

SPECIFICATION

Nicotinic and 2-(4-chlorophenoxy)-2-methylpropanoic acid derivatives

It is known that atherosclerosis is caused by the accumulation of lipids in the aorta and the coronary, cerebral and peripheral arteries. This results in an increased risk of thromboses or artery obstruction. Dependent on the nature of the increased plasma protein level, either the elevated cholesterol or triglyceride level is of importance. Cholesterol levels exceeding 200—300 mg/100 ml serum and triglyceride levels of 45—66 mg/100 ml serum may be considered as extremely elevated.

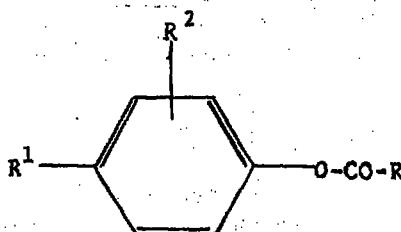
The two most widely known classes of active substances used in the treatment of hyperlipidemias comprise clofibrate (2-(4-chlorophenoxy)-2-methylpropionic acid ethyl ester) and its salts, and nicotinic acid, which influence the serum lipids by different modes of action. While in test animals, doses of 30—500 mg/kg body weight mainly effect a lowering of the cholesterol level in addition to a slight reduction of the free fatty acids, nicotinyl alcohol and nicotinic acid and its salts bring about a great reduction of the free fatty acids even at low dosages of between 0.5 and 430 mg/kg body weight. However, none of these substances has a significant reducing influence on triglycerides. Besides, owing to its unpleasant and known side effects (flush, headache, nausea, vomiting), nicotinic acid can only be used conditionally, so that therapy often has to be discontinued prematurely.

It is known that clofibrate effects a fall of the initial values of triglycerides (TG) and pre- β -lipoproteins by up to 50%, this degree of lowering not being achieved in the case of cholesterol. In about 20% of cases, the cholesterol (CH) in the β - and α -lipoproteins is even further increased. Nicotinic acid and its derivatives, on the contrary, act predominantly on elevated cholesterol values and free fatty acids, whereas the decrease of the endogenous resynthesis of the triglycerides via inhibition of tissue lipolysis is only a secondary effect (cf. Verhandlungen der Deutschen Gesellschaft für innere Medizin, 82. Kongress, gehalten zu Wiesbaden vom 25. bis 29.4. 1976, Teil I, J. F. Bergmann Verlag München).

French Patent Specification No. 6,975 disclosed clofibric acid nicotinyl ester as an effective lipid- and cholesterol-lowering component. This compound, although being predominantly used in the form of the nicotinate, can only be administered in low dosage owing to the high portion of its pyridine component and the resulting side effects. It is, therefore, of only little therapeutic benefit.

All the aforementioned substances effect a significant reduction of only one of the lipid components, e.g., the triglycerides, while the other lipid components are not, or only slightly, influenced, therapeutically. Such a therapeutic effect can only be achieved by a dose increase.

We have now discovered novel compounds which, even when administered in low dosages, can have a strong effect on both serum TG and CH levels. The novel compounds of this invention are nicotinic acid or 2-(4-chlorophenoxy)-2-methylpropanoic acid esters of the formula



wherein R is 3-pyridinyl or 2-(4-chlorophenoxy)-2-methyl-ethyl;

R¹ is hydrogen, C₅₋₁₄ cycloalkyl, (C₅₋₁₄ cycloalkyl)methyl, (C₅₋₁₄ cycloalkyl)carbonyl, (C₅₋₁₄ cycloalkyl)acetyl (preferably, the cycloalkyl group is monocyclic or 1-adamantyl), cumyl, *p*-chlorobenzoyl, piperidino or 2-pyrimidinyl; and

R² is hydrogen, —(CH₂)₄—, halogen, C₁₋₈ alkyl, cycloalkyl, methoxy, ethoxy, trifluoromethyl or nitro;

provided that R² is C₁₋₈ cycloalkyl or —(CH₂)₄— when R¹ is hydrogen;

and include the pharmaceutically acceptable acid addition salts, which may be formed with organic or inorganic acids, thereof.

The compounds of the invention may be prepared by conventional esterification procedures. For example equimolar amounts of nicotinic acid or clofibric acid and the appropriately R¹/R²-substituted phenol may be reacted together, often in the presence of an equimolar amount of an acid-binding substance such as pyridine.

A pharmaceutical composition according to the invention comprises an ester of the invention in association with a physiologically acceptable excipient. Such compositions may be administered orally or parenterally.

Solid preparations for oral administration include capsules, tablets, pills, powders and granulates. In such solid preparations, the active substance is mixed with at least one inert diluent such as sugar cane, lactose or starch. Additional substances such as lubricants or buffers may also be added.

The tablets or pills may be enterically coated.

Liquids for oral application include emulsions, solutions and suspensions containing the commonly used inert diluents such as water. Additionally, such liquid compositions may contain wetting, emulsifying and dispersing agents as well as sweeteners, flavourants and fragrances.

Preparations for parenteral application include sterile, aqueous or non-aqueous solutions, suspensions or emulsions. Substances known for this form of presentation are used as carrier material. 5

Depending on the mode of application and duration of treatment, the dosage of the active substances in the preparation may vary.

The following Examples illustrate how compounds of this invention may be prepared. The compounds of Examples 1 to 7 are preferred compounds of the invention, in free base or 10 pharmaceutically acceptable acid addition salt form, e.g. the compound of Example 1 and its hydrochloride salt. 10

EXAMPLE 1

Preparation of *p*-cyclohexylphenyl nicotinate

17.6 g (100 mmol) of cyclohexylphenol and 19 g (106 mmol) of nicotinic acid chloride 15 hydrochloride were mixed with 250 ml of dry pyridine and kept at 40°C for 4 hours. Subsequently, the mixture was cooled in an ice bath, and water added in portions. After addition of 10 ml of water, a clear solution was obtained. Water (50 ml) was admixed until strong turbidity appeared. After stirring the mixture for a longer period of time the product crystallized in the ice bath. The precipitate was 20 sucked off, freed from pyridine by washing with water and dried. A second fraction was obtained from the filtrate by further adding water (60 ml). 20

Yield: 70% of the theoretical value.

MP: 103°C

		Analysis	
		calculated	found
25	C	76.86	76.83
	H	6.76	6.76
	N	4.98	5.05

EXAMPLE 2

Preparation of *p*-(1-adamantyl)phenyl nicotinate

11.4 g (50 mmol) of *p*-(1-adamantyl)phenol and 10 g (56 mmol) of nicotinic acid chloride 30 hydrochloride were mixed with 150 ml of dry pyridine and kept at 45°C for 4 hours. By adding 40 ml of water and stirring in an ice bath, the product formed a precipitate which was sucked off, washed with water and dried. 30

Yield: 78% of the theoretical value.

MP.: 199°C

		Analysis	
		calculated	found
35	C	79.27	78.01
	H	6.90	6.82
	N	4.20	4.50

EXAMPLE 3

40 Preparation of 2-(*p*-chlorophenoxy)isobutyric acid *p*-(1-adamantylacetyl)phenyl ester 40
6.75 g (25 mmol) of *p*-(1-adamantylacetyl)phenol and 6 g (25.7 mmol) of 2-(*p*-chlorophenoxy)isobutyric acid chloride were mixed with 60 ml of dry pyridine and kept at 40°C for 4 hours. After adding 40 ml of water, a crystalline product was obtained which was sucked off, washed with water and dried.

45 Yield: 77% of the theoretical value. MP.: 114°C 45

		Analysis	
		calculated	found
	C	72.03	72.12
	H	6.64	6.61

EXAMPLE 4Preparation of *p*-cyclododecylphenyl nicotinate

- 8 g (308 mmol) of *p*-cyclododecylphenol and 5.9 g (33.2 mmol) of nicotinic acid chloride hydrochloride were mixed with 140 ml of dry pyridine and kept at 30°C for 15 hours. Subsequently, 42 ml of water were added slowly drop by drop, and the mixture cooled to 0°C. The crystallized precipitate was sucked off, freed from pyridine by washing with water and dried.

Yield: 85% of the theoretical value. M.P.: 98°C

		Analysis	
		calculated	found
10	C	78.91	79.01
	H	8.50	8.54

EXAMPLE 5Preparation of *p*-(cyclohexylacetyl)phenyl nicotinate

- 11 g (50 mmol) of *p*-cyclohexylacetylphenol and 9.6 g (54 mmol) of nicotinic acid chloride hydrochloride were mixed with 160 ml of dry pyridine and stirred for 8 hours at 40°C. Subsequently, water (86 ml) was added drop by drop until the solution was turbid. The solution was placed in the ice bath, the precipitate sucked off, freed from pyridine by washing with water and dried.

Yield: 55% of the theoretical value. MP.: 103°C

		Analysis	
		calculated	found
20	C	74.30	74.07
	H	6.50	6.51

EXAMPLE 6Preparation of *o*-cyclohexylphenyl nicotinate hydrochloride

- 15 g (85 mmol) of *o*-cyclohexylphenol and 16.5 g (93 mmol) of nicotinic acid chloride hydrochloride were mixed with 200 ml of dry pyridine and stirred for 24 hours at 30°C. After cooling, precipitated pyridine hydrochloride was sucked off and 300 ml of water added. The precipitated raw product was washed with two 200 ml portions of water, dissolved in alcohol and reduced by means of a rotary evaporator. The remaining viscous oil was dissolved in 500 ml of dry ether and hydrochlorinated with HCl gas. Subsequently, the mixture was filtered, washed with ether and dried.

Yield: 52% of the theoretical value. MP.: 151—2°C

		Analysis	
		calculated	found
35	C	68.03	68.11
	H	6.29	6.30
	Cl	11.18	11.20

EXAMPLE 7

Preparation of 5,6,7,8-tetrahydro-1-naphthyl-nicotinate

- 7 g (47 mmol) of 5,6,7,8-tetrahydro-1-naphthol and 9 g (50 mmol) of nicotinic acid chloride hydrochloride were mixed with 130 ml of dry pyridine and stirred for 24 hours at 30°C. After cooling, precipitated pyridine hydrochloride was sucked off, and the filtrate mixed with 300 ml of water. The crude precipitate was washed with two 200 ml portions of water and recrystallized from methanol.

15

Yield: 65% of the theoretical value. MP.: 86°C

	Analysis calculated	found
C	75.88	75.81
H	5.93	6.07

EXAMPLE 8

In a similar manner, *p*-cumylphenyl nicotinate was prepared.

EXAMPLE 9

In a similar manner, *p*-(*p*-chlorobenzoyl)phenyl nicotinate was prepared.

10 Toxicity tests have been conducted on the compounds of Examples 1 and 2 and on, as standards, 10
clofibrate (A) and nicotinic acid (B). The results are given in Table I.

TABLE I

Compound	LD ₅₀ (mouse) (mg/kg)	Human daily dose (mg)	Therapeutic Index
1	2200	300	0.13
2	3200	300	0.093
A	1500	1500	1.0
B	4000	3000	0.75

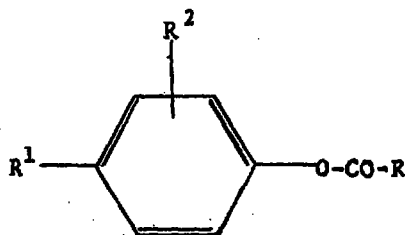
15 Additionally, experiments on female Wistar rats have been conducted. For a period of three weeks, 15
the animals received a special diet with a very high fat content. Starting from the second week, half the
rats were treated with 100 mg/kg body weight of an active compound selected from those of Examples
1, 2, 3, 8 and 9 and the standards A and B. After the third week, blood samples were taken 18 hours
after the administration of the last dose. Triglyceride and cholesterol concentrations (determined by the
Boehringer enzymatic test) were compared with those of the untreated animals. The results are shown
in Table II.

TABLE II

Compound	% reduction of cholesterol	% reduction of triglycerides
1	45	19
2	28	47
3	27	35
8	24	1
9	29	—
A	—	8
B	7	—

CLAIMS

1. An ester of the formula



wherein R is 3-pyridinyl or 2-(4-chlorophenoxy)-2-methyl-ethyl;

- 5 R¹ is hydrogen, C₅₋₁₄ cycloalkyl, (C₅₋₁₄ cycloalkyl)methyl, (C₅₋₁₄ cycloalkyl)carbonyl, (C₅₋₁₄ cycloalkyl)acetyl, cumyl, *p*-chlorobenzoyl, piperidino or 2-pyrimidinyl; and
 R² is hydrogen, —(CH₂)₄—, halogen, C₁₋₆ alkyl, cycloalkyl, methoxy, ethoxy, trifluoromethyl or
 nitro;
 provided that R² is C₁₋₆ cycloalkyl or —(CH₂)₄— when R¹ is hydrogen;
 or a pharmaceutically acceptable acid addition salt thereof.
- 10 2. A compound as claimed in claim 1, wherein any cycloalkyl group in R¹ is monocyclic or 1-adamantyl.
3. *p*-Cyclohexylphenyl nicotinate or a pharmaceutically acceptable acid addition salt thereof.
4. *p*-Cyclohexylphenyl nicotinate.
- 15 5. *p*-Cyclohexylphenyl nicotinate hydrochloride.
6. *p*-(1-Adamantyl)phenyl nicotinate or a pharmaceutically acceptable acid addition salt thereof.
7. 2-(4-Chlorophenoxy)-2-methylpropanoic acid 4-(1-adamantylacetyl)phenyl ester or a
 pharmaceutically acceptable salt thereof.
8. *p*-Cyclododecylphenyl nicotinate or a pharmaceutically acceptable acid addition salt thereof.
- 20 9. *p*-(Cyclohexylacetyl)phenyl nicotinate or a pharmaceutically acceptable acid addition salt
 thereof.
10. *o*-Cyclohexylphenyl nicotinate or a pharmaceutically acceptable acid addition salt thereof.
11. *o*-Cyclohexylphenyl nicotinate hydrochloride.
12. 5,6,7,8-Tetrahydro-1-naphthyl nicotinate or a pharmaceutically acceptable acid addition salt
- 25 thereof.
13. A compound as claimed in claim 1, substantially as described in any of the Examples.
14. A pharmaceutical composition comprising a compound as claimed in any preceding claim in
 association with a physiologically acceptable excipient.

