH ₃) ₂	(+)-enantiomer		
29	H ₃ C-O-(CH ₂) ₂ -	2-F	3-CF ₃	-CH(CH ₃) ₂	(-)-enantiomer		

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Continuation of Table 1:

Ex. No.	R ¹	R ⁴	R ⁵	R ³	Racemate/ enantiomer	M.p. (°C)	[α] _D ²⁰
30	H ₃ C-O-(CH ₂) ₂ -	2-Cl	3-CN		racemate	119-120	
31	H ₃ C-O-(CH ₂) ₂ -	2-Cl	3-CN		(+)-enantiomer		
32	H ₃ C-O-(CH ₂) ₂ -	2-Cl	3-CN		(-)-enantiomer		
33	-C(CH ₃) ₃	H	3-CN	-(CH ₂) ₂ -OCH ₃	racemate	108-109	
34	-C(CH ₃) ₃	H	3-CN	-(CH ₂) ₂ -OCH ₃	(+)-enantiomer		
35	-C(CH ₃) ₃	H	3-CN	-(CH ₂) ₂ -OCH ₃	(-)-enantiomer		
36	H ₃ C-O-(CH ₂) ₂ -	2-F	3-CF ₃		racemate	105	
37	H ₃ C-O-(CH ₂) ₂ -	2-F	3-CF ₃		(+)-enantiomer		
38	H ₃ C-O-(CH ₂) ₂ -	2-F	3-CF ₃		(-)-enantiomer		

Continuation of Table 1:

Ex. No.	R ¹	R ⁴	R ⁵	R ³	Racemate/ enantiomer	M.p. (°C)	[α] _D ²⁰
39	H ₃ C-O-(CH ₂) ₂ -	2-F	3-CF ₃	-CH ₃	racemate	128	
40	H ₃ C-O-(CH ₂) ₂ -	2-F	3-CF ₃	-CH ₃	(+)-enantiomer		
41	H ₃ C-O-(CH ₂) ₂ -	2-F	3-CF ₃	-CH ₃	(-)-enantiomer		
42		H	3-CN	-(CH ₂) ₂ -OCH ₃	racemate	138-140	
43		H	3-CN	-(CH ₂) ₂ -OCH ₃	(+)-enantiomer	98-99	+21.8 (c=0.96; CHCl ₃)
44	-CH(CH ₃) ₂	2-F	H	-(CH ₂) ₂ -OCH ₃	(+)-enantiomer	oil	+21.9 (c=0.96; CHCl ₃)
45	-CH(CH ₃) ₂	2-F	H	-(CH ₂) ₂ -OCH ₃	(-)-enantiomer	oil	-23.5 (c=0.96; CHCl ₃)
46		2-CN	3-Cl	-(CH ₂) ₂ -OCH ₃	racemate	128-130	
47		2-CN	3-Cl	-(CH ₂) ₂ -OCH ₃	(+)-enantiomer		
48		2-CN	3-Cl	-(CH ₂) ₂ -OCH ₃	(-)-enantiomer		
49	H ₃ C-O-(CH ₂) ₂ -	2-Cl	5-CN	-CH(CH ₃) ₂	racemate	155-157	
50		H	3-CN	-(CH ₂) ₂ -OCH ₃	(-)-enantiomer	98-99	-24.2 (c=0.9, CHCl ₃)

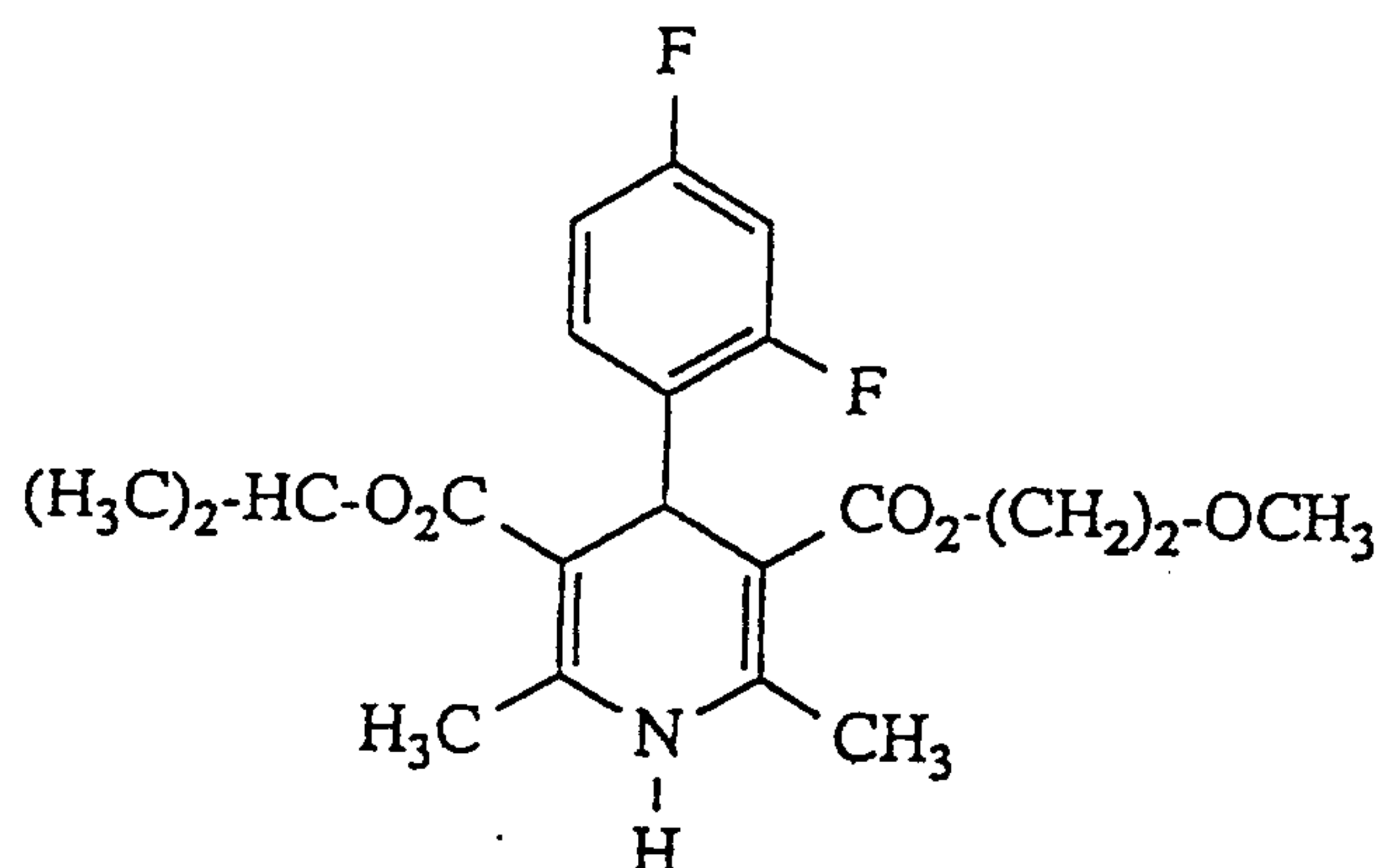
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Example 51

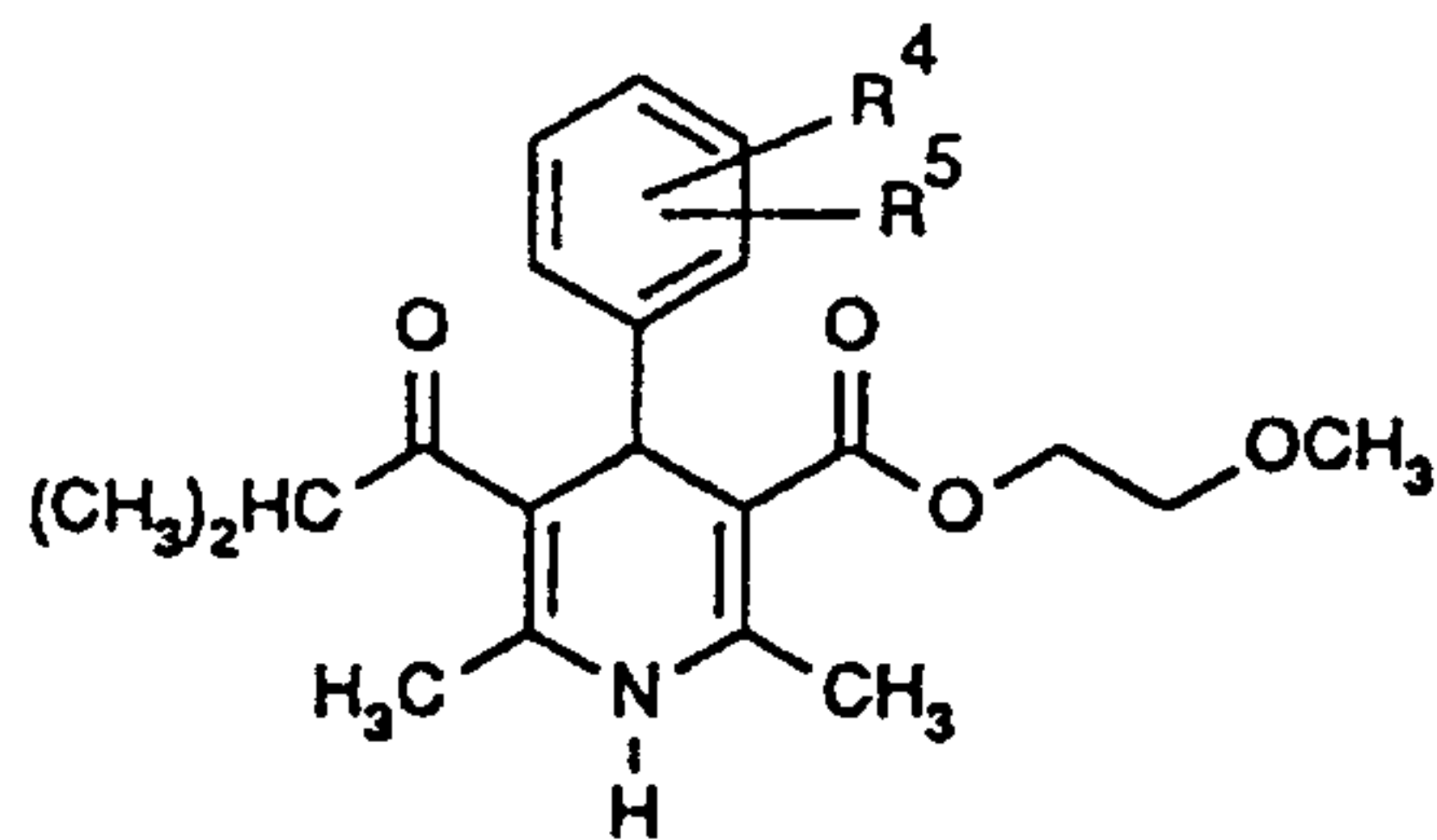
2-Methoxyethyl isopropyl 4-(2,4-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate



5.0 g (about 18 mmol) of the compound from Example II are
 5 heated to reflux overnight in 50 ml of isopropanol with
 2.5 g (18 mmol) of isopropyl 3-amino-2-butenate. After
 thin-layer chromatographic checking (SiO₂, toluene/ethyl
 acetate 5:1) shows complete conversion, the reaction
 mixture is concentrated, the residue is taken up with
 10 toluene, the solution is concentrated again and the
 residue is then purified by crystallization from a little
 methanol. 2.8 g (39%) of the target compound are
 obtained.

M.p.: 123-126°C

15 The compounds shown in Tables 2, 3, 4, 5, 6 and 7 are
 prepared in analogy to the procedure of Examples 1, 2 and
 51:

Table 2:

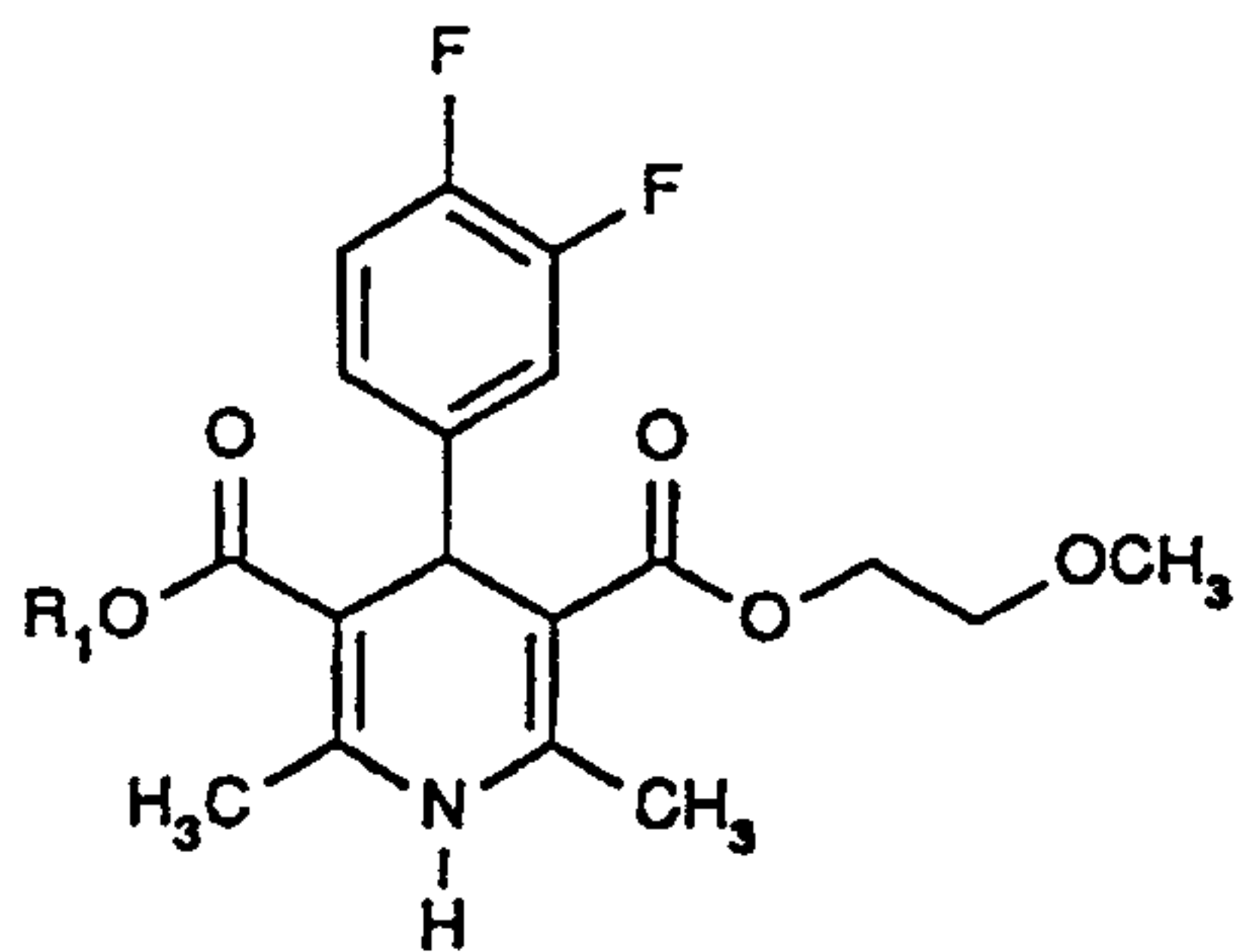
Ex. No.	R ⁴	R ⁵	M.p. [°C]	
52	3-F	H	90-93	
53	2-Cl	4-Cl	116-118	
5	54	3-Cl	4-Cl	55-60
55	3-Cl	5-Cl	100-102	
56	2-Cl	6-Cl	100	
57	2-F	5-Cl	100-101	
58	3-Cl	4-Cl	79-81	
10	59	2-CH ₃	3-F	136
60	2-C≡CH	3-Cl	146	
61	2-Cl	5-C≡CH	100-103	
62	2-C≡CH	4-F	82-85	

Continuation of Table 2:

	Ex. No.	R ⁴	R ⁵	M.p. [°C]/R _f *
	63	3-OCF ₃	H	45
	64	2-SCH ₃	5-Br	97-98
5	65	2-OCH ₃	3-F	136
	66	2-OCH ₃	6-F	112
	67	2-OCH ₃	5-F	104
	68	2-F	5-OCH ₃	0.35 ^{a)}
	69	3-Cl	H	143
10	70	2-OCH ₃	6-Cl	135
	71	2-Cl	5-CN	155-157
	72	2-OCH ₃	5-Cl	143
	73	2-F	5-F	oil

a) = cyclohexane : ethyl acetate 1:1

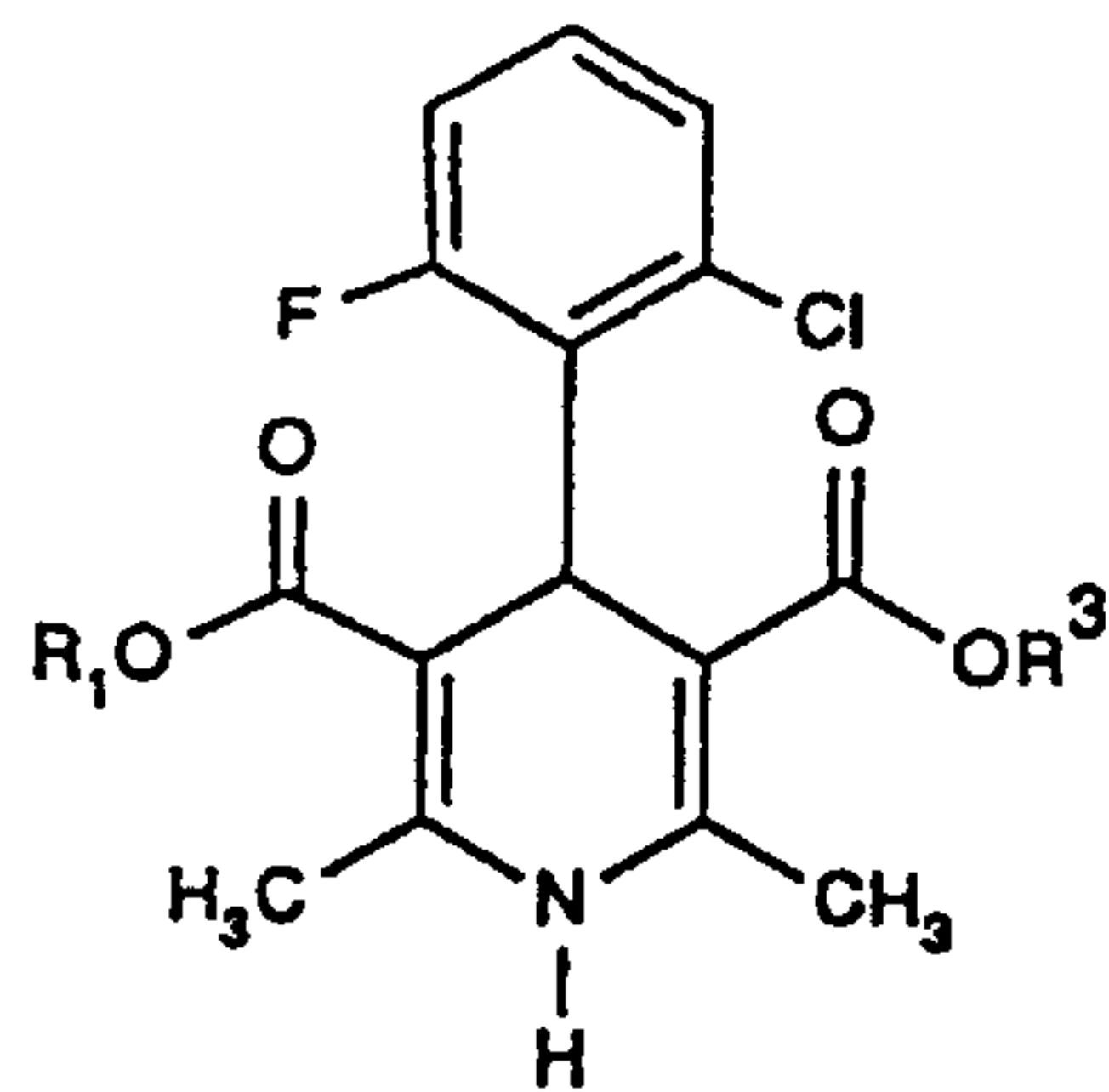
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Table 3:

Ex. No.	R ¹	M.p. [°C]/R _f *
74		0.15 ^{b)}
75		90
5 76		104
77		88

b) toluene : ethyl acetate 10:1

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Table 4:

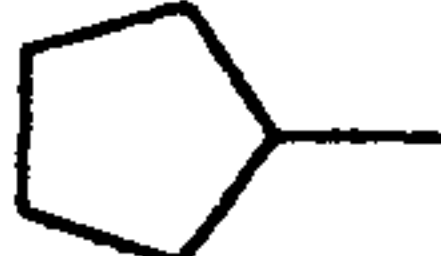
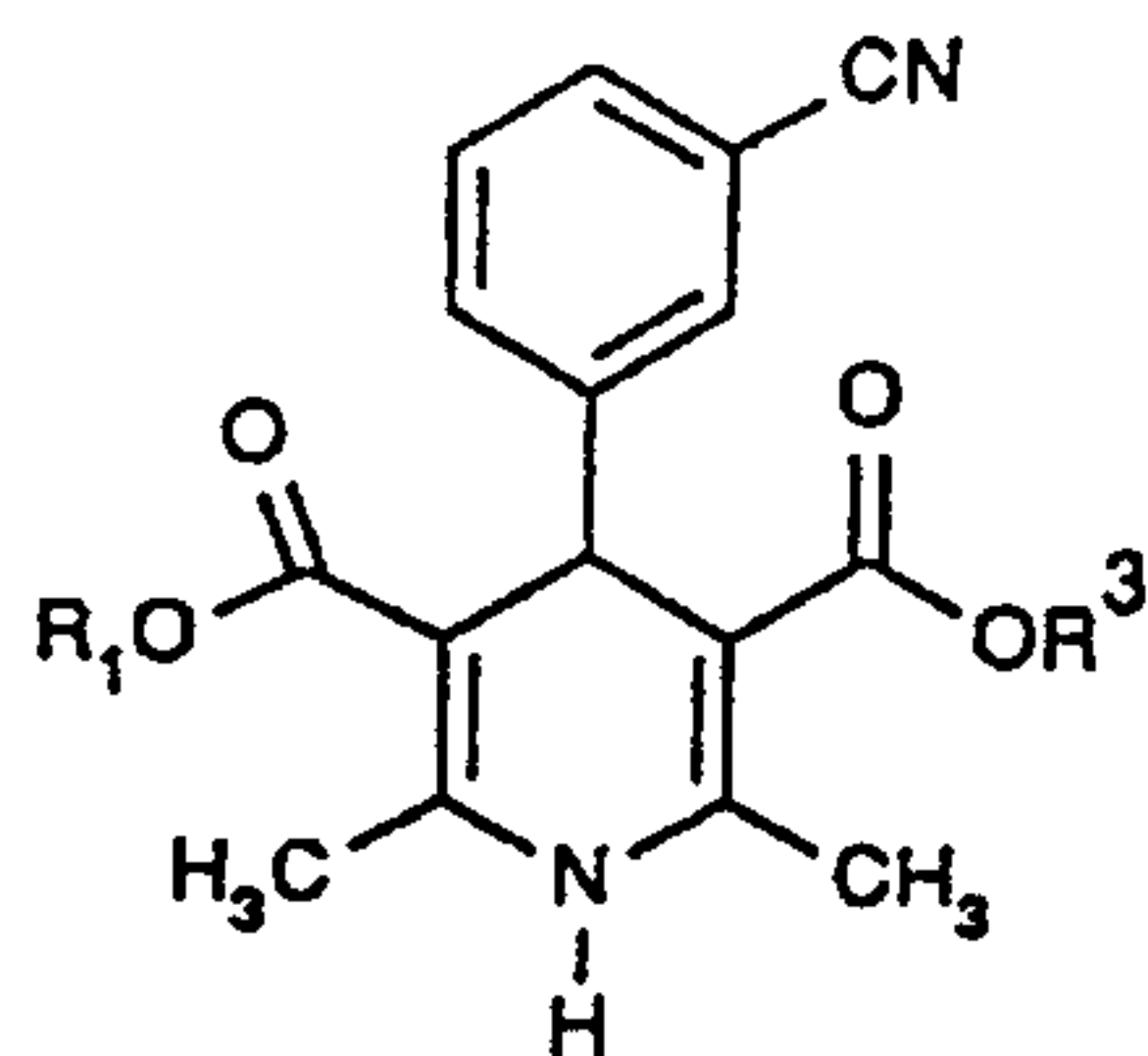
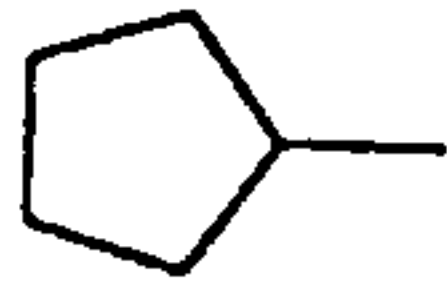

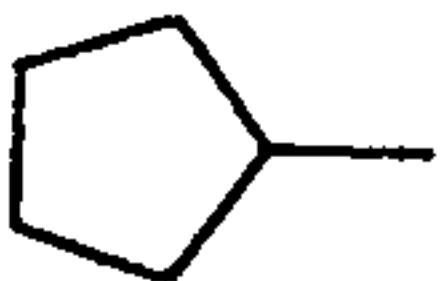

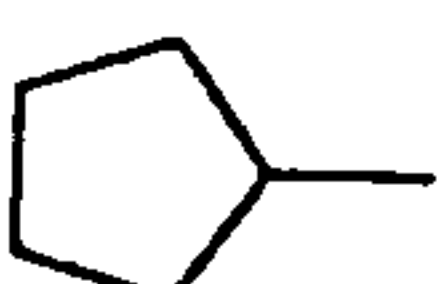

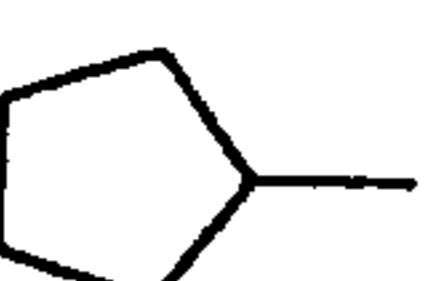

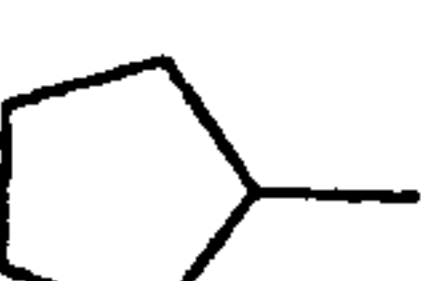

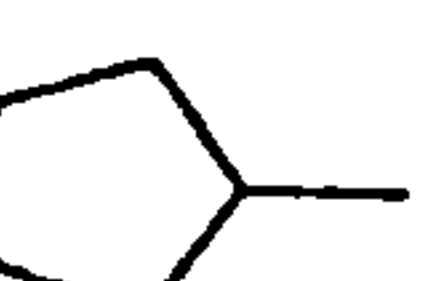

Ex. No.	R ¹	R ³	M.p. [°C]/R _f *
78	-CH(CH ₃) ₂	n-(CH ₂) ₃ CH ₃	112
79		n-(CH ₂) ₃ CH ₃	109

Table 5:

Ex. No.	R ¹	R ³	M.p. [°C] / R _f *
80	-CH ₃		131
81	-CH(CH ₃) ₂		138
5 82	-CH(CH ₃) ₂		103
83	-CH(CH ₃) ₂		99
84	-CH(CH ₃) ₂		67-70
85	-CH(CH ₃) ₂		103-104
86	-CH(CH ₃) ₂		0.24 ^{c)}
10 87	-CH(CH ₃) ₂		0.16 ^{c)}
88	-CH ₂ -CH(CH ₃) ₂		136

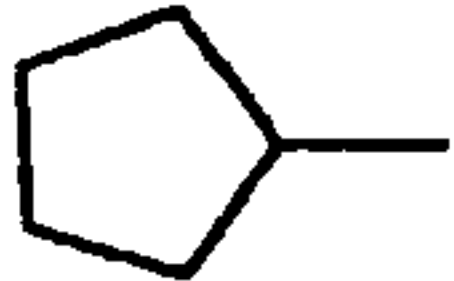
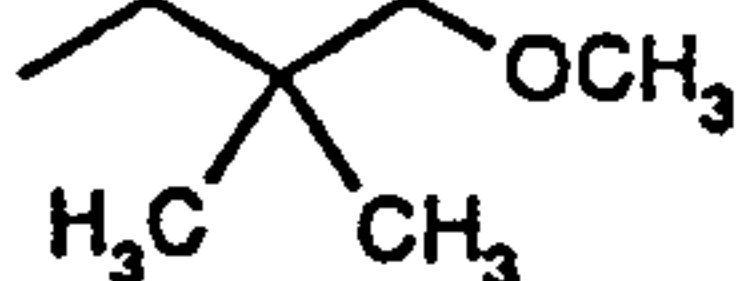
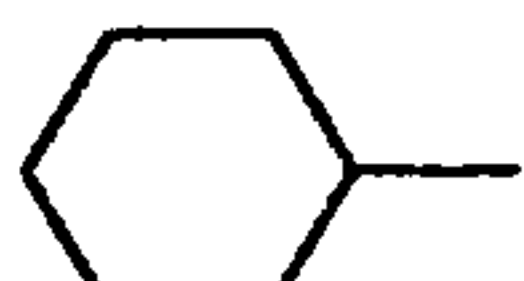

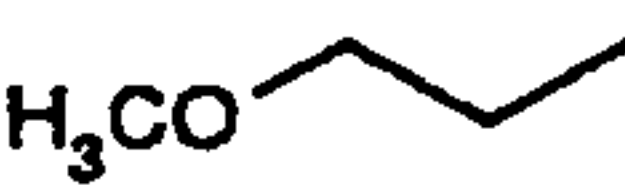

c) = toluene : ethyl acetate 3:1

Continuation of Table 5:

Ex. No.	R ¹	R ³	M.p. [°C]/R _f *
89			152-153
90			162-163
5 91			127-128
92			106-107
93			99
94			122-123





c) = toluene : ethyl acetate 3:1

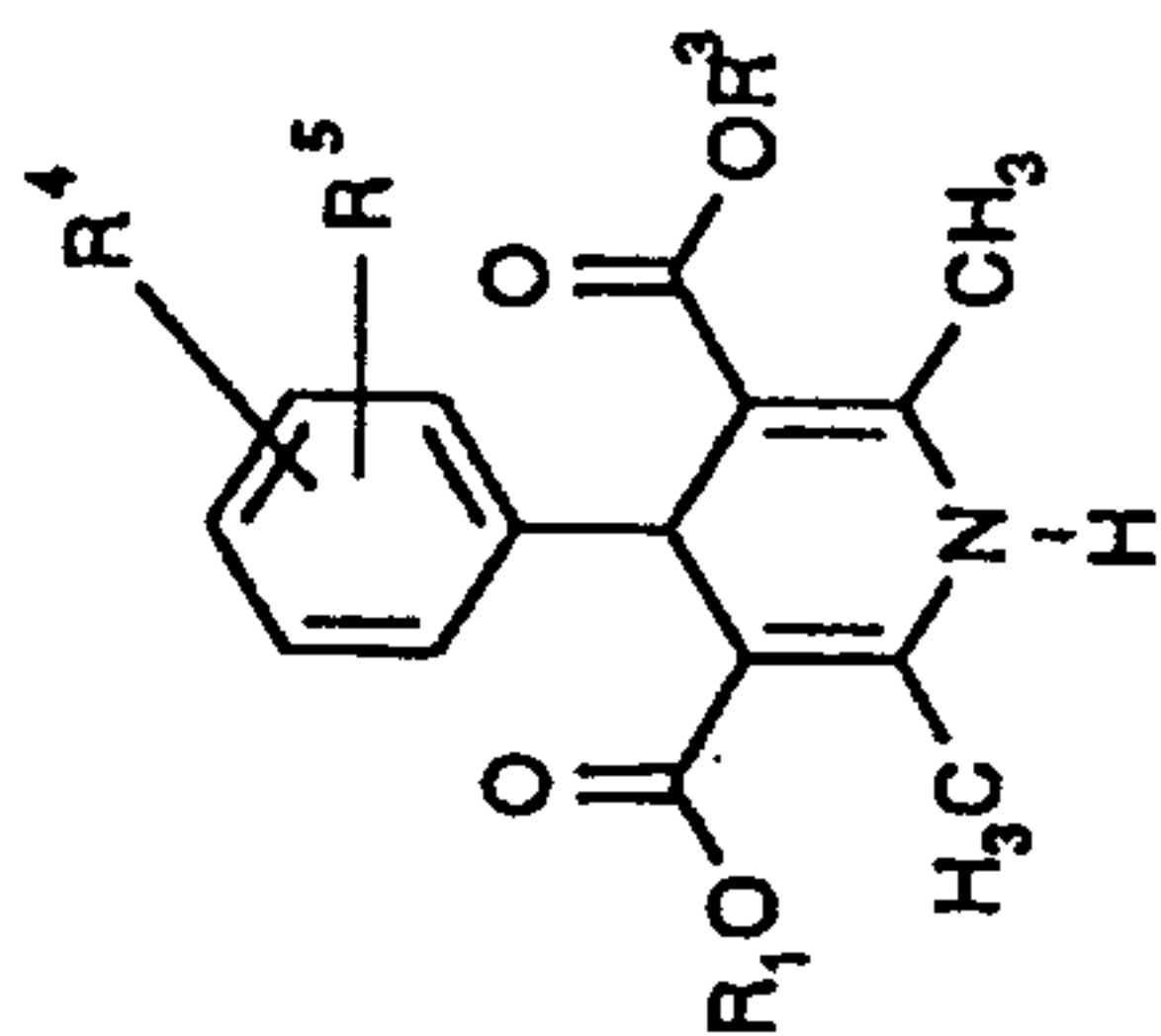
Continuation of Table 5:

Ex. No.	R ¹	R ³	M.p. [°C]/R _f *
95			0.56 ^{d)}
96			125-127
5 97			126

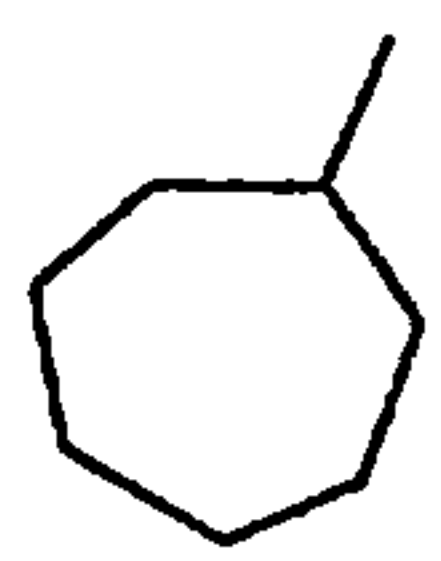
d) = toluene : ethyl acetate 1:1

Table 6:

Ex. No.	R ¹	R ⁴	R ⁵	R ³	M.p. (°C)
98	H ₃ CO	2-Cl	5-CN		176-177
99	CH ₃	2-CN	3-Cl		221-222
100	-C(CH ₃) ₃	2-F	6-F	-(CH ₂) ₂ OCH ₃	0.23 ^d
101		2-F	3-F	-(CH ₂) ₂ -O-CH(CH ₃) ₂	85-86.5
102		2-F	3-F	-(CH ₂) ₂ OH	141-142



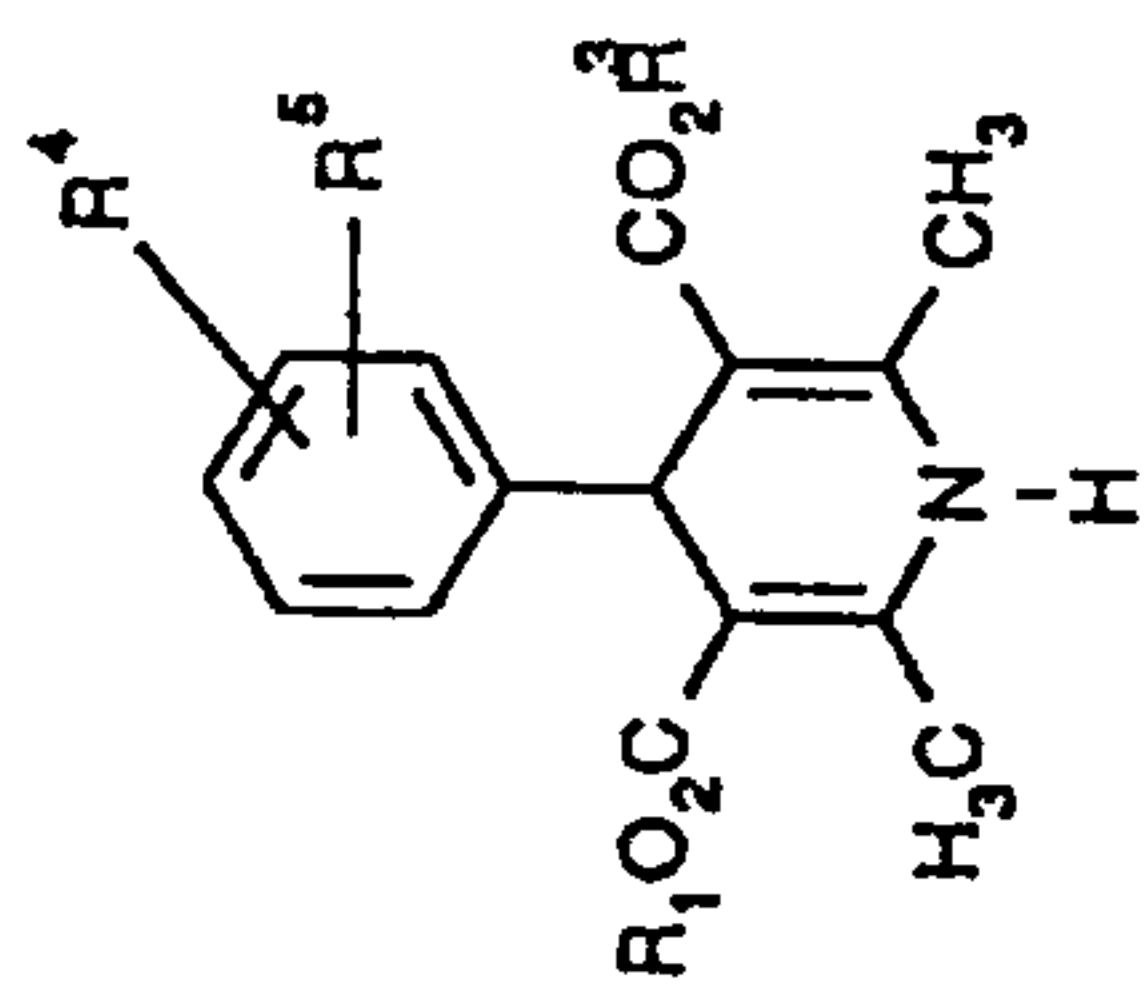
Continuation of Table 6:

Ex. No.	R ¹	R ⁴	R ⁵	R ³	M.p. (°C)	Preparation analogously to Example No.
103	-CH(CH ₃) ₂	2-F	3-F	-(CH ₂) ₂ -OH	139	2
104	-CH(CH ₃) ₂	2-F	3-F	-(CH ₂) ₂ -O-CH(CH ₃) ₂	96	2
105		2-F	5-F	-(CH ₂) ₂ OCH ₃	0.17°	2

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Table 7:

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Ex. No.	R ¹	R ⁴	R ⁵	R ³	Yield (% of theory)	R _f *	Preparation analogously to Example No.
106	-CH(CH ₃) ₂	2-F	5-F	$\begin{array}{c} \text{CH}_3 \\ \\ \text{-H}_2\text{C}-\text{C}-\text{OH} \\ \\ \text{CH}_3 \end{array}$	77	0.3 ^{d)}	2

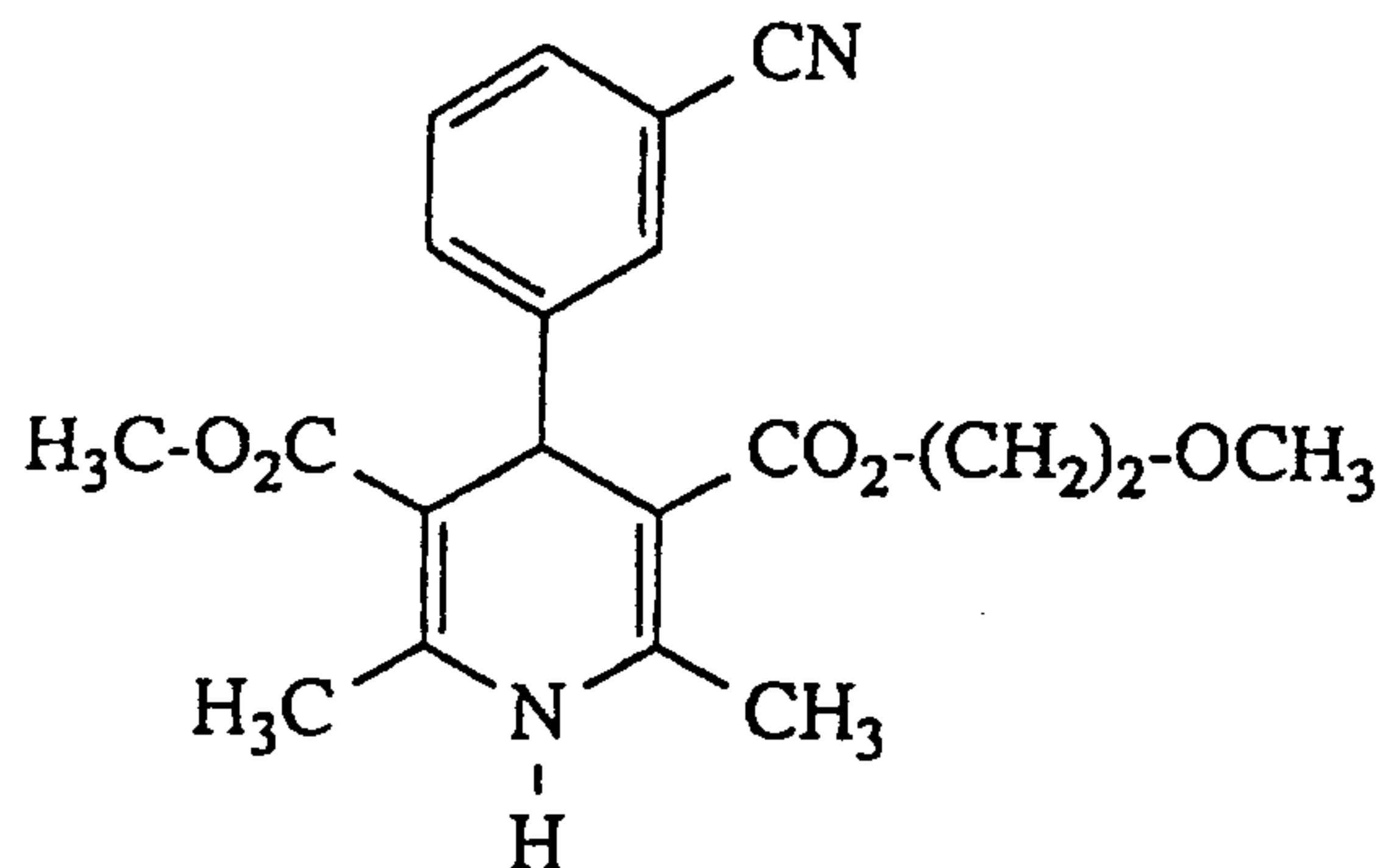
- 47 -

d) toluene/ethyl acetate 1:1

* Use of 1.1 mol equivalent each of alcohol (R³OH) and NaH suspension (relative to imidazolide) in THF

Example 107

Methyl 2-methoxyethyl (-)-4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate



3.6 g (10 mmol) of (-)-4-(3-cyanophenyl)-1,4-dihydro-3-
 5 (2-methoxy)ethoxycarbonyl-2,6-dimethylpyridine-5-
 carboxylic acid are stirred over molecular sieve (4 A)
 for 30 min in 40 ml of tetrahydrofuran. 1.6 g (10 mmol)
 of carbonyldiimidazole are then added and the mixture is
 heated at 60°C for 0.5 h, the molecular sieve is filtered
 10 off and the filtrate is concentrated. The residue is
 taken up in 40 ml of methanol and heated at 80°C for 6 h.
 Repeated chromatography on silica gel using toluene/ethyl
 acetate mixtures (1:0 to 3:1) yields 1.4 g of oily sub-
 stance which are crystallized by triturating with diethyl
 15 ether. 1.1 g (30%) of colourless crystals of m.p. 103-
 104°C are thus obtained.

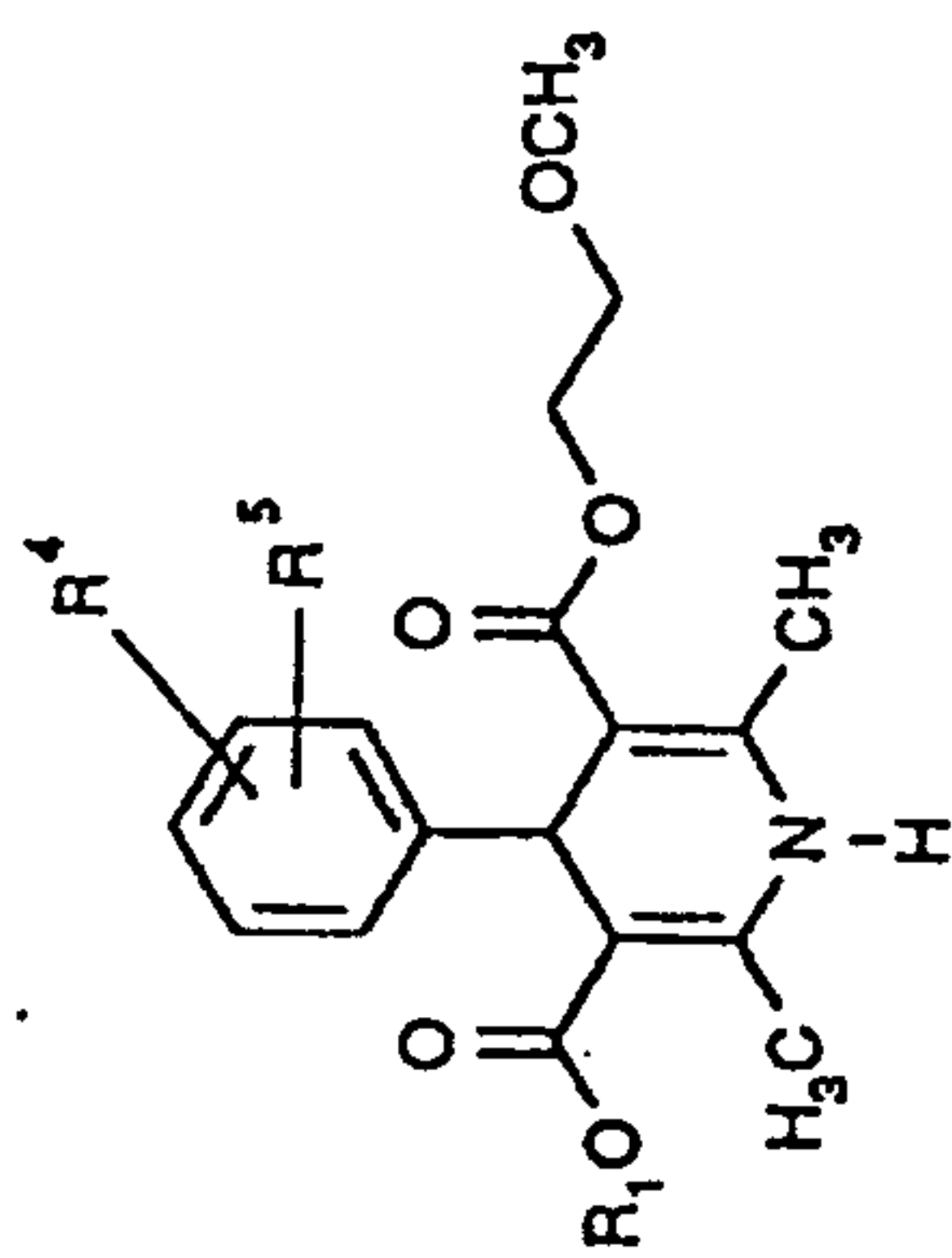
$[\alpha]_D^{20} = -7.0^\circ$ (c = 1.2; CHCl₃)

The compounds shown in Table 8 are obtained in analogy to
 Example 107 or by subjecting the racemic products to

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chromatographic separation into the enantiomerically pure target compounds (A* in the following) on chiral stationary phases (ChiralcelTM and ChiralpakTM, Daicel):

Table 8:

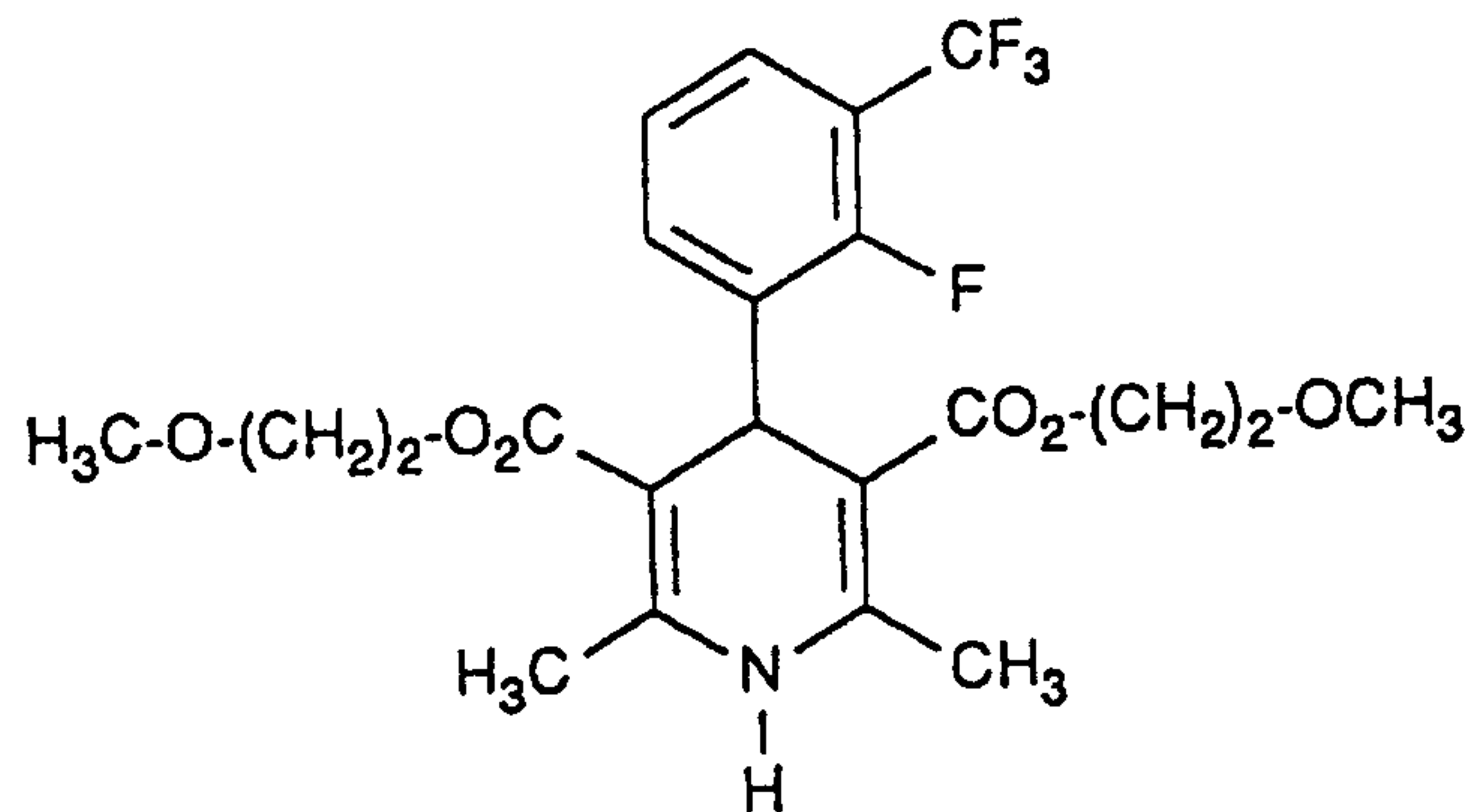


Ex. No.	R ¹	R ⁴	R ⁵	Enantiomer	M.p. (°C)	[α] _D ²⁰	Preparation analogously to Process/Example No.
108	-CH ₃	H	3-CN	(+)	103-104	+5.4 (c=1.0, CHCl ₃)	107
109	-CH(CH ₃) ₂	H	3-CN	(+)	127-128	+14 (c=1.0, CHCl ₃)	107
110	-CH(CH ₃) ₂	H	3-CN	(-)	127-128	-13.3 (c=1.2, CHCl ₃)	107
111	-CH(CH ₃) ₂	2-Cl	5-CN	(+)	+ 33	(c=1.0, CH ₃ OH)	A*
112	-CH(CH ₃) ₂	2-Cl	5-CN	(-)	-30	(c=0.3; CH ₃ OH)	A*

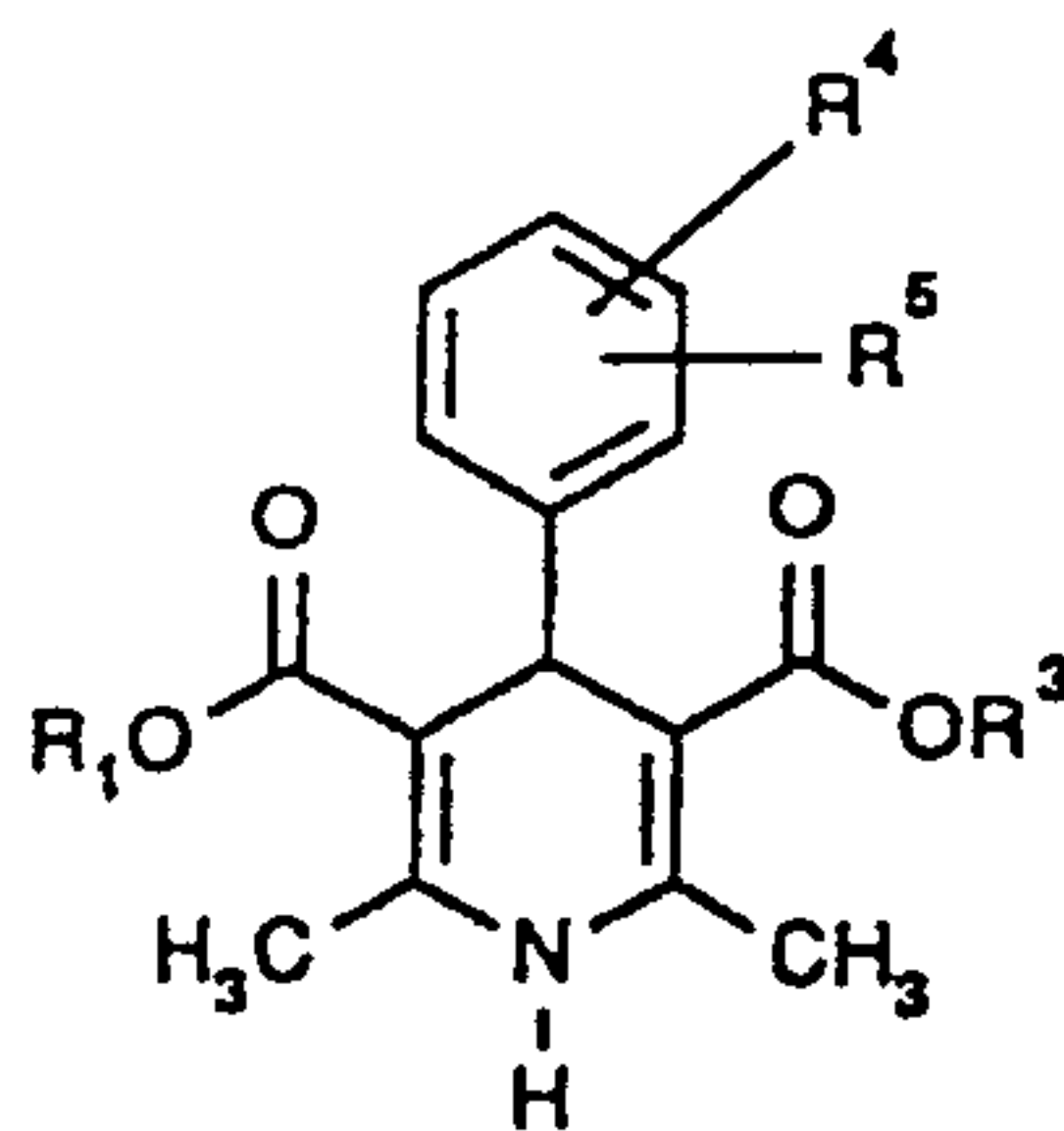
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Example 113

Bis-(2-methoxyethyl) 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate



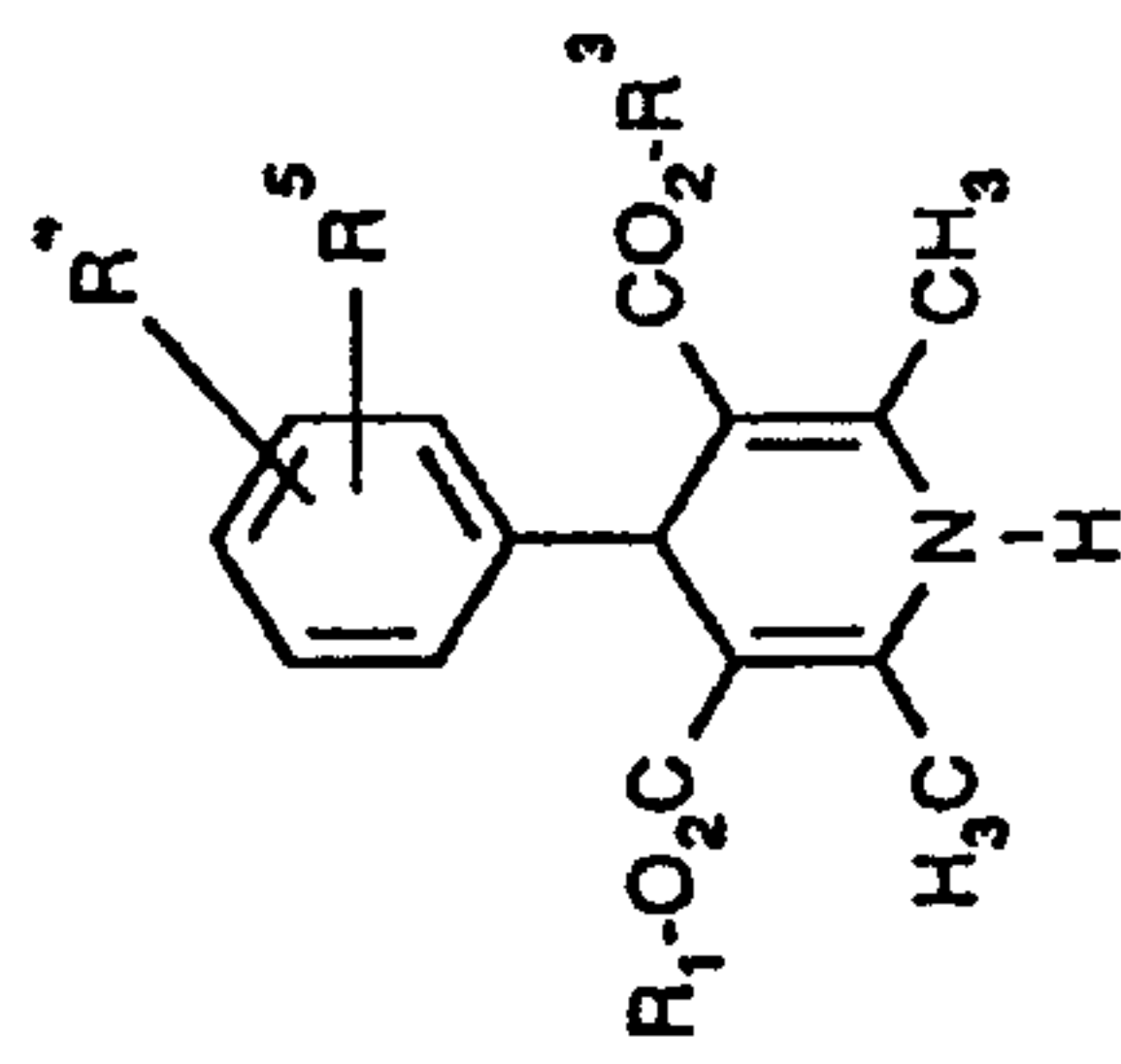
- 5 5 ml of a 25% strength ammonia solution and 5.0 g (31.2 mmol) of 2-methoxyethyl acetoacetate are added to a solution of 3.0 g (15.6 mmol) of 2-fluoro-3-trifluoromethylbenzaldehyde in 50 ml of dioxane and the mixture is heated to reflux until TLC checking (silica gel, toluene/ethyl acetate 5:1) indicates complete conversion. The mixture is concentrated, the residue is taken up twice in toluene and the solution is concentrated again. Crystallization from toluene yields 1.4 g (19%) of the target compound of melting point 148°C.
- 10
- 15 The examples shown in Table 9 are prepared in analogy to the procedure of Example 113:

Table 9:

Ex. No.	R ¹ and R ³	R ⁴	R ⁵	M.p. (°C)/R _f	
5	114	-(CH ₂) ₂ -OCH ₃	2-Cl	5-Cl	78
	115	-(CH ₂) ₂ -OCH ₃	2-F	5-F	130
	116	-(CH ₂) ₃ -OCH ₃	2-Cl	5-Cl	76
	117	-(CH ₂) ₃ -OCH ₃	2-F	5-F	97
	118		2-Cl	5-Cl	0.29 (cyclohexane/ethyl acetate 2:1)
10	119		2-F	5-F	106

The compounds shown in Table 10 are prepared from the corresponding imidazolide in analogy to the procedure of Example 107:

Table 10:

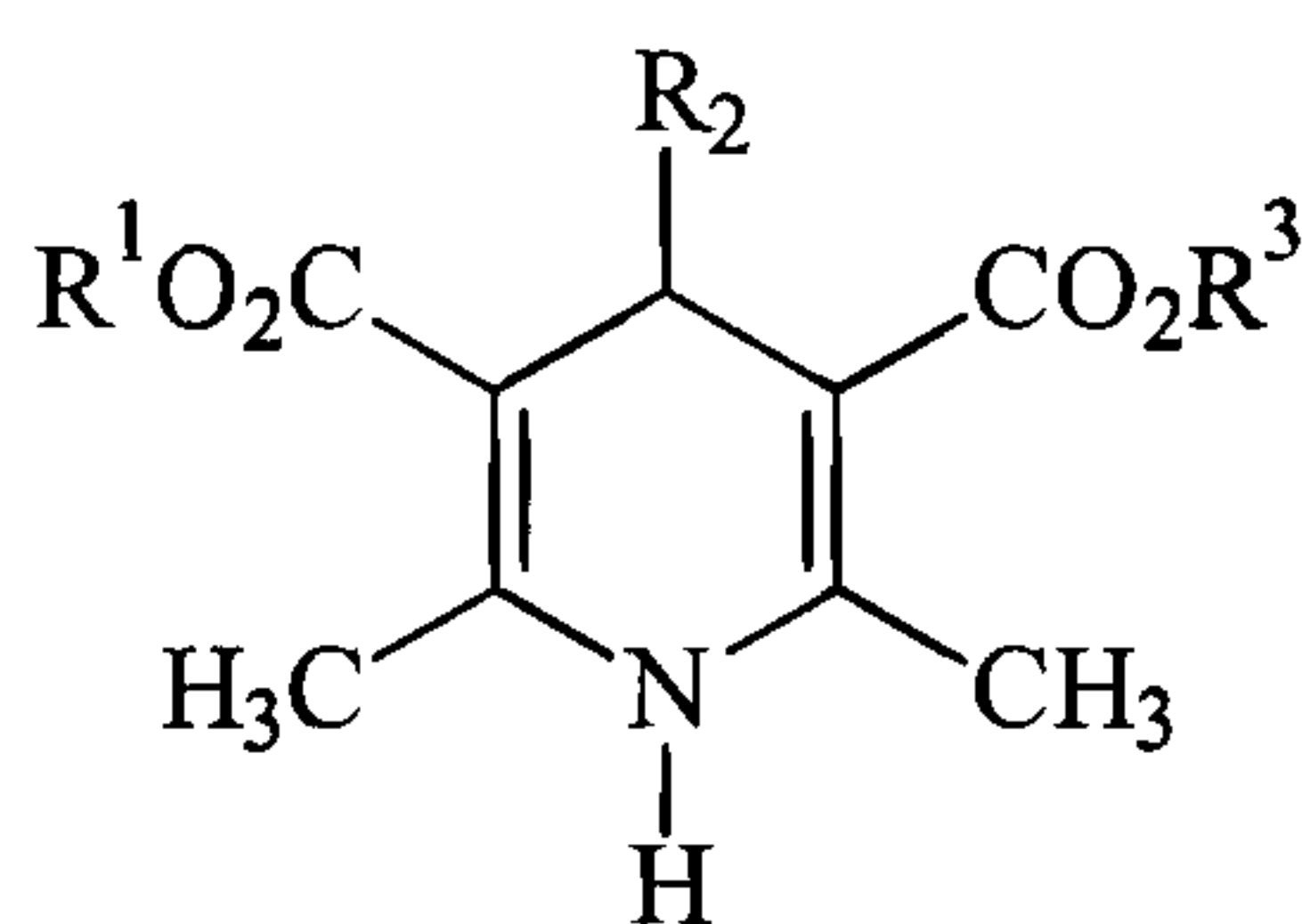


Ex. No.	R ¹	R ⁴	R ⁵	R ³	M.p. (°C) / R _f *
120	-CH ₃	2-F	3-F	--(CH ₂) ₂ -OCH ₃	123
121	H ₃ CO-(CH ₂) ₂	2-F	3-F	--(CH ₂) ₂ -OCH ₃	141-142
122	H ₃ CO-(CH ₂) ₂ -	2-Cl	H	--(CH ₂) ₂ -OCH ₃	126-127
123	-CH(CH ₃) ₂	2-Cl	H	--(CH ₂) ₂ -OCH ₃	105
124	-CH(CH ₃) ₂	2-Cl	H	--CH ₂ -C(CH ₃) ₂ -CH ₂ OH	128-129

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CLAIMS:

1. A composition for the treatment of a dementia or depression, comprising: (a) an inert non-toxic pharmaceutically suitable auxiliary or excipient; and (b) a phenyl-substituted 1,4-dihydropyridines of the general formula:



(I)

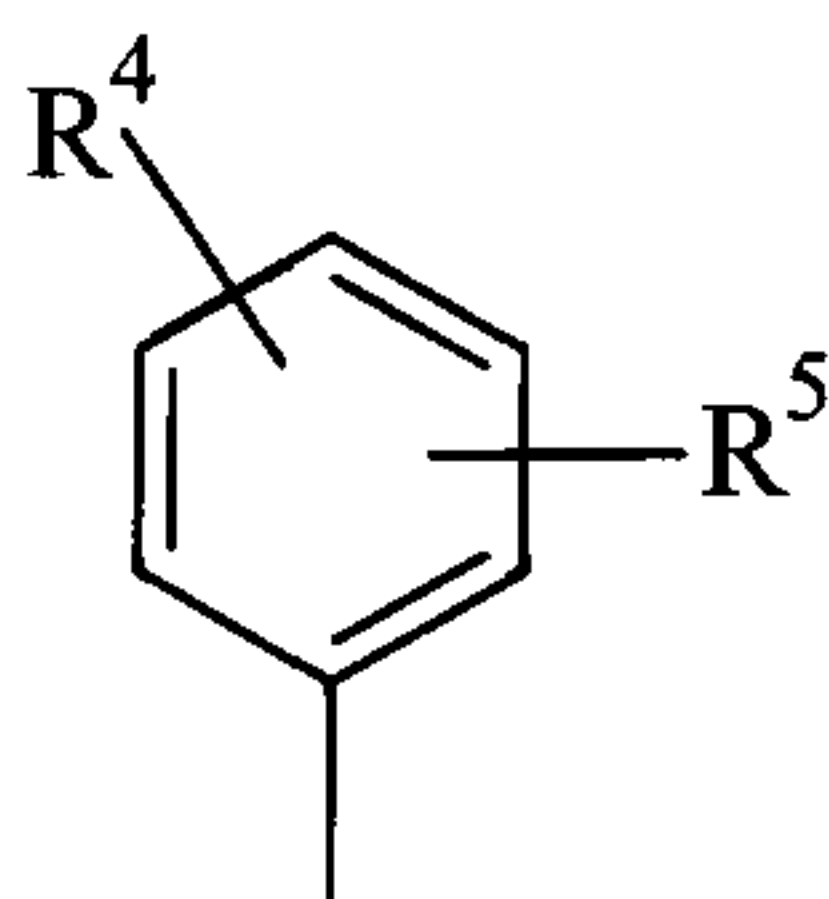
wherein:

R^1 and R^3 are identical or different and represent:

(i) straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by straight-chain or branched alkoxy having up to 6 carbon atoms or hydroxyl, or

(ii) cycloalkyl having 3 to 7 carbon atoms; and

R^2 represents the radical:



wherein:

R^4 and R^5 are identical or different and represent a halogen atom, cyano, ethinyl, trifluoromethoxy, methyl,

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methylthio, trifluoromethyl, straight-chain or branched alkoxy having up to 4 carbon atoms or a hydrogen atom, with the proviso that R⁴ and R⁵ are not a hydrogen atom simultaneously; or

5 a physiologically acceptable salt thereof.

2. The composition of claim 1, wherein:

R¹ and R³ are identical or different and represent:

(i) straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by straight-
10 chain or branched alkoxy having up to 5 carbon atoms or hydroxyl, or

(ii) cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl; and

R⁴ and R⁵ are identical or different and represent
15 a fluorine atom, a chlorine atom, a bromine atom, cyano, ethynyl, trifluoromethoxy, methyl, methylthio, trifluoromethyl, straight-chain or branched alkoxy having up to 3 carbon atoms, or a hydrogen atom, with the proviso that R⁴ and R⁵ are not a hydrogen atom simultaneously.

20 3. The composition of claim 2, wherein:

R¹ and R³ are identical or different and represent:

(i) straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by methoxy or hydroxyl, or

25 (ii) as defined in claim 2; and

R⁴ and R⁵ are as defined in claim 2.

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4. The composition of claim 1, wherein:

R^3 represents the radical: $-(CH_2)_n-OR^6$, wherein n represents a number from 2 to 4 and R^6 represents a hydrogen atom or alkyl having 1 to 4 C atoms;

5 R^1 is identical to or different from R^3 and represents cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl, or represent alkyl having up to 8 C atoms, which is optionally substituted by hydroxyl or alkoxy having 1 to 4 C atoms; and

10 R^3 and R^4 are as defined in claim 2.

5. The composition of claim 1, wherein:

R^1 and R^3 are as defined in claim 4; and

15 R^2 represents a phenyl radical which is substituted in the 2- and 3-positions by identical or different fluorine atom, chlorine atom, cyano or CF_3 substituents, 2,3-dichlorophenyl being excluded.

6. The composition of claim 4, wherein:

R^3 represents the radical $-CH_2-CH_2-OCH_3$; and

R^1 and R^2 are as defined in claim 4.

20 7. (\pm) Isopropyl 2-methoxyethyl 4-(2-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

8. (+) Isopropyl 2-methoxyethyl 4-(2-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a
25 physiologically acceptable salt thereof.

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9. (-) Isopropyl 2-methoxyethyl 4-(2-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.
10. (±) Isopropyl 2-methoxyethyl
5 4-(2,3-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.
11. (+) Isopropyl 2-methoxyethyl
10 4-(2,3-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.
12. (-) Isopropyl 2-methoxyethyl
15 4-(2,3-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.
13. (±) Isopropyl 2-methoxyethyl
4-(2,5-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.
- 20 14. (+) Isopropyl 2-methoxyethyl
4-(2,5-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.
15. (-) Isopropyl 2-methoxyethyl
25 4-(2,5-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.
16. (±) Isopropyl 2-methoxyethyl
4-(2,6-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-

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3,5-dicarboxylate, or a physiologically acceptable salt thereof.

17. (+) Isopropyl 2-methoxyethyl

4-(2,6-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-

5 3,5-dicarboxylate, or a physiologically acceptable salt thereof.

18. (-) Isopropyl 2-methoxyethyl

4-(2,6-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-

10 3,5-dicarboxylate, or a physiologically acceptable salt thereof.

19. (±) Isopropyl 2-methoxyethyl

4-(2,5-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-

3,5-dicarboxylate, or a physiologically acceptable salt thereof.

15 20. (+) Isopropyl 2-methoxyethyl

4-(2,5-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-

3,5-dicarboxylate, or a physiologically acceptable salt thereof.

21. (-) Isopropyl 2-methoxyethyl

20 4-(2,5-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-

3,5-dicarboxylate, or a physiologically acceptable salt thereof.

22. (±) Isopropyl 2-methoxyethyl 4-(2-chloro-

6-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-

25 3,5-dicarboxylate, or a physiologically acceptable salt thereof.

23. (+) Isopropyl 2-methoxyethyl 4-(2-chloro-

6-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-

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3,5-dicarboxylate, or a physiologically acceptable salt thereof.

24. (-) Isopropyl 2-methoxyethyl 4-(2-chloro-6-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-

5 3,5-dicarboxylate, or a physiologically acceptable salt thereof.

25. (±) Isopropyl 2-methoxyethyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-

10 3,5-dicarboxylate, or a physiologically acceptable salt thereof.

26. (+) Isopropyl 2-methoxyethyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-

3,5-dicarboxylate, or a physiologically acceptable salt thereof.

15 27. (-) Isopropyl 2-methoxyethyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-

3,5-dicarboxylate, or a physiologically acceptable salt thereof.

28. (±) Isopropyl 2-methoxyethyl 4-(3-chloro-

20 2-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

29. (+) Isopropyl 2-methoxyethyl 4-(3-chloro-2-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-

25 3,5-dicarboxylate, or a physiologically acceptable salt thereof.

30. (-) Isopropyl 2-methoxyethyl 4-(3-chloro-2-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-

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3,5-dicarboxylate, or a physiologically acceptable salt thereof.

31. (±) Isopropyl 2-methoxyethyl 4-(2-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a
5 physiologically acceptable salt thereof.

32. (+) Isopropyl 2-methoxyethyl 4-(2-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a
physiologically acceptable salt thereof.

33. (-) Isopropyl 2-methoxyethyl 4-(2-cyanophenyl)-
10 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a
physiologically acceptable salt thereof.

34. (±) tert-Butyl 2-methoxyethyl 4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a
physiologically acceptable salt thereof.

15 35. (+) tert-Butyl 2-methoxyethyl 4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a
physiologically acceptable salt thereof.

36. (-) tert-Butyl 2-methoxyethyl 4-(3-cyanophenyl)-
1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a
20 physiologically acceptable salt thereof.

37. (±) Cycloheptyl 2-methoxyethyl 4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a
physiologically acceptable salt thereof.

38. (+) Cycloheptyl 2-methoxyethyl 4-(3-cyanophenyl)-
25 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a
physiologically acceptable salt thereof.

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39. (-) Cycloheptyl 2-methoxyethyl 4-(3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

40. (±) Cyclopentyl 2-methoxyethyl 4-(2-chloro-3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

41. (+) Cyclopentyl 2-methoxyethyl 4-(2-chloro-3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

42. (-) Cyclopentyl 2-methoxyethyl 4-(2-chloro-3-cyanophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

43. (±) Cyclopentyl 2-methoxyethyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

44. (+) Cyclopentyl 2-methoxyethyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

45. (-) Cyclopentyl 2-methoxyethyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

46. (±) 2-Methoxyethyl methyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-

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3,5-dicarboxylate, or a physiologically acceptable salt thereof.

47. (+) 2-Methoxyethyl methyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

48. (-) 2-Methoxyethyl methyl 4-(2-fluoro-3-trifluoromethylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

49. (±) Cyclopentyl 2-methoxyethyl 4-(2-cyano-3-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

50. (+) Cyclopentyl 2-methoxyethyl 4-(2-cyano-3-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

51. (-) Cyclopentyl 2-methoxyethyl 4-(2-cyano-3-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, or a physiologically acceptable salt thereof.

52. A composition for the treatment of a dementia or depression, comprising: (a) an inert non-toxic pharmaceutically suitable auxiliary or excipient and (b) a compound as defined in any one of claims 7 to 51, or a physiologically acceptable salt thereof.

53. Use of a compound as defined in any one of claims 1 to 51, or a physiologically acceptable salt

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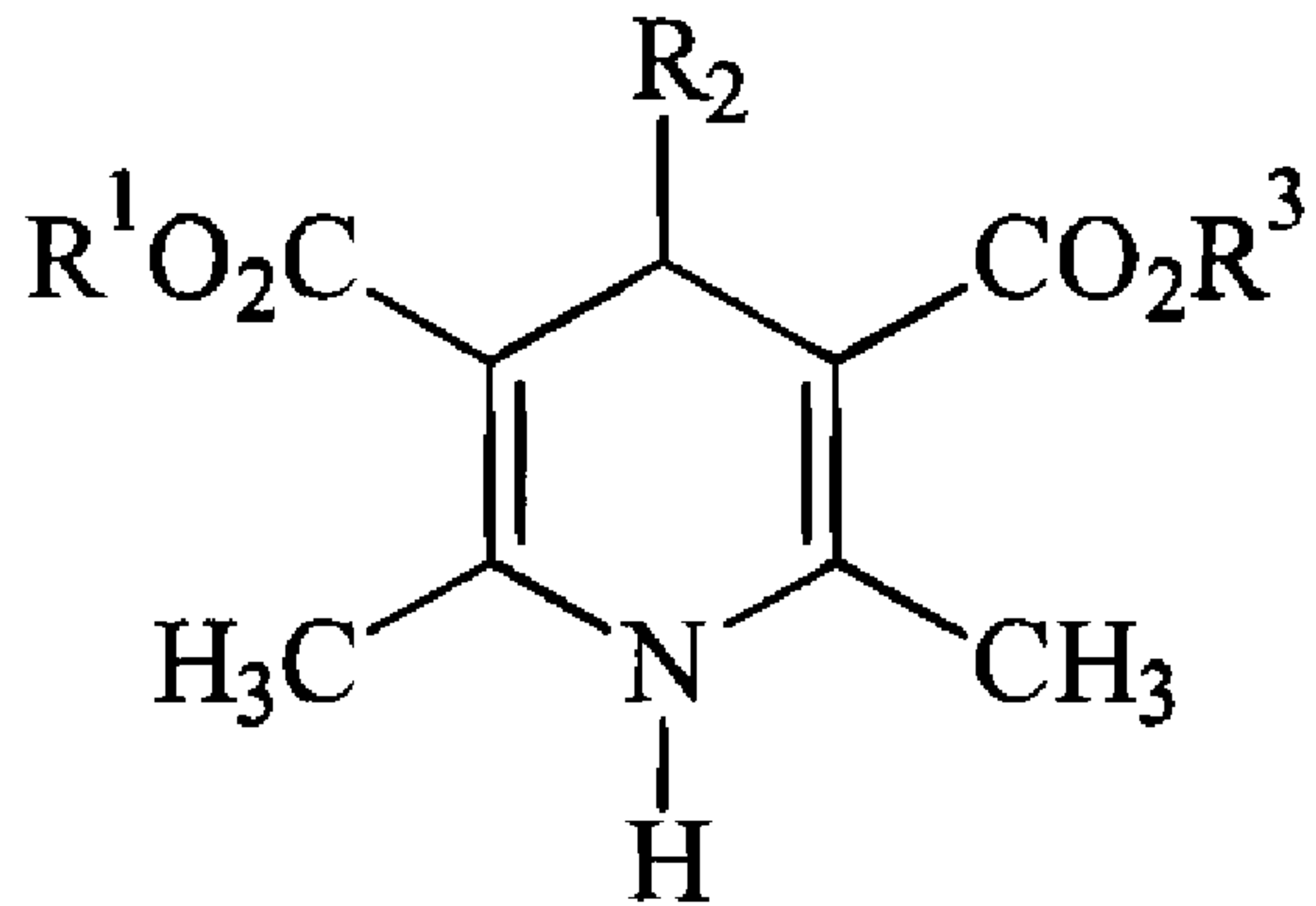
thereof, or a composition according to any one of claims 1 to 6 and 52, for treating a dementia or depression.

54. Use of a compound as defined in any one of claims 1 to 51, or a physiologically acceptable salt thereof, or a composition according to any one of claims 1 to 6 and 52, for preparing a medicament for treating a dementia or depression.

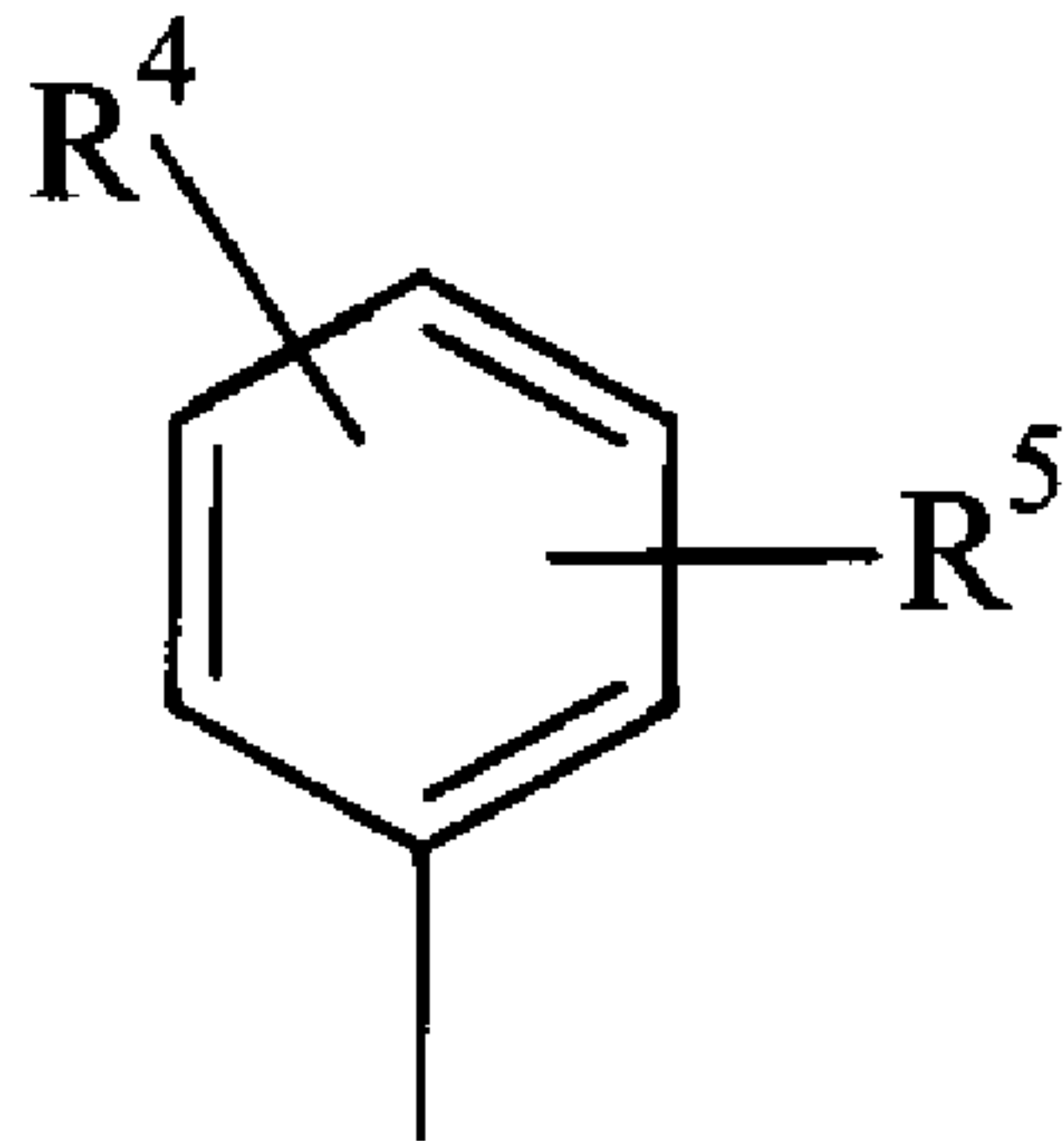
55. A commercial package comprising, a compound as defined in any one of claims 1 to 51, or a physiologically acceptable salt thereof, or a composition according to any one of claims 1 to 6 and 52, and associated therewith instructions for the use thereof for treating a dementia or depression.

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PATENT AGENTS



(I)



(II)