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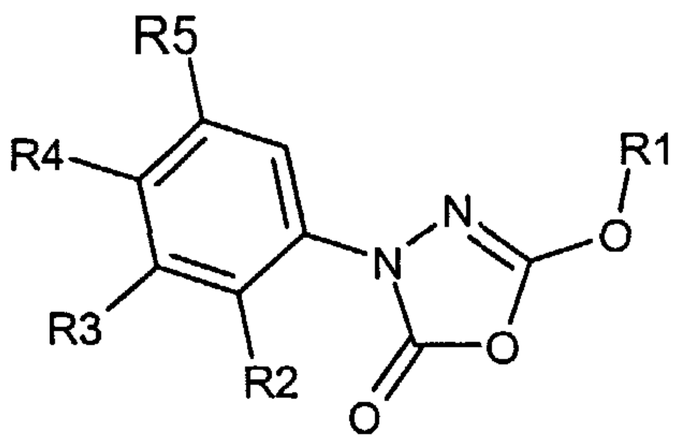
(54) Titre : 3-PHENYL-5-ALCOXY-1,3,4-OXDIAZOL-2-ONES SUBSTITUES, AINSI QUE LEUR PRODUCTION ET LEUR UTILISATION DANS DES MEDICAMENTS

(54) Title: SUBSTITUTED 3-PHENYL-5-ALKOXY-1,3,4-OXADIAZOL-2-ONES, THE PRODUCTION THEREOF AND THEIR USE IN MEDICAMENTS



(I)

(57) Abrégé/Abstract:
The invention relates to substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-ones, of general formula (I), wherein R^1 represents C_7-C_{22} alkyl, C_2-C_4 alkyl that is substituted by C_4-C_{20} alkoxy, C_6-C_{10} aryl, C_6-C_{10} aryloxy or C_4-C_{12}-alkoxy-C_2-C_4-alkoxy, and represents C_7-C_{20} alkenyl, 3β-cholestan-3-yl or substituted phenyl; R^2, R^3, R^4 and R^5 represent hydrogen, halogen, nitro, C_1-C_4 alkyl, C_1-C_9 alkyloxy, trifluoromethyl, trifluoromethoxy or C_6-C_{10}-aryl-$C_{1-}C_4$-alkyloxy, $C_{6-}C_{10}$ aryloxy, C_6-C_{10} aryl, C_3-C_8 cycloalkyl or O-C_3-C_8-cycloalkyl, whereby all of these can be substituted. The invention also relates to methods for producing these compounds. The compounds of formula (I) have an inhibiting effect on the pancreatic lipase and can be used as active substances for treating obesity.

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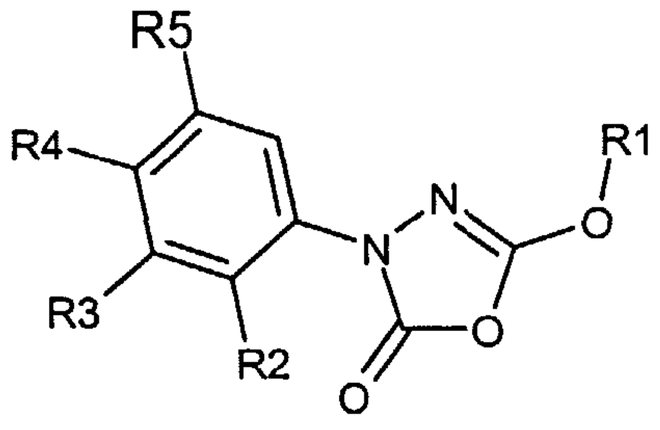
Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: SUBSTITUTED 3-PHENYL-5-ALKOXY-1,3,4-OXADIAZOL-2-ONES, THE PRODUCTION THEREOF AND THEIR USE IN MEDICAMENTS

(54) Bezeichnung: SUBSTITUIERTE 3-PHENYL-5-ALKOXY-1,3,4-OXADIAZOL-2-ONE SOWIE IHRE HERSTELLUNG UND VERWENDUNG IN ARZNEISTOFFEN



(I)

(57) Abstract: The invention relates to substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-ones, of general formula (I), wherein R^1 represents C_7-C_{22} alkyl, C_2-C_4 alkyl that is substituted by C_4-C_{20} alkoxy, C_6-C_{10} aryl, C_6-C_{10} aryloxy or C_4-C_{12}-alkoxy-C_2-C_4-alkoxy, and represents C_7-C_{20} alkenyl, 3β-cholestan-3-yl or substituted phenyl; R^2, R^3, R^4 and R^5 represent hydrogen, halogen, nitro, C_1-C_4 alkyl, C_1-C_9 alkyloxy, trifluoromethyl, trifluoromethoxy or C_6-C_{10}-aryl-C_1-C_4-alkyloxy, C_6-C_{10} aryloxy, C_6-C_{10} aryl, C_3-C_8 cycloalkyl or O-C_3-C_8-cycloalkyl, whereby all of these can be substituted. The invention also relates to methods for producing these compounds. The compounds of formula (I) have an inhibiting effect on the pancreatic lipase and can be used as active substances for treating obesity.

(57) Zusammenfassung: Es werden substituierte 3-Phenyl-5-alkoxy-1,3,4-oxadiazol-2-one der allgemeinen Formel (I) beschrieben, worin R^1 C_7-C_{22}-Alkyl; durch C_4-C_{20}-Alkoxy, C_6-C_{10}-Aryl, C_6-C_{10}-Aryloxy oder C_4-C_{12}-Alkoxy-C_2-C_4-Alkoxy substituiertes C_2-C_4-Alkyl, C_7-C_{20}-Alkenyl; 3β-Cholestan-3-yl oder substituiertes Phenyl; R^2, R^3,R^4 und R^5 Wasserstoff, Halogen, Nitro, C_1-C_4-Alkyl, C_1-C_9-Alkyloxy, Trifluormethyl, Trifluormethoxy, oder C_6-C_{10}-Aryl-C_1-C_4-Alkyloxy, C_6-C_{10}-Aryloxy, C_6-C_{10}-Aryl, C_3-C_8-Cycloalkyl oder O-C_3-C_8-Cycloalkyl, die substituiert sein können, bedeuten sowie deren Herstellungsverfahren. Die Verbindungen der Formel (I) üben eine hemmende Wirkung auf die pankreatische Lipase aus und können als Wirkstoffe zur Behandlung von Obesitas eingesetzt werden.

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SUBSTITUTED 3-PHENYL-5-ALKOXY-1,3,4-OXDIAZOL-2-ONES, THE PRODUCTION THEREOF AND THEIR USE IN MEDICAMENTS

Substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-ones, their preparation and use in medicaments

The invention relates to substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-ones which have an inhibitory effect on pancreatic lipase, PL.

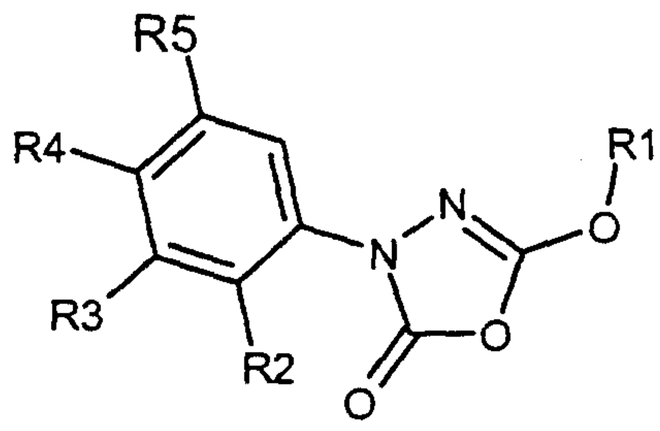
Certain 5-alkoxy-1,3,4-oxadiazol-2-ones with an ortho-substituted phenyl ring as substituent or with fused-on five- or six-membered rings have an anthelmintic (DE-A 26 04 110) and insecticidal action (DE-A 26 03 877, EP-B 0 048 040, EP-B 0 067 471).

Certain 5-phenoxy-1,3,4-oxadiazol-2-ones with an ortho-substituted phenyl ring as substituent show an endoparasiticidal action (EP-A 0 419 918).

Substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-ones with an inhibitory effect on hormone-sensitive lipase are disclosed in WO 01/17981 (HMR 1999/L 052) and WO 01/66531 (AVE-D 2000/A 015K).

The object of the invention was to find compounds which show an inhibitory effect on pancreatic lipase, PL.

This was achieved with the substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-ones of the formula 1



in which the meanings are:

R^1 C_7-C_{22}-alkyl; C_4-C_{20}-alkoxy-, C_6-C_{10}-aryl-, C_6-C_{10}-aryloxy- or C_4-C_{12}-alkoxy-C_2-C_4-alkoxy-substituted C_2-C_4-alkyl, where aryl may be a phenyl or naphthyl radical which is substitued one or more times by halogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, nitro or CF_3; C_7-C_{20}-alkenyl; 3β-cholestan-3-yl; phenyl which is substituted by C_6-C_{12}-alkyl or by phenoxy;

R^2, R^3, R^4 and R^5 independently of one another hydrogen, halogen, nitro, C_1-C_4-alkyl, C_1-C_9-alkyloxy, trifluoromethyl, trifluoromethoxy, or C_6-C_{10}-aryl-C_1-C_4-alkyloxy, C_6-C_{10}-aryloxy, C_6-C_{10}-aryl, C_3-C_8-cycloalkyl or O-C_3-C_8-cycloalkyl, each of which may be substituted once, twice or three times by halogen, trifluoromethyl, C_1-C_4-alkyloxy or C_1-C_4-alkyl;

and their pharmacologically acceptable salts and acid addition salts.

Said aryl radicals may optionally be substituted one or more times by C_1-C_9-alkyl, C_1-C_8-alkyloxy, halogen, trifluoromethyl. Said cycloalkyl radicals may optionally be substituted one or more times by C_1-C_4-alkyl, C_6-C_{10}-aryl, and said alkyl radicals may be substituted by hydroxyl, di-C_1-C_4-alkylamino and fluorine. Halogen is fluorine, chlorine, bromine, preferably fluorine and chlorine. Alkyl, alkenyl, alkoxy etc. may be branched or unbranched.

Preferred compounds are those of the formula 1 in which R^1 is C_7-C_{22}-alkyl, C_7-C_{20}-alkenyl, 3β-cholestan-3-yl or phenyl which is substitued by C_6-C_{12}-alkyl or by phenoxy.

Further preferred compounds are those of the formula 1 in which the meanings are:

R^2 hydrogen, halogen, C_1-C_4-alkyl or C_1-C_9-alkyloxy;

and/or

R^3 hydrogen, C_1-C_4-alkyl, trifluoromethoxy, C_6-C_{10}-aryl-C_1-C_4-alkyloxy, which may optionally be substituted in the aryl moiety by halogen;

and/or

R^4 hydrogen, trifluoromethoxy or chlorophenoxy;

and/or

R^5 hydrogen.

Particularly preferred compounds of the formula 1 are those in which R^1 is C_8-C_{16}-alkyl.

Very particularly preferred compounds are those of the formula 1 in which the meanings are:

R^1 C_8-C_{16}-alkyl,

R^2 hydrogen,

R^3 hydrogen or trifluoromethyloxy,

R^4 hydrogen, trifluoromethyloxy or 4-chlorophenoxy and

R^5 hydrogen.

Additional very particularly preferred compounds of the formula 1 are those which are mentioned in Examples 1, 2, 3, 4, 5, 6 and 16.

The compounds according to the invention of the formula 1 have an inhibitory effect on pancreatic lipase, PL.

The invention relates to the use of compounds of the formula I in the form of their racemates, racemic mixtures and pure enantiomers, and to their diastereomers and mixtures thereof.

Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater solubility in water compared with the initial compounds on which they are based. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the formula 1 are salts of inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric, metaphosphoric, nitric, sulfamic and sulfuric acids, and of organic

acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic, tartaric and trifluoroacetic acids. It is particularly preferred to use the chloride salt and the tartaric acid salt for medical purposes. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts).

Salts with a pharmaceutically unacceptable anion likewise fall within the scope of the invention as useful intermediates for preparing or purifying pharmaceutically acceptable salts and/or for use in non-therapeutic, for example in vitro, applications.

The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound according to the invention, for example an ester, which is able on administration to a mammal, such as, for example, to humans, to form (directly or indirectly) such a compound or an active metabolite thereof.

A further aspect of this invention is the use of prodrugs of compounds of the formula 1. Such prodrugs can be metabolized in vivo to a compound of the formula 1. These prodrugs may themselves be active or not.

The compounds of the formula 1 may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the formula 1 fall within the scope of the invention and are a further aspect of the invention.

All references hereinafter to "compound(s) of the formula 1" refer to compound(s) of the formula 1 as described above and to the salts, solvates and physiologically functional derivatives thereof as described herein.

The amount of a compound of the formula 1 necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day and per kilogram of body weight, for example 3-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.3 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Infusion solutions suitable for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and single dose formulations which can be administered orally, such as, for example, tablets or capsules, may contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. In the case of pharmaceutically acceptable salts, the above weight data are based on the weight of the salt of the compound of the formula 1. The compounds of the formula 1 can be used for prophylaxis or therapy of the abovementioned states themselves as compound, but they are preferably in the form of a pharmaceutical composition with a compatible carrier. The carrier must, of course, be compatible in the sense of compatibility with other ingredients of the composition and not be harmful to the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as single dose, for example as tablet, which may contain from 0.05% to 95% by weight of the active ingredient. Further pharmaceutically active substances may likewise be present, including further compounds of the formula 1. The pharmaceutical compositions according to the invention may be produced by one of the known pharmaceutical methods which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions according to the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the

nature and severity of the condition to be treated and on the nature of the compound of the formula 1 used in each case. Coated formulations and coated slow-release formulations also fall within the scope of the invention. Acid- and gastric fluid-resistant formulations are preferred. Suitable gastric fluid-resistant coatings comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethyl-cellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical compounds for oral administration may be in the form of separate units such as, for example, capsules, cachets, pastilles or tablets, each of which contains a defined amount of the compound of the formula 1; as powder or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. In general, the compositions are produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely dispersed solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or shaping a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets may be produced by tabletting the compound in free-flowing form, such as, for example, a powder or granules, where appropriate mixed with a binder, lubricant, inert diluent and/or one (or more) surface-active/dispersing agents in a suitable machine. Shaped tablets can be produced by shaping, in a suitable machine, the compound which is in powder form and has been moistened with an inert liquid diluent.

Pharmaceutical compositions suitable for peroral (sublingual) administration comprise suckable tablets which contain a compound of the formula 1 with a flavoring, normally sucrose, and gum arabic or tragacanth, and pastilles which contain the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

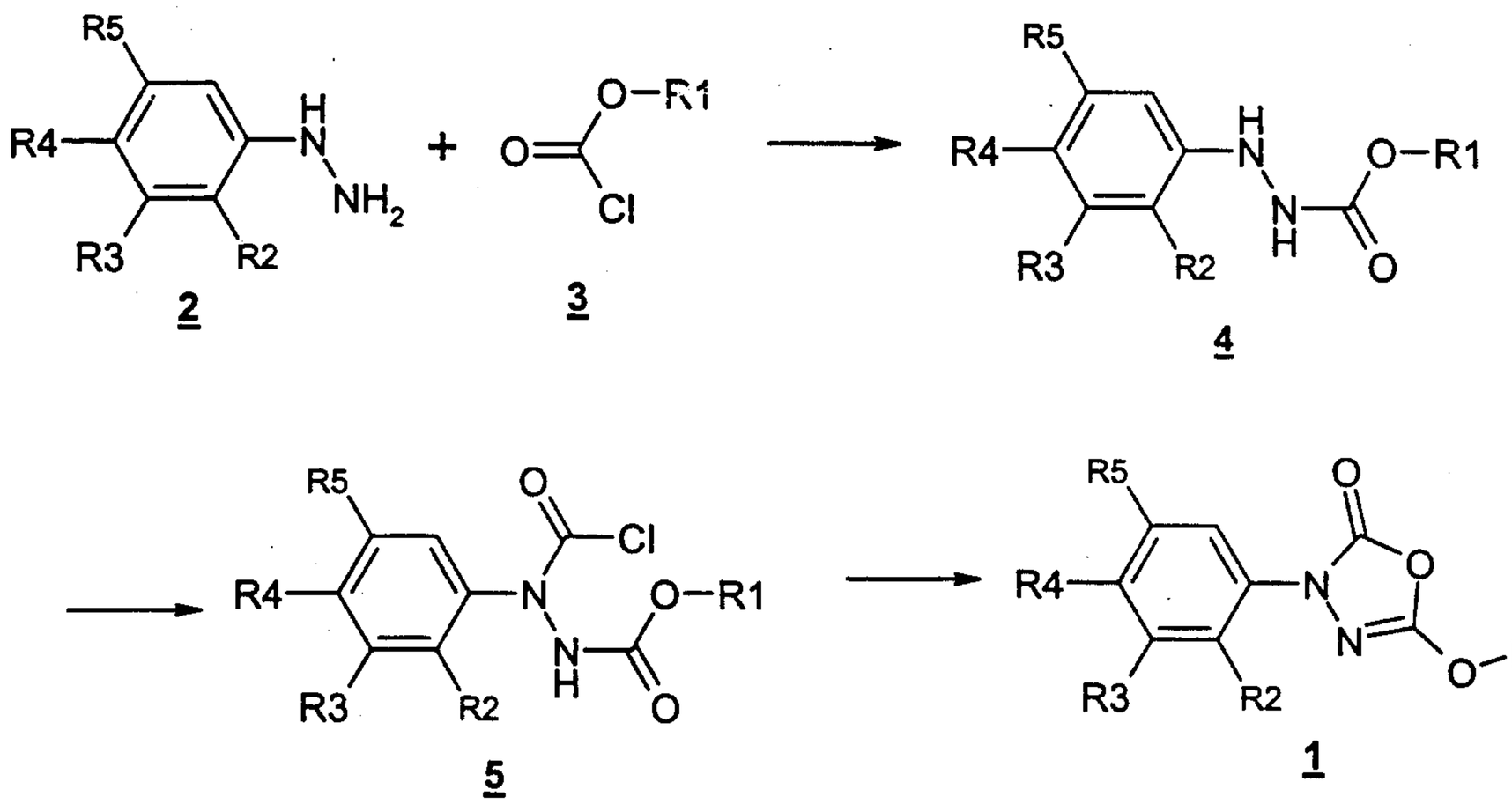
Suitable pharmaceutical compositions for parenteral administration comprise preferably sterile aqueous preparations of a compound of the formula 1, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration can also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions according to the invention generally contain from 0.1 to 5% by weight of the active compound.

Suitable pharmaceutical compositions for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of the formula 1 with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Suitable pharmaceutical compositions for topical use on the skin are preferably in the form of an ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

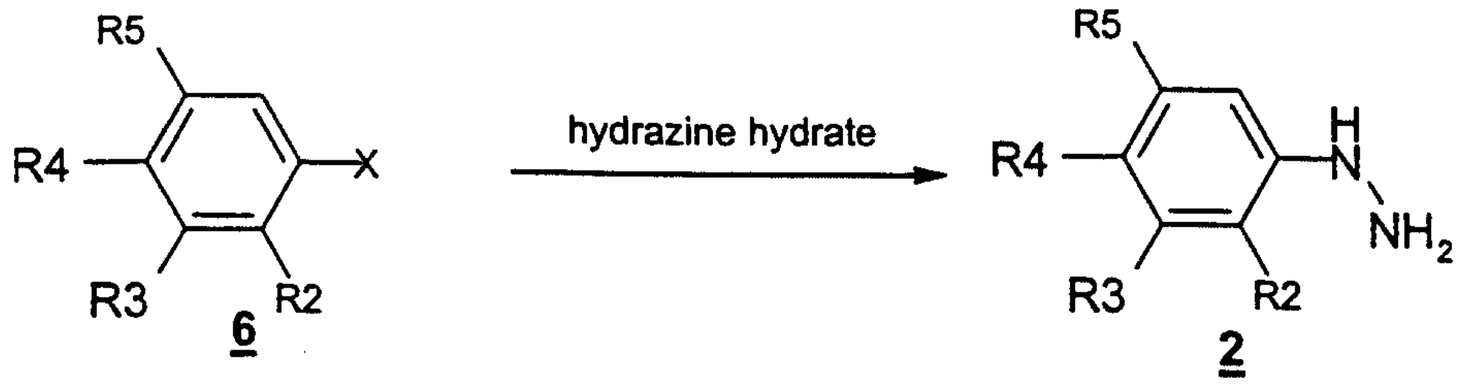
Transdermal administration is also possible. Suitable pharmaceutical compositions for transdermal applications may be in the form of single plasters which are suitable for long-term close contact with the patient's epidermis. Plasters of this type suitably contain the active ingredient in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. As a particular option, the active ingredient can be released by electrotransport or iontophoresis as described, for example, in Pharmaceutical Research, 2 (6): 318 (1986).

The compounds according to the invention of the formula 1 can be prepared in various ways by methods known per se.



For example, substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-ones of the formula 1 can be prepared by reacting hydrazines of the formula 2 with chloroformic esters of the formula 3 or other reactive carbonic ester derivatives, in which R^1, R^2, R^3, R^4 and R^5 are as defined above, to give the compounds of the formula 4, which are acylated with phosgene, carbonyldiimidazole, diphosgene or triphosgene, cyclized and converted where appropriate by further chemical modification of the radicals R^2-R^5, such as, for example, by reduction of nitro to amino radicals by known processes, and subsequent acylation or alkylation, into compounds of the formula 1. Since acids are usually liberated in these reactions, promotion is advisable by adding bases such as pyridine, triethylamine, sodium hydroxide solution or alkali metal carbonates. The reactions can be carried out in wide temperature ranges. It has proved advantageous as a rule to operate at 0°C to the boiling point of the solvent used. Examples of solvents employed are methylene chloride, THF, DMF, toluene, ethyl acetate, n-heptane, dioxane, diethyl ether.

The hydrazines of the formula 2 can be prepared by known methods, for example by diazotization of the corresponding anilines and



subsequent reduction by known methods or by nucleophilic substitution of suitably substituted phenyl derivatives 6 (X = F, Cl, Br, I, OSO_2CF_3) with hydrazine hydrate. Such suitable phenyl derivatives may be nitro-substituted halobenzenes, preferably fluoro- and chloronitrobenzenes, from which the compounds according to the invention can be prepared by known methods at a suitable point in the synthetic route by reduction and reaction with acylating or alkylating agents such as, for example, acid chlorides, anhydrides, isocyanates, chloroformic esters, sulfonyl chlorides or alkyl and arylalkyl halides, or by reductive alkylation with aldehydes.

The effect of the compounds according to the invention of the formula 1 was tested using the following enzyme assay system:

The compounds of the formula 1 show an inhibitory effect on pancreatic lipase (PL). As PL inhibitors, they are able to prevent absorption of fat consumed with the diet and thus lead to a reduction in the fat uptake and the body weight or prevent an increase in body weight. The compounds of the formula 1 are particularly suitable for treating obesity but may also have a very beneficial effect in various metabolic derangements such as, for example, diabetes, and cardiovascular disorders such as, for example, hypertension and myocardial infarction.

The activity of the compounds was assayed as follows:

1. Preparation of the substrate:

80 µl of tripalmitin (85 mM in chloroform) are mixed with 5 µl of glycerol tri[9,10(*n*)-^{3}H]oleate (5 mCi/ml in toluene) in a 12 ml polypropylene vessel. Evaporation in a rotary evaporator (50°C) and addition of 4 ml of 200 mM Tris/HCl (pH 7.6), 0.8% TX-100 are followed by ultrasound treatment of the mixture (Branson B-12 sonifier,

output level 4, 3 × 2 min with 1 min intervals on ice) until a homogeneous milky suspension is produced.

2. Assay:

Lipase buffer: 80 mM Tris/HCl (pH 7.6), 600 mM NaCl, 8 mM $CaCl_2$, 8 mM benzamidine, 2 mM Pefabloc (Roche Biochemicals) (add the inhibitors only on the day of the assay)

Pancreatic lipase: Enriched preparation from porcine pancreas (Sigma order No. L-0382) dissolved in lipase buffer (100 000 units/500 µl)

Procedure:

5 µl of test substance (in 100% DMSO) or DMSO (control) are mixed with 10 µl of substrate and 5 µl of lipase (in this sequence) and incubated at 30°C (Eppendorf Thermomixer, 350 min^{-1}) for 30 min. After addition of 325 µl of methanol/chloroform/n-heptane (10/9/7) and 105 µl of 0.1 M K_2CO_3, 0.1 M H_3BO_3 (pH 10.5 adjusted with 1 M KOH) and vigorous mixing, the phases are separated by centrifugation (8000 rpm, Eppendorf centrifuge, 4°C). 140 µl portions of the aqueous supernatant (contains the liberated radiolabeled oleate; 70% recovery) are transferred into 20 ml scintillation vials and mixed with 6 ml of scintillation cocktail (Beckman ReadySafe). After vigorously mixing and incubating at room temperature for 2 h, the radioactivity is measured in a liquid scintillation counter (Beckman, L8008, tritium channel with quench curve, measurement time 20 min).

Evaluation:

Substances are routinely tested in each concentration in three independent incubation mixtures each with duplicate determination after phase separation (SD < 0.02). Background values (reaction under the same conditions but without lipase) are subtracted from all values (corresponds predominantly to the content of glycerol trioleate or free oleate in the substrate preparation in the aqueous phase, < 5% of the radioactivity employed). The inhibition of the pancreatic lipase enzymatic activity

by a test substance is determined by comparison with an uninhibited control reaction (presence of lipase = 0% inhibition; absence of lipase 100% inhibition in each case after background correction). The IC_{50} is calculated from an inhibition plot with up to 8 concentrations of the test substance. The software package GRAPHIT (Elsevier-BIOSOFT) is used for curve fitting and IC_{50} determination.

The compounds showed the following effect in this assay:

Compound Example No.:	IC_{50} (μM)
1	0.03
2	0.25
3	0.35
4	2.5
5	2.0
6	0.9
15	0.6

The following examples illustrate the preparation methods in greater detail without restricting them.

Examples:

Example 1:

5-Dodecyloxy-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

0.43 ml of dodecyl chloroformate was cautiously added dropwise to a mixture consisting of 0.84 g of 4-trifluoromethoxyphenylhydrazine, 15 ml of NMP and 2 ml of pyridine while cooling in ice, and the mixture was then stirred for 2 hours while slowly warming to RT. After dilution with 50 ml of water, extraction by shaking was carried out with 30 ml of methylene chloride, the organic phase was dried with sodium sulfate and, while stirring and cooling in ice, 5 ml of pyridine and 3 ml of a 20% strength solution of phosgene in toluene were added dropwise. This mixture was allowed to stand overnight at room temperature and was diluted with a further 10 ml of methylene chloride and then washed 3 times with water. After drying over sodium sulfate, the mixture was concentrated in vacuo and the product was purified by column chromatography (silica gel, solvents:methanol:methylene chloride = 2 : 98).
Yield : 0.85 g M.p.: 41°C

The compounds of the following examples were prepared analagously:

Example 2:

5-Hexadecyloxy-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 56°C

Example 3:

5-Octyloxy-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: oil

Example 4:

5-Hexadecyloxy-3-(3-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 53°C

Example 5:

5-Hexadecyloxy-3-(4-(4-chlorophenoxy)-phenyl)-3H-(1,3,4)-oxadiazol-2-one
M.p.: 52°C

Example 6:
5-Octyloxy-3-phenyl-3H-(1,3,4)-oxadiazol-2-one
M.p.: 38°C

Example 7:
5-Octyloxy-3-(3-fluoro-phenyl)-3H-(1,3,4)-oxadiazol-2-one
M.p.: oil

Example 8:
5-Hexadecyloxy-3-(3-fluoro-phenyl)-3H-(1,3,4)-oxadiazol-2-one
M.p.: 58°C

Example 9:
5-Hexadecyloxy-3-(3-benzyloxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one
M.p.: 65°C

Example 10:
5-Hexadecyloxy-3-phenyl-3H-(1,3,4)-oxadiazol-2-one
M.p.: 63°C

Example 11:
5-Hexadecyloxy-3-(4-nitro-phenyl)-3H-(1,3,4)-oxadiazol-2-one
M.p.: 72°C

Example 12:
5-Hexadecyloxy-3-(4-methoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one
M.p.: 66°C

Example 13:

5-Hexadecyloxy-3-(4-benzyloxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 73°C

Example 14:

5-Decyloxy-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: oil

Example 15:

5-Undecyloxy-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 38°C

Example 16:

5-Tetradecyloxy-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 46°C

Example 17:

5-Tridecyloxy-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 50°C

Example 18:

5-(2-(2-Hexyloxy-ethoxy)-ethoxy)-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: oil

Example19:

5-((Z)-Octadec-9-enyloxy)-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: oil

Example 20:

5-(Dodecyloxy-ethoxy)-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: oil

Example 21:

5-(2-(4-Fluorophenyl)-ethoxy)-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 60°C

Example 22:

5-((3β-Cholestan-3-yl)-oxy)-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 127°C

Example 23:

5-(2-Butoxy-ethoxy)-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: resin

Example 24:

5-(7-Phenyl-heptyloxy)-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: resin

Example 25:

5-(Docosyloxy-ethoxy)-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 71°C

Example 26:

5-(2-(1-Naphthyloxy)-ethoxy)-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: resin

Example 27:

5-(4-Octylphenoxy)-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: resin

Example 28:

5-(3-Phenoxy-phenoxy)-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: resin

Example 29:

5-(Dodecyloxy)-3-(4-trifluoromethoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 41°C

Example 30:

5-(Dodecyloxy)-3-(3,4-dichloro-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 74°C

Example 31:

5-(Dodecyloxy)-3-(3,5-dichloro-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 48°C

Example 32:

5-(Dodecyloxy)-3-(3-methoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 51°C

Example 33:

5-(Dodecyloxy)-3-(4-methoxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 57°C

Example 34:

5-(Dodecyloxy)-3-(3-nitro-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 64°C

Example 35:

5-(Dodecyloxy)-3-(3-trifluoromethyl-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 43°C

Example 36:

5-(Dodecyloxy)-3-(3,5-bis-trifluoromethyl-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: oil

Example 37:

5-(Dodecyloxy)-3-(4-benzyloxy-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 65°C

Example 38:

5-(Dodecyloxy)-3-(3-fluoro-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 44°C

Example 39:

5-(Dodecyloxy)-3-(3-(4-fluorobenzyloxy)-4-nitro-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 71°C

Example 40:

5-(Dodecyloxy)-3-(2-methyl-4-nitro-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 63°C

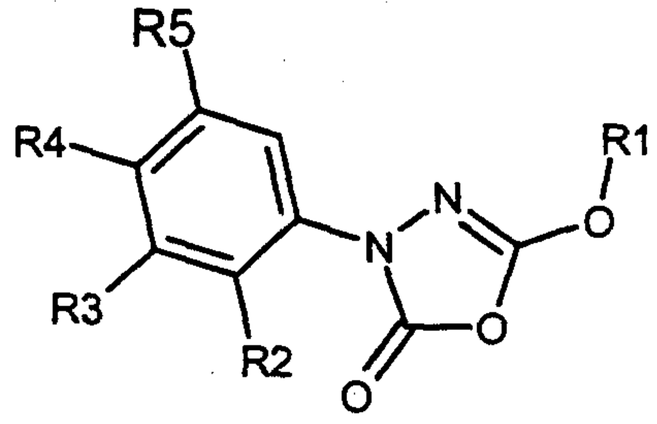
Example 41:

5-(Dodecyloxy)-3-(3-methyl-4-nitro-phenyl)-3H-(1,3,4)-oxadiazol-2-one

M.p.: 62°C

Patent claims:

1. A compound of the formula 1



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in which the meanings are:

R^1 C_7-C_{22}-alkyl; C_4-C_{20}-alkoxy-, C_6-C_{10}-aryl-, C_6-C_{10}-aryloxy- or C_4-C_{12}-alkoxy-C_2-C_4-alkoxy-substituted C_2-C_4-alkyl, where aryl may be a phenyl or naphthyl radical which is substitued one or more times by halogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, nitro or CF_3; C_7-C_{20}-alkenyl; 3β-cholestan-3-yl; phenyl which is substituted by C_6-C_{12}-alkyl or by phenoxy;

R^2, R^3, R^4 and R^5 independently of one another hydrogen, halogen, nitro, C_1-C_4-alkyl, C_1-C_9-alkyloxy, trifluoromethyl, trifluoromethoxy, or C_6-C_{10}-aryl-C_1-C_4-alkyloxy, C_6-C_{10}-aryloxy, C_6-C_{10}-aryl, C_3-C_8-cycloalkyl or O-C_3-C_8-cycloalkyl, each of which may be substituted once, twice or three times by halogen, CF_3, C_1-C_4-alkyloxy or C_1-C_4-alkyl;

and the pharmacologically acceptable salts and acid addition salts thereof.

2. A compound of the formula 1 as claimed in claim 1, in which

R^1 is C_7-C_{22}-alkyl, C_7-C_{20}-alkenyl, 3β-cholestan-3-yl, or phenyl which is substituted by C_6-C_{12}-alkyl or by phenoxy.

3. A compound of the formula 1 as claimed in claims 1 to 2, in which

R^2 is hydrogen, halogen, C_1-C_4-alkyl or C_1-C_9-alkoxy.

4. A compound of the formula 1 as claimed in claims 1 to 3, in which
R^3 is hydrogen, C_1-C_4-alkyl, trifluoromethoxy, C_6-C_{10}-aryl-C_1-C_4-alkyloxy which may optionally be substituted in the aryl moiety by halogen.

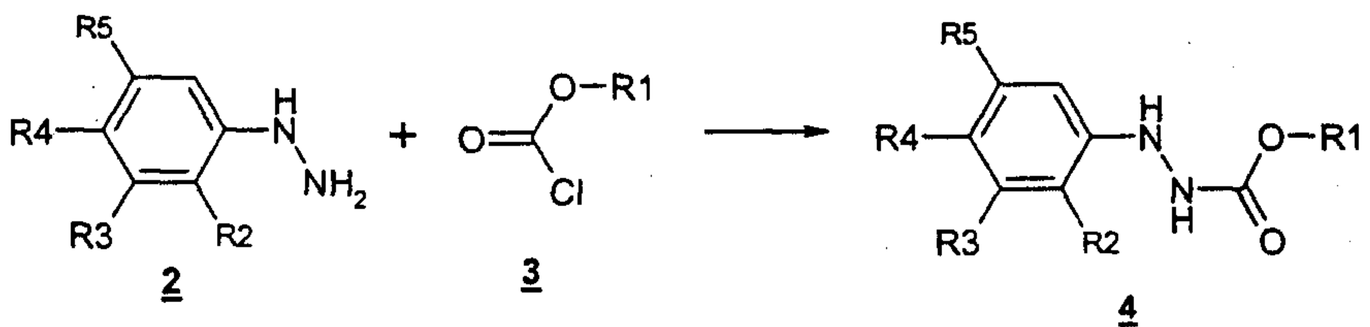
5. A compound of the formula 1 as claimed in claims 1 to 4, in which
R^4 is hydrogen, trifluoromethoxy or chlorophenoxy.

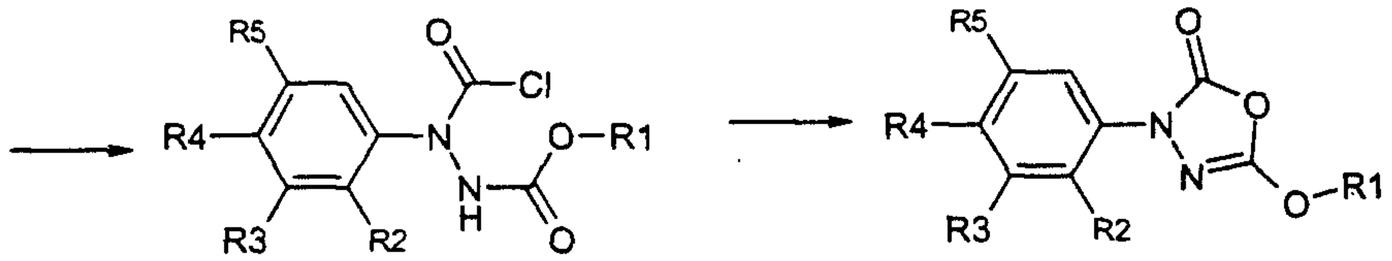
6. A compound of the formula 1 as claimed in claims 1 to 5, in which
R^5 is hydrogen.

7. A compound of the formula 1 as claimed in claims 1 to 6, in which
R^1 is C_8-C_{16}-alkyl.

8. A compound of the formula 1 as claimed in claims 1 to 7, in which
R^1 is C_8-C_{16}-alkyl,
R^2 is hydrogen,
R^3 is hydrogen or trifluoromethyloxy,
R^4 is hydrogen, trifluoromethyloxy or 4-chlorophenoxy and
R^5 is hydrogen.

9. A process for preparing the compounds of the formula 1 as claimed in claims 1 to 8, which comprises



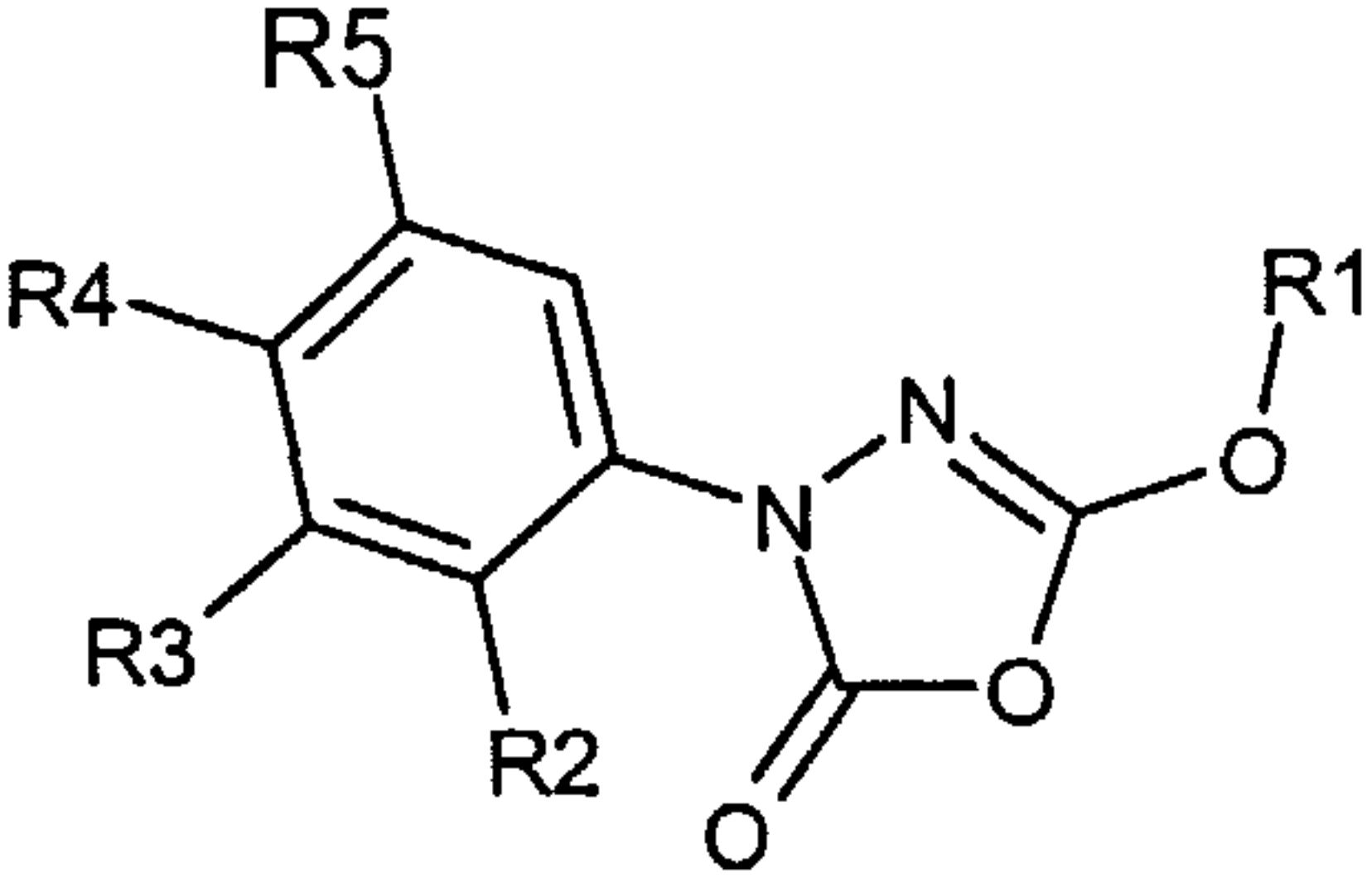


reacting hydrazines of the formula 2 with chloroformic esters of the formula 3 or other reactive carbonic ester derivatives, in which R^1, R^2, R^3, R^4 and R^5 are as defined in claims 1 to 8, to give the compounds of the formula 4, which are acylated with phosgene, carbonyldiimidazole, diphosgene or triphosgene, cyclized and converted where appropriate by further chemical modification of the radicals R^2-R^5 into compounds of the formula 1.

10. A medicament comprising at least one compound of the formula 1 as claimed in claims 1 to 8.

11. A medicament for the treatment of obesity comprising at least one compound of the formula 1 as claimed in claims 1 to 8.

12. The use of at least one of the compounds of the formula 1 as claimed in claims 1 to 8 as a medicine.



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