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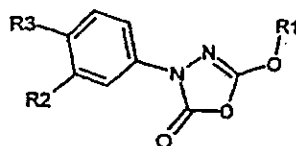
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(54) Title: SUBSTITUTED 3-PHENYL-5-ALKOXI-1,3,4-OXDIAZOL-2-ONES AND THEIR USE AS LIPASE INHIBITORS

(54) Bezeichnung: SUBSTITUIERTE 3-PHENYL-5-ALKOXI-1,3,4-OXDIAZOL-2-ONE UND IHRE VERWENDUNG ALS LI-PASE-HEMMER



(1)

(57) Abstract: The invention relates to substituted 3-phenyl-5-alkoxy-1,3,4-oxdiazol-2-ones of formula (1) and their physiologically compatible salts and optical isomers, R¹ meaning C₁-C₆-alkyl, C₃-C₉-cycloalkyl, both of which can be optionally substituted, and R² and R³ meaning, independently of each other, hydrogen, C₆-C₁₀-aryl, C₃-C₈-cycloalkyl, C₆-C₁₀-aryloximethyl, O-benzyl, O-C₆-C₁₀-aryl, O-C₃-C₈-cycloalkyl, O-C₁-C₆-alkyl, SO₂-NH-C₁-C₆-alkyl, SO₂-NH-(2,2,6,6-tetramethylpiperidin-4-yl), SO₂-NH-C₃-C₈-cycloalkyl, SO₂-N(C₁-C₆-alkyl)₂ or COX, X representing O-C₁-C₆-alkyl, NH-C₁-C₆-alkyl, NH-C₃-C₈-cycloalkyl or N(C₁-C₆-alkyl)₂; on the condition that the substituents R² and R³ can be partially optionally substituted and that they do not mean hydrogen at the same time. The invention also relates to a method for producing the inventive 3-phenyl-5-alkoxy-1,3,4-oxdiazol-2-ones. The compounds present an inhibiting effect on the hormone-sensitive lipase HSL.

(57) Zusammenfassung: Es werden substituierte 3-Phenyl-5-alkoxy-1,3,4-oxdiazol-2-onen der Formel (1) beschrieben sowie deren physiologisch verträglichen Salze und optischen Isomere, worin R¹ C₁-C₆-Alkyl, C₃-C₉-Cycloalkyl, die beide gegebenenfalls substituiert sein können, und R² und R³ unabhängig voneinander Wasserstoff, C₆-C₁₀-Aryl, C₃-C₈-Cycloalkyl, C₆-C₁₀-Aryloximethyl, O-Benzyl, O-C₆-C₁₀-Aryl, O-C₃-C₈-Cycloalkyl, O-C₁-C₆-Alkyl, SO₂-NH-C₁-C₆-Alkyl, SO₂-NH-(2,2,6,6-tetramethylpiperidin-4-yl), SO₂-NH-C₃-C₈-Cycloalkyl, SO₂-N(C₁-C₆-Alkyl)₂ oder COX bedeuten, wobei X für O-C₁-C₆-Alkyl, NH-C₁-C₆-Alkyl, NH-C₃-C₈-Cycloalkyl oder N(C₁-C₆-Alkyl)₂ steht, und der Massgabe, dass die Substituenten R² und R³ zum Teil gegebenenfalls substituiert sein können und beide nicht gleichzeitig Wasserstoff bedeuten. Ebenfalls beschrieben ist ein Verfahren zu deren Herstellung. Die Verbindungen zeigen eine hemmende Wirkung an der hormonsensitiven Lipase, HSL.

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- Before expiry of the period provided for amending the claims, will be republished if such amendments are received.

For an explanation of the two-letter codes and the other abbreviations, reference is made to the explanations ("Guidance Notes on Codes and Abbreviations") at the beginning of each regular edition of the PCT Gazette.

Description

SUBSTITUTED 3-PHENYL-5-ALKOXY-1,3,4-OXDIAZOL-2-ONES AND THEIR USE AS LIPASE INHIBITORS

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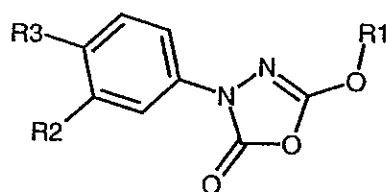
The invention relates to substituted 3-phenyl-5-alkoxy-1,3,4-oxdiazol-2-ones which have an inhibitory effect on the hormone-sensitive lipase HSL.

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

15 Certain 5-phenoxy-1,3,4-oxdiazol-2-ones having an ortho-substituted phenyl ring as substituent have endoparasitocidal action (EP-A 0 419 918).

It is an object of the present invention to provide compounds having an inhibitory effect on the hormone-sensitive lipase HSL.

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

1

25 in which

R^1 is C_1 - C_6 -alkyl or C_3 - C_9 -cycloalkyl, where both groups are unsubstituted or mono- or polysubstituted by O - C_1 - C_4 -alkyl, S - C_1 - C_4 -alkyl, $N(C_1$ - C_4 -alkyl) $_2$ and/or phenyl which for its part may be mono- or polysubstituted by halogen, C_1 - C_4 -alkyl, O - C_1 - C_4 -alkyl, nitro, CF_3 , and

30 R^2 and R^3 independently of one another are hydrogen, C_6 - C_{10} -aryl, C_3 - C_8 -cycloalkyl, optionally C_1 - C_4 -alkyl-substituted C_6 - C_{10} -aryloxymethyl, O - C_3 - C_8 -cycloalkyl, O - C_6 - C_{10} -aryl or O -benzyl,

unsubstituted or mono- or polysubstituted by halogen, CF₃ or C₁-C₄-alkyl, O-C₁-C₆-alkyl which is mono- or polysubstituted by fluorine, C₆-C₁₀-aryl or amino, where amino for its part may be mono- or polysubstituted by C₁-C₄-alkyl, are SO₂-NH-C₁-C₆-alkyl, unsubstituted or substituted by N(C₁-C₆-alkyl)₂, are SO₂-NH-(2,2,6,6-tetramethylpiperidin-4-yl), SO₂-NH-C₃-C₈-cycloalkyl, unsubstituted or mono- or polysubstituted by C₁-C₄-alkyl, are SO₂-N(C₁-C₆-alkyl)₂ or COX, where X is O-C₁-C₆-alkyl, NH-C₁-C₆-alkyl, NH-C₃-C₈-cycloalkyl or N(C₁-C₆-alkyl)₂, and N(C₁-C₆-alkyl)₂ may also be pyrrolidino, piperidino, morpholino, thiomorpholino or piperazino which may be unsubstituted or substituted by C₁-C₄-alkyl, benzyl, C₆-C₁₀-aryl, CO-C₁-C₄-alkyl, CO-C₆-C₁₀-aryl, CO-O-C₁-C₄-alkyl, SO₂-C₁-C₄-alkyl or SO₂-C₆-C₁₀-aryl, with the proviso that R² and R³ are not simultaneously hydrogen, and their physiologically acceptable salts and optical isomers.

The aryl radicals mentioned can be unsubstituted or mono- or polysubstituted by C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen, trifluoromethyl. The cycloalkyl radicals mentioned can be unsubstituted or mono- or polysubstituted by C₁-C₄-alkyl, and the alkyl radicals mentioned can be substituted by hydroxyl, di-C₁-C₄-alkylamino and fluorine. Halogen denotes fluorine, chlorine, bromine, preferably fluorine and chlorine.

Preference is given to substituted 3-phenyl-5-alkoxy-1,3,4-oxdiazol-2-ones of the formula 1, in which one of the radicals R² or R³ is hydrogen.

Particular preference is given to substituted 3-phenyl-5-alkoxy-1,3,4-oxdiazol-2-ones of the formula 1, in which R¹ is C₁-C₆-alkyl which may be unsubstituted or substituted by phenyl.

Particular preference is furthermore given to substituted 3-phenyl-5-alkoxy-1,3,4-oxdiazol-2-ones of the formula 1, in which R² and R³ independently of one another are hydrogen, C₆-C₁₀-aryl, C₃-C₈-cycloalkyl, unsubstituted or C₁-C₄-alkyl-substituted C₆-C₁₀-aryloxymethyl, O-C₃-C₈-cycloalkyl, O-C₆-C₁₀-aryl or O-benzyl, unsubstituted or mono- or polysubstituted by C₁-C₄-alkyl or halogen,

O-C₁-C₆-alkyl which is mono- or polysubstituted by fluorine, C₆-C₁₀-aryl or amino, where amino for its part may be mono- or polysubstituted by C₁-C₄-alkyl, are SO₂-NH-C₁-C₆-alkyl, optionally substituted by N(C₁-C₆-alkyl)₂, are SO₂-NH-(2,2,6,6-tetramethylpiperidin-4-yl), SO₂-NH-C₃-C₈-cycloalkyl, substituted by C₁-C₄-alkyl, are SO₂-N(C₁-C₆-alkyl)₂ or CO-N(C₁-C₆-alkyl)₂, and N(C₁-C₆-alkyl)₂ may also be piperidino, morpholino or piperazino which can be unsubstituted or substituted by C₁-C₄-alkyl.

10 Very particular preference is also given to substituted 3-phenyl-5-alkoxy-1,3,4-oxdiazol-2-ones of the formula 1, in which

15 R^2 is hydrogen, C₆-C₁₀-aryl, O-C₆-C₁₀-aryl, unsubstituted or C₁-C₄-alkyl-substituted C₆-C₁₀-aryloxymethyl, O-benzyl, is O-C₁-C₆-alkyl which is mono- or polysubstituted by fluorine or amino, where amino for its part may be mono- or polysubstituted by C₁-C₄-alkyl, is O-C₃-C₈-cycloalkyl which is unsubstituted or mono- or polysubstituted by C₁-C₄-alkyl, and

20 R^3 is hydrogen, C₆-C₁₀-aryl, C₃-C₈-cycloalkyl, O-C₃-C₈-cycloalkyl or O-C₆-C₁₀-aryl which is unsubstituted or mono- or polysubstituted by C₁-C₄-alkyl or halogen, is O-C₁-C₆-alkyl which is mono- or polysubstituted by fluorine, is SO₂-NH-C₁-C₆-alkyl, unsubstituted or substituted by N(C₁-C₆-alkyl)₂, is SO₂-NH-(2,2,6,6-tetramethylpiperidin-4-yl), SO₂-NH-C₃-C₈-cycloalkyl, mono- or polysubstituted by C₁-C₄-alkyl, is SO₂-N(C₁-C₆-alkyl)₂ or CO-N(C₁-C₆-alkyl)₂, and

25 N(C₁-C₆-alkyl)₂ is also piperidino, morpholino or piperazino, which may be unsubstituted or substituted by C₁-C₄-alkyl.

30 Very particular preference is given to substituted 3-phenyl-5-alkoxy-1,3,4-oxdiazol-2-ones of the formula 1, in which

R^1 is methyl, ethyl, butyl, isopropyl or benzyl and

R^2 is hydrogen, trifluoromethoxy, trifluorobutoxy, 3,3,5,5-tetramethylcyclohexyloxy, benzyloxy, phenoxy, phenyl, 2-diethylaminoethyloxy or 3-methylphenoxymethyl, and

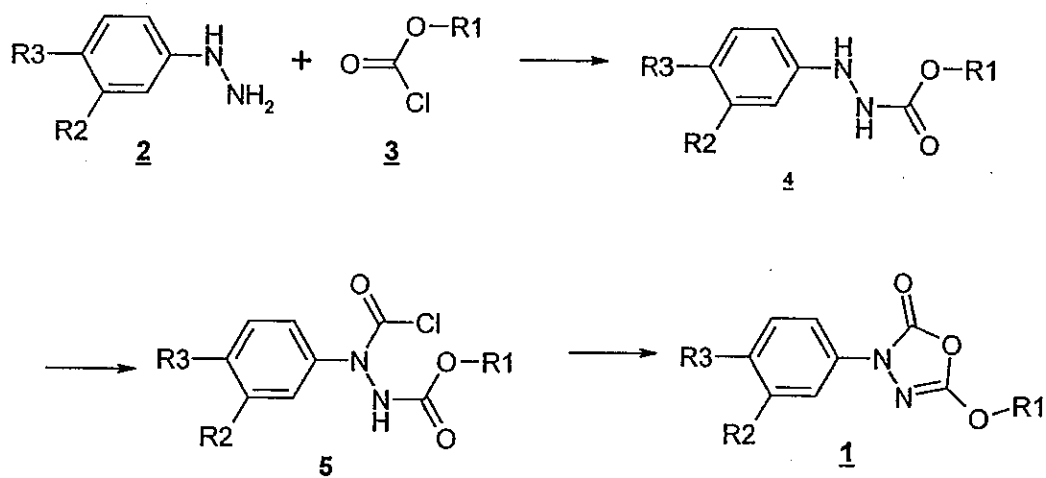
35 R^3 is hydrogen, trifluoromethoxy, 3,3,5,5-tetramethylcyclohexyloxy, phenoxy, 4-chlorophenoxy, cyclohexyl, phenyl, morpholinosulfonyl, 3,3,5-trimethylcyclohexylaminosulfonyl, 2,2,6,6-tetramethylpiperidin-4-yl-aminosulfonyl, 2-(diisopropylaminoethyl)aminosulfonyl, 4-

methylpiperazin-1-yl-sulfonyl, 3,3-dimethylpiperidinocarbonyl or 3,5-dichlorophenoxy.

Very particular preference is furthermore given to substituted 3-phenyl-5-alkoxy-1,3,4-oxdiazol-2-ones of the formula 1, in which
 5 R^1 is methyl, ethyl, butyl, isopropyl or benzyl and
 R^2 is hydrogen, trifluoromethoxy, 3,3,5,5-tetramethylcyclohexyloxy, benzyloxy or phenoxy and
 R^3 is hydrogen, trifluoromethoxy, 3,3,5,5-tetramethylcyclohexyloxy,
 10 phenoxy, cyclohexyl, phenyl, morpholinosulfonyl or 3,3,5-trimethylcyclohexylaminosulfonyl.

The compounds of the formula 1 according to the invention have an unexpected inhibitory effect on the hormone-sensitive lipase HSL, an
 15 allosteric enzyme in adipocytes which is inhibited by insulin and responsible for the degradation of fats in fat cells and thus for the transfer of fat components into the bloodstream. Thus, an inhibition of this enzyme corresponds to an insulin-like effect of the compounds according to the invention which in the end results in a reduction of free fatty acids in the
 20 blood and of blood sugar. Accordingly, they can be used for metabolic disorders such as, for example, for non-insulin-dependent diabetes mellitus, for diabetic syndrome and in cases where the pancreas is damaged directly.

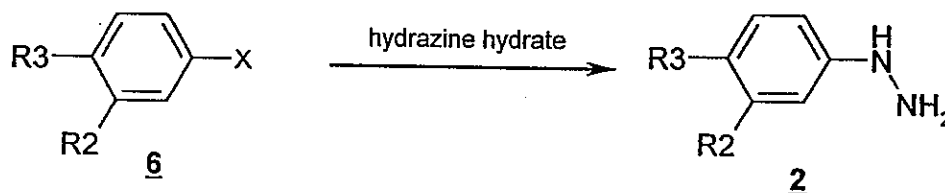
25 The compounds of the formula 1 according to the invention



can be prepared by different routes using methods known per se.

For example, the substituted 3-phenyl-5-alkoxy-1,3,4-oxdiazol-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 acid ester derivatives, in which R^1 , R^2 and R^3 are as defined above, to give compounds of the formula 4 which are acylated with phosgene, carbonyldiimidazole or diphosgene and cyclized to give the compounds of the formula 1. Since in general acids are liberated in these reactions, it is recommended to add bases such as pyridine, triethylamine, aqueous sodium hydroxide solution or alkali metal carbonates to accelerate the reaction. The reactions can be carried out in wide temperature ranges. In general, it has been found to be advantageous to carry out the reactions at from 0°C to the boiling point of the solvent used. Suitable solvents are, for example, methylene chloride, THF, DMF, toluene, ethyl acetate, n-heptane, dioxane, diethylether.

The hydrazines of the formula 2 are commercially available or can be prepared by known methods, for example by diazotization of the corresponding anilines



with subsequent reduction or by nucleophilic substitution of appropriately substituted phenyl derivatives 6 ($X = \text{F}, \text{Cl}, \text{Br}, \text{I}, \text{OSO}_2\text{CF}_3$) with hydrazine hydrate. Such suitable phenyl derivatives can be nitro-substituted halogenated benzenes, preferably fluoro- and chloronitrobenzenes, from which, at a suitable point in the synthesis path, the compounds according to the invention can be prepared by reduction and reaction with acylating or alkylating agents, such as, for example, acid chlorides, anhydrides, isocyanates, chloroformic esters, sulfonyl chlorides or alkyl halides and arylalkyl halides.

The activity of the compounds of the formula 1 according to the invention was examined using the following enzyme test system:

Enzyme preparation:

Preparation of the partially purified HSL:

Isolated rat fat cells are obtained from epididymal fatty tissue from untreated male rats (Wistar, 220-250 g) by collagenase treatment according to published processes (e.g. S. Nilsson et al., *Anal. Biochem.* 158, 1986, 399 - 407; G. Fredrikson et al., *J. Biol. Chem.* 256, 1981, 6311 - 6320; H. Tornquist et al., *J. Biol. Chem.* 251, 1976, 813 - 819). The fat cells from 10 rats are washed three times by flotation with 50 ml each of homogenization buffer (25 ml tris/HCl, pH 7.4, 0.25 M sucrose, 1 mM EDTA, 1 mM DTT, 10 µg/ml of leupeptin, 10 µg/ml of antipain, 20 µg/ml of pepstatin) and finally taken up in 10 ml of homogenization buffer. The fat cells are homogenized in a Teflon-in-glass homogenizer (Braun-Melsungen) by 10 strokes at 1500 rpm and 15°C. The homogenizate is centrifuged (Sorvall SM24 tubes, 5000 rpm, 10 min, 4°C). The bottom layer between the overlying fatty layer and the pellet is removed and the centrifugation is repeated. The bottom layer resulting from this is centrifuged again (Sorvall SM24 tubes, 20,000 rpm, 45 min, 4°C). The bottom layer is removed and treated with 1 g of heparin-Sepharose (Pharmacia Biotech, CL-6B, washed 5 x with 25 mM tris/HCl, pH 7.4, 150 mM NaCl). After incubation for 60 min at 4°C (shake at intervals of 15 min), the batch is centrifuged (Sorvall SM24 tubes, 3000 rpm, 10 min, 4°C). The supernatant is brought to pH 5.2 by addition of glacial acetic acid and incubated at 4°C for 30 min. The precipitates are collected by centrifugation (Sorvall SS34, 12,000 rpm, 10 min, 4°C) and suspended in 2.5 ml of 20 mM tris/HCl, pH 7.0, 1 mM EDTA, 65 mM NaCl, 13% sucrose, 1 mM DTT, 10 µg/ml of leupeptin/pepstatin/antipain. The suspension is dialyzed overnight at 4°C against 25 mM tris/HCl, pH 7.4, 50% glycerol, 1 mM DTT, 10 µg/ml of leupeptin, pepstatin, antipain and then applied to a hydroxylapatite column (0.1 g per 1 ml of suspension, equilibrated with 10 mM potassium phosphate, pH 7.0, 30% glycerol, 1 mM DTT). The column is washed with four volumes of equilibration buffer at a flow rate of 20 to 30 ml/h. The HSL is eluted with a volume of equilibration buffer which contains 0.5 M potassium phosphate, then dialyzed (see above) and concentrated 5 to 10 times by ultrafiltration (Amicon Diaflo PM 10 filter) at 4°C. The partially purified HSL can be stored at -70°C for 4 to 6 weeks.

Assay:

For the preparation of the substrate, 25-50 μCi of [^3H]trioleoylglycerol (in toluene), 6.8 μMol of unlabeled trioyleglycerol and 0.6 mg of phospholipids (phosphatidylcholine/phosphatidylinositol 3:1 w/v) are mixed, dried over N_2 and then taken up in 2 ml of 0.1 M KPi (pH 7.0) by ultrasonic treatment (Branson 250, microtip, setting 1-2, 2 x 1 min at a 1 min interval). After addition of 1 ml KPi and fresh ultrasonic treatment (4 x 30 sec on ice at 30 sec intervals), 1 ml of 20% BSA (in KPi) is added (final concentration of trioyleglycerol 1.7 mM). For the reaction, 100 μl of substrate solution are pipetted into 100 μl of HSL solution (HSL prepared as above, diluted in 20 mM KPi , pH 7.0, 1 mM EDTA, 1 mM DTT, 0.02% BSA, 20 $\mu\text{g/ml}$ of pepstatin, 10 $\mu\text{g/ml}$ of leupeptin) and incubated at 37°C for 30 min. After addition of 3.25 ml of methanol/chloroform/heptane (10:9:7) and of 1.05 ml of 0.1 M K_2CO_3 , 0.1 M boric acid (pH 10.5), the batch is well mixed and finally centrifuged (800xg, 20 min). After phase separation, one equivalent of the upper phase (1 ml) is taken and the radioactivity is determined by liquid scintillation measurement.

Analysis:

Substances are customarily tested in four independent batches. The inhibition of the enzymatic activity of the HSL by a test substance is determined by comparison with an uninhibited control reaction. The IC_{50} value is calculated by means of an inhibition curve using at least 10 concentrations of the test substance. For the analysis of the data, the software package GRAPHIT, Elsevier-BIOSOFT is used.

In this test, the compounds had the following activity:

Compound Example No.	IC ₅₀ (μM)
8	15
10	6
11	10
12	10
13	10
14	50
15	2
16	2
17	2
18	<1
19	5
33	4
34	3
35	3
36	2
37	3
38	<1
39	60

The examples below illustrate the preparation methods in more detail without limiting them.

Examples:

Example 1:

4-Fluorobenzenesulfonic acid morpholide (intermediate)

- 5 20 g of morpholine were added dropwise to a solution, cooled with ice, of 19.5 g of 4-fluorobenzenesulfonyl chloride in 100 ml of toluene, and the mixture was heated under reflux for 1 hour. After cooling, the mixture was concentrated under reduced pressure, the residue was stirred with water and the precipitate was filtered off with suction, washed with water and
- 10 recrystallized from isopropanol.

Yield: 16.9 g m.p.: 140°C

Example 2:

4-Hydrazinobenzenesulfonic acid morpholide (intermediate)

- 15 5 g of 4-fluorobenzenesulfonic acid morpholide were dissolved in 15 ml of N-methylpyrrolidone and mixed with 2.5 g of hydrazine hydrate, and the mixture was heated at 100°C for 1 hour. After cooling to room temperature, 75 ml of water were added and the mixture was stirred at room temperature. After 2 hours, the solid was filtered off with suction and
- 20 recrystallized from isopropanol.

Yield: 3.2 g m.p.: 164°C

The following example was prepared in a similar manner:

25 Example 3:

N-(3,3,5-Trimethylcyclohexyl)-4-hydrazinobenzenesulfonamide
(intermediate)

m.p.: 129°C

30 Example 4:

4-(3,3,5,5-Tetramethylcyclohexyloxy)nitrobenzene (intermediate)

- 1.3 g of sodium hydride are added to a solution of 7.8 g of 3,3,5,5-tetramethylcyclohexanol in 50 ml of dimethylformamide, and the mixture is stirred at 40-50°C for 30 min. A total of 7.0 g of 4-fluoronitrobenzene are
- 35 then added a little at a time, and the mixture is subsequently heated at 100°C for three hours and cooled to room temperature. 250 ml of ice-water are added, the mixture is stirred and the resulting solid is filtered off with suction and dried under reduced pressure.

Yield: 8.6 g m.p.: 70°C

Example 5:

4-(3,3,5,5-Tetramethylcyclohexyloxy)aniline (intermediate)

Under atmospheric pressure, 8.3 g of 4-(3,3,5,5-tetramethylcyclohexyloxy) nitrobenzene in 500 ml of methanol are hydrogenated in the presence of
5 400 mg of platinum dioxide until the uptake of hydrogen has ended. The catalyst is filtered off, the solution is then concentrated using a rotary evaporator and the residue, a brownish oil which slowly solidifies, is used for the further reactions without any further purification.

Yield: 7.3 g

10

Example 6:

4-(3,3,5,5-Tetramethylcyclohexyloxy)phenylhydrazine hydrochloride (intermediate)

A stirred mixture, cooled to -10°C , of 3.7 g of 4-(3,3,5,5-
15 tetramethylcyclohexyloxy)aniline, 7.5 ml of water and 15.5 ml of conc. HCl is mixed dropwise with a solution of 1.13 g of sodium nitrite in 7.5 ml of water, and the mixture is stirred at -10°C for 45 min and subsequently added dropwise to a suspension of 9.3 g of tin dichloride dihydrate in 7 ml of conc. HCl. The precipitate is filtered off with suction, washed with water,
20 suspended under nitrogen in 200 ml of water and decomposed at $10-15^{\circ}\text{C}$ using 100 ml of 30% strength aqueous sodium hydroxide solution. The precipitate that is then formed is filtered off with suction, washed with water, taken up in 200 ml of ether and dried with sodium sulfate. The product is precipitated using ethereal HCl, filtered off with suction and dried under
25 reduced pressure.

Yield: 2.1 g m.p.: 171°C

Example 7:

Ethyl N'-(4-morpholinosulfonylphenyl)hydrazinoformate (intermediate)

30 With ice-cooling, 114 mg of ethyl chloroformate were carefully added dropwise to a mixture of 0.275 g of 4-hydrazinobenzenesulfonic acid morpholide, 5 ml of methylene chloride and 1 ml of pyridine, and the mixture was then stirred and slowly warmed to RT. After dilution with 10 ml of water, the product was extracted with ethyl acetate and the ethyl acetate
35 phase was washed repeatedly with water, dried over sodium sulfate and concentrated. The resulting oily crude product was reacted further without further purification.

Yield: 0.25 g

Example 8:

3-(4-Morpholinosulfonylphenyl)-5-ethoxy-1,3,4-oxdiazol-2-one

The oil from Example 3 was taken up in 5 ml of methylene chloride and, with stirring and ice-cooling, admixed with 1 ml of a 20% strength solution of phosgene and toluene. This mixture was allowed to stand at room temperature overnight and 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 under reduced pressure and the product was purified by column chromatography (silica gel, solvent: methanol: methylene chloride = 2 : 98).

Yield: 130 mg m.p.: 195°C

The following examples were prepared similarly to Example 4:

15 Example 9:

3-(4-Morpholinosulfonylphenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: 164°C

Example 10:

20 3-(4-Trifluoromethoxyphenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: 52°C

Example 11:

3-(4-Trifluoromethoxyphenyl)-5-ethoxy-1,3,4-oxdiazol-2-one

25 m.p.: 63°C

Example 12:

3-(4-Trifluoromethoxyphenyl)-5-isopropoxy-1,3,4-oxdiazol-2-one

m.p.: Oil

30

Example 13:

3-(4-Trifluoromethoxyphenyl)-5-butoxy-1,3,4-oxdiazol-2-one

m.p.: Oil

35 Example 14:

3-(4-Trifluoromethoxyphenyl)-5-benzyloxy-1,3,4-oxdiazol-2-one

m.p.: Oil

Example 15:

3-(4-(3,3,5-Trimethylcyclohexylaminosulfonyl)phenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: 164°C

5

Example 16:

3-(4-(3,3,5,5-Tetramethylcyclohexyloxy)phenyl)-5-ethoxy-1,3,4-oxdiazol-2-one

m.p.: 111°C

10

Example 17:

3-(3-Benzyloxyphenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: Oil

15

Example 18:

3-(3-Benzyloxyphenyl)-5-ethoxy-1,3,4-oxdiazol-2-one

m.p.: 85°C

Example 19:

20 3-(3-Trifluoromethoxyphenyl)-5-ethoxy-1,3,4-oxdiazol-2-one

m.p.: Oil

Example 20:

3-(3-Trifluoromethoxyphenyl)-5-methoxy-1,3,4-oxdiazol-2-one

25 m.p.: Oil

Example 21:

3-(3-Trifluoromethoxyphenyl)-5-isopropoxy-1,3,4-oxdiazol-2-one

m.p.: Oil

30

Example 22:

3-(4-(2,2,6,6-Tetramethylpiperidin-4-yl-aminosulfonyl)phenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: Resin

35

Example 23:

3-(4-(2,2,6,6-Tetramethylpiperidin-4-yl-aminosulfonyl)phenyl)-5-isopropoxy-1,3,4-oxdiazol-2-one

m.p.: Resin

Example 24:

3-(4-(2-(Diisopropylaminoethyl)aminosulfonyl)phenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: Oil

5

Example 25:

3-(4-(2-(Diisopropylaminoethyl)aminosulfonyl)phenyl)-5-isopropoxy-1,3,4-oxdiazol-2-one

m.p.: Oil

10

Example 26:

3-(4-(4-Methylpiperazin-1-yl-sulfonyl)phenyl)-5-isopropoxy-1,3,4-oxdiazol-2-one

m.p.: Resin

15

Example 27:

3-(4-(4-Methylpiperazin-1-yl-sulfonyl)phenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: Resin

20

Example 28:

3-(3-(4,4,4-Trifluorobutyloxy)phenyl)-5-ethoxy-1,3,4-oxdiazol-2-one

m.p.: Oil

25

Example 29:

3-(3-(2-Diethylaminoethyloxy)phenyl)-5-ethoxy-1,3,4-oxdiazol-2-one

m.p.: Resin

Example 30:

30 3-(4-(4-Chlorophenoxy)phenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: 68°C

Example 31:

3-(4-(4-Chlorophenoxy)phenyl)-5-isopropoxy-1,3,4-oxdiazol-2-one

35 m.p.: Oil

Example 32:

3-(4-(3,3,5-Trimethylcyclohexylaminosulfonyl)phenyl)-5-isopropoxy-1,3,4-oxdiazol-2-one

m.p.: Oil

5

Example 33:

3-(3-Phenoxyphenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: 89°C

10 Example 34:

3-(3-Phenoxyphenyl)-5-ethoxy-1,3,4-oxdiazol-2-one

m.p.: 50°C

Example 35:

15 3-(3-Phenoxyphenyl)-5-isopropoxy-1,3,4-oxdiazol-2-one

m.p.: 58°C

Example 36:

3-(4-Phenoxyphenyl)-5-methoxy-1,3,4-oxdiazol-2-one

20 m.p.: 83°C

Example 37:

3-(4-Cyclohexylphenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: Resin

25

Example 38:

3-(3-(3,3,5,5-Tetramethylcyclohexyloxy)phenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: 68°C

30

Example 39:

3-(4-Phenylphenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: >260°C (decomp.)

35 Example 40:

3-(3-(3-Methylphenoxyethyl)phenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: 47°C

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15

Example 41:

3-(3-Phenylphenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: 80°C

5 Example 42:

3-(4-(3,3-Dimethylpiperidinocarbonyl)phenyl)-5-methoxy-1,3,4-oxdiazol-2-one

m.p.: Resin

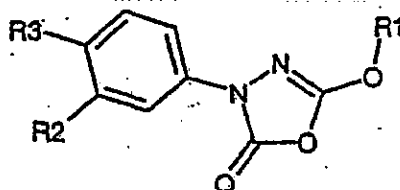
10 Example 43:

3-(4-(3,3,5,5-Tetramethylcyclohexyloxy)phenyl)-5-isopropoxy-1,3,4-oxdiazol-2-one

m.p.: Resin

Claims

1. A substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-one of the formula 1,



1

In which

- R¹** is C₁-C₆-alkyl or C₃-C₈-cycloalkyl, where both groups are unsubstituted or mono- or polysubstituted by O-C₁-C₄-alkyl, S-C₁-C₄-alkyl, N(C₁-C₄-alkyl)₂ and/or phenyl which for its part may be mono- or polysubstituted by halogen, C₁-C₄-alkyl, O-C₁-C₄-alkyl, nitro, CF₃, and
- R² and R³** independently of one another are hydrogen; C₆-C₁₀-aryl; C₃-C₈-cycloalkyl; optionally C₁-C₄-alkyl-substituted C₆-C₁₀-aryloxymethyl; O-C₃-C₈-cycloalkyl; O-C₆-C₁₀-aryl or O-benzyl, unsubstituted or mono- or polysubstituted by halogen, CF₃ or C₁-C₄-alkyl; O-C₁-C₆-alkyl which is mono- or polysubstituted by fluorine, C₆-C₁₀-aryl or amino, where amino for its part may be mono- or polysubstituted by C₁-C₄-alkyl; are SO₂-NH-C₁-C₆-alkyl, unsubstituted or substituted by N(C₁-C₆-alkyl)₂; are SO₂-NH-(2,2,6,6-tetramethylpiperidin-4-yl); are SO₂-NH-C₃-C₈-cycloalkyl, unsubstituted or mono- or polysubstituted by C₁-C₄-alkyl; are SO₂-N(C₁-C₆-alkyl)₂ or COX, where X is O-C₁-C₆-alkyl, NH-C₁-C₆-alkyl, NH-C₃-C₈-cycloalkyl or N(C₁-C₆-alkyl)₂, and N(C₁-C₆-alkyl)₂ may also be pyrrolidino, piperidino, morpholino, thiomorpholino or piperazino which may be unsubstituted or substituted by C₁-C₄-alkyl, benzyl, C₆-C₁₀-aryl, CO-C₁-C₄-alkyl, CO-C₆-C₁₀-aryl, CO-O-C₁-C₄-alkyl, SO₂-C₁-C₄-alkyl or SO₂-C₆-C₁₀-aryl, with the proviso that R² and R³ are not simultaneously hydrogen, and its physiologically acceptable salts and optical isomers.
2. The substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-one of the formula 1 as claimed in claim 1 in which one of the radicals R² or R³ is hydrogen.
3. The substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-one of the formula 1 as claimed in claim 1 or 2 in which
- R¹** is C₁-C₆-alkyl which may be unsubstituted or substituted by phenyl.
4. The substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-one of the formula 1 as claimed in any of claims 1 to 3 in which
- R² and R³** independently of one another are hydrogen; C₆-C₁₀-aryl; C₃-C₈-cycloalkyl; unsubstituted or C₁-C₄-alkyl-substituted C₆-C₁₀-aryloxymethyl; O-C₃-C₈-cycloalkyl, O-C₆-C₁₀-aryl or O-benzyl, unsubstituted or mono- or polysubstituted by C₁-C₄-alkyl or halogen; O-C₁-C₆-alkyl which is mono- or polysubstituted by fluorine, C₆-C₁₀-aryl or amino, where amino for its part may be mono- or polysubstituted by C₁-C₄-alkyl; are SO₂-NH-C₁-C₆-alkyl, optionally substituted by N(C₁-C₆-alkyl)₂; are SO₂-NH-(2,2,6,6-tetramethylpiperidin-4-yl); are SO₂-NH-C₃-C₈-cycloalkyl, substituted by C₁-C₄-alkyl; are SO₂-N(C₁-C₆-alkyl)₂ or CO-N(C₁-C₆-alkyl)₂, and N(C₁-C₆-alkyl)₂ may also be piperidino, morpholino or piperazino which can be unsubstituted or substituted by C₁-C₄-alkyl.
5. The substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-one of the formula 1 as claimed in any of claims 1 to 4 in which
- R²** is hydrogen; C₆-C₁₀-aryl; O-C₆-C₁₀-aryl; unsubstituted or C₁-C₄-alkyl-substituted C₆-C₁₀-aryloxymethyl, O-benzyl; is O-C₁-C₆-alkyl which is mono- or polysubstituted by fluorine or amino, where amino for its part may be mono- or polysubstituted by C₁-C₄-alkyl; is O-C₃-C₈-cycloalkyl which is unsubstituted or mono- or polysubstituted by C₁-C₄-alkyl; and
- R³** is hydrogen; C₆-C₁₀-aryl; C₃-C₈-cycloalkyl; O-C₃-C₈-cycloalkyl or O-C₆-C₁₀-aryl which are unsubstituted or mono- or polysubstituted by C₁-C₄-alkyl or halogen; is O-C₁-C₆-alkyl which is mono- or polysubstituted by fluorine; is SO₂-NH-C₁-C₆-alkyl, unsubstituted or substituted by N(C₁-C₆-alkyl)₂; is SO₂-NH-(2,2,6,6-tetramethylpiperidin-4-yl);

ethylpiperidin-4-yl); is $\text{SO}_2\text{-NH-C}_3\text{-C}_8\text{-cycloalkyl}$, mono- or polysubstituted by $\text{C}_1\text{-C}_4\text{-alkyl}$; is $\text{SO}_2\text{-N(C}_1\text{-C}_6\text{-alkyl)}_2$ or $\text{CO-N(C}_1\text{-C}_6\text{-alkyl)}_2$, and $\text{N(C}_1\text{-C}_6\text{-alkyl)}_2$ is also piperidino, morpholino or piperazino, which may be unsubstituted or substituted by $\text{C}_1\text{-C}_4\text{-alkyl}$.

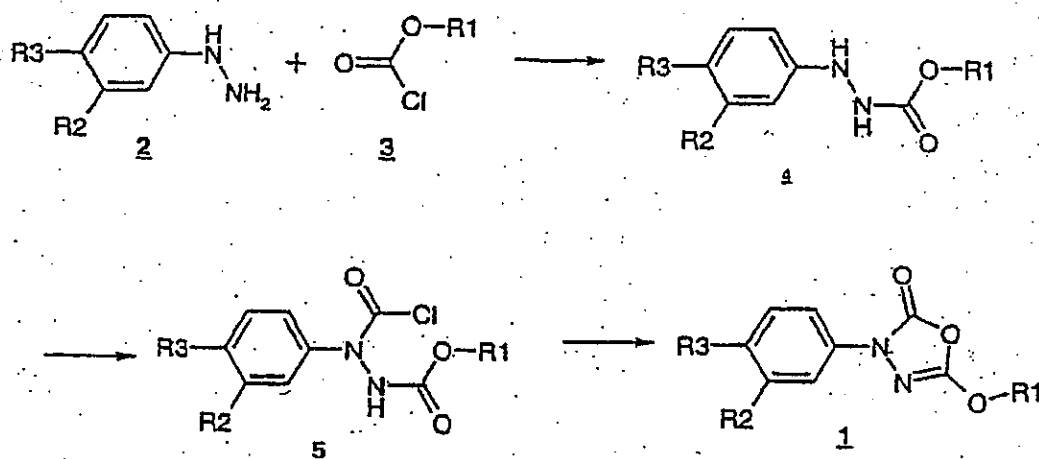
6. The substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-one of the formula 1 as claimed in any of claims 1 to 5 in which

R^1 is methyl, ethyl, butyl, isopropyl or benzyl and
 R^2 is hydrogen, trifluoromethoxy, trifluorobutoxy, 3,3,5,5-tetramethylcyclohexyloxy, benzyloxy, phenoxy, phenyl, 2-diethylaminoethyloxy or 3-methylphenoxyethyl, and
 R^3 is hydrogen, trifluoromethoxy, 3,3,5,5-tetramethylcyclohexyloxy, phenoxy, 4-chlorophenoxy, cyclohexyl, phenyl, morpholinosulfonyl, 3,3,5-trimethylcyclohexylaminosulfonyl, 2,2,6,6-tetramethylpiperidin-4-yl-aminosulfonyl, 2-(diisopropylaminoethyl)aminosulfonyl, 4-methylpiperazin-1-yl-sulfonyl, 3,3-dimethylpiperidino-carbonyl or 3,5-dichlorophenoxy.

7. The substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-one of the formula 1 as claimed in any of claims 1 to 6 in which

R^1 is methyl, ethyl, butyl, isopropyl or benzyl and
 R^2 is hydrogen, trifluoromethoxy, 3,3,5,5-tetramethylcyclohexyloxy, benzyloxy or phenoxy and
 R^3 is hydrogen, trifluoromethoxy, 3,3,5,5-tetramethylcyclohexyloxy, phenoxy, cyclohexyl, phenyl, morpholinosulfonyl or 3,3,5-trimethylcyclohexylaminosulfonyl.

8. A process for preparing the substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-one of the formula 1 as claimed in any of claims 1 to 7, which comprises



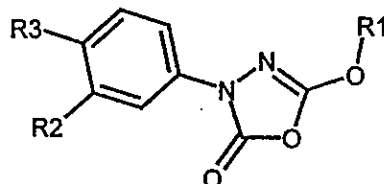
reacting hydrazines of the formula 2 with chloroformic esters of the formula 3 or other reactive carbonic acid ester derivatives, in which R^1 , R^2 and R^3 are as defined in any of claims 1 to 7, to give compounds of the formula 4 which are acylated with phosgene, carbonyldiimidazole or diphosgene and cyclized to give the compounds of the formula 1.

9. The substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-one of the formula 1 as claimed in any of claims 1 to 7 having an inhibiting effect on the hormone-sensitive lipase HSL.
10. A medicament, comprising a substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-one of the formula 1 as claimed in any of claims 1 to 7.
11. The use of the substituted 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-one of the formula 1 as claimed in any of claims 1 to 7 for preparing a therapeutic.

Abstract:

SUBSTITUTED 3-PHENYL - 5-ALKOXY-1,3,4-OXDIAZOL-2-ONES
AND THEIR USE AS LIPASE INHIBITORS

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



1

Substituted 3-phenyl-5-alkoxy-1,3,4-oxdiazol-2-ones of the formula 1 and their physiologically acceptable salts and optical isomers are described, where R¹ is C₁-C₆-alkyl, C₃-C₉-cycloalkyl, both of which may be unsubstituted or substituted, and R² and R³ independently of one another are hydrogen, C₆-C₁₀-aryl, C₃-C₈-cycloalkyl, C₆-C₁₀-aryloxymethyl, O-benzyl, O-C₆-C₁₀-aryl, O-C₃-C₈-cycloalkyl, O-C₁-C₆-alkyl, SO₂-NH-C₁-C₆-alkyl, SO₂-NH-(2,2,6,6-tetramethylpiperidin-4-yl), SO₂-NH-C₃-C₈-cycloalkyl, SO₂-N(C₁-C₆-alkyl)₂ or COX, where X is O-C₁-C₆-alkyl, NH-C₁-C₆-alkyl, NH-C₃-C₈-cycloalkyl or N(C₁-C₆-alkyl)₂, with the proviso that the substituents R² and R³ may in some instances be unsubstituted or substituted and are not both simultaneously hydrogen. Also described is a process for their preparation. The compounds have an inhibitory effect on the hormone-sensitive lipase, HSL.