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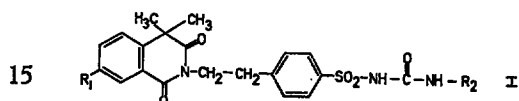


(54) SULPHONYL UREAS

(71) We, DR. KARL THOMAE G.M.B.H., a German Body Corporate of Biberach an der Riss, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to isoquinoline derivatives having interesting physiological activities and processes for the preparation thereof.

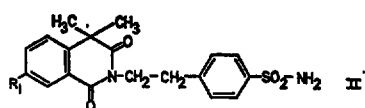
According to one feature of the invention there are provided compounds of the general formula



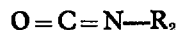
(wherein R_1 represents a hydrogen, chlorine or bromine atom or an alkoxy group containing from 1 to 4 carbon atoms and R_2 represents a cyclohexyl or adamant-1-yl group) and non-toxic salts thereof. Preferred salts of the compounds of formula I are their alkali metal salts.

The expression "non-toxic salt" is used herein to designate a salt which is physiologically acceptable at the dosages at which it is administered.

According to a further feature of the invention there is provided a process for the preparation of compounds of formula I wherein a sulfonamide of formula



(wherein R_1 is as hereinbefore defined) or an alkali metal salt thereof is reacted with an isocyanate of formula



III

(wherein R_2 is as hereinbefore defined) and the compound of formula I thus produced is if desired converted into a non-toxic salt thereof.

The compounds according to the invention have interesting pharmacological properties, and in particular they in general possess a strong hypoglycemic activity even at relatively low doses. The compounds according to the invention also in general have relatively low toxicities.

Preferred compounds of formula I by virtue of their particularly interesting physiological properties include those where R_1 represents a methoxy, ethoxy, isopropoxy or n-butoxy group.

Compounds C, D, F and G as defined below and the alkali metal salts thereof are especially interesting by virtue of their hypoglycemic activity and constitute particularly preferred features of the present invention.

The compounds

A = N-cyclohexyl - N' - { 4 - [2 - (1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl } - urea,

B = N - cyclohexyl - N' - { 4 - [2 - (7 - chloro - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4-dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl } - urea,

C = N - cyclohexyl - N' - { 4 - [2 - (7 - bromo - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl } - urea,

- D = N - adamant - 1 - yl - N' - { 4 - [2 - (1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl } - urea,
- 5 E = N - adamant - 1 - yl - N' - { 4 - [2 - (7 - chloro - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl } - urea,
- 10 F = N - adamant - 1 - yl - N' - { 4 - [2 - (7 - bromo - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl } - urea and
- 15 G = N - cyclohexyl - N' - { 4 - [2 - (7 - methoxy - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl } - urea
- 20 H = N - (4 - chlorobenzenesulfonyl) - N' - n - propyl - urea.

The minimum effective oral dose and the resultant depression of blood-glucose levels (in mg%) were determined in male rats which were fed and had an average body weight of

180 g. The sodium salts of substances A—H were suspended in methyl cellulose and applied orally by stomach tube. Blood samples were collected hourly from the tail blood vessels (20 μ l per test).

The glucose content was determined using a Technicon-Auto Analyzer [see U. Harding, G. Heinzel, Zeitschr. f. klin. Chem. u. klin. Biochem. 7, Part 6 (1969)] according to the "Hexokinase" method (phosphorylation of the glucose with ATP to obtain glucose-6-phosphate, followed by reduction with glucose-6-phosphate dehydrogenase to the gluconate-6-phosphate, the NADPH₂ being simultaneously formed from the NADP was measured photometrically at 334 nm).

The effect of the sodium salts of compounds A—H on blood pressure was determined in anesthetized cats [α -D-(+)-glucochloralose 50 mg/kg i.v.; urethane 250 mg/kg i.v., weight: 2—3 kg] using a Grass-Polygraph. The substances to be investigated were injected in solution into the right femoral vein.

The following table shows the results obtained:

Substance	minimal effective dose mg/kg p.o.	depression of blood-glucose mg %	blood-pressure side effect after oral application of
A	0.62	— 14	8 mg/kg: none
B	0.62	— 12	8 mg/kg: none
C	0.31	— 8	8 mg/kg: none
D	0.31	— 9	8 mg/kg: none
E	0.62	— 20	16 mg/kg: none
F	0.31	— 11	16 mg/kg: none
G	0.20	— 10	16 mg/kg: no significant
H	10.0	— 20	16 mg/kg: long lasting fall of blood-pressure

The acute toxicity was determined in another study.

- a) Determination of the acute toxicity (i.v.) of the sodium salts was carried out in white mice of our own breed and having an average body weight of from 18 to 25 g. They were deprived of food for 16 hours before the test but were free to receive water. Each compound was tested at at least 4 dosage levels (10 animals per dose).

The sodium salts were dissolved in 0.01N-

sodium hydroxide solution and administered at 0.2 ml/kg of body weight by injection into the tail vein for 30 seconds. The LD₅₀, the dose at which 50% of the animals died within 7 days, was calculated according to the method of Behrens-Kärber.

b) The peroral LD₅₀ was determined analogously and the sodium salts or the free acids (granulated: grain size of 10 μ) of the compounds to be investigated were administered as a homogenizate at 1% in methyl cellulose,

the quantity being maintained at 2 ml/ 25 g of body weight of methyl cellulose suspension.

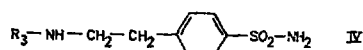
The following table shows the results obtained:

Substance	Toxicity of		
	Sodium salts		Free acids LD ₅₀ g/kg p.o.
	LD ₅₀ g/kg p.o.	LD ₅₀ mg/kg i.v.	
A	>2.0	234	>15
B	~2.0		
C	>2.0		>15
D	>2.5	260	>15
E	>2.5	210	
F	>2.5	191	>15
G	1.5	300	>15
H	1.116	400	1.25

The process according to the invention is preferably effected by dissolving a sulfonamide of formula II in an inert solvent, preferably in a dipolar aprotic solvent, for example in dimethylformamide, acetone or N-methyl pyrrolidone. The sulfonamide is then advantageously converted into an alkali metal salt thereof, conveniently with a strong anhydrous basic alkali metal compound for example comprising an alkali metal alcoholate such as potassium tert.-butoxide, an alkali metal hydride or an alkali metal hydroxide. Subsequently an isocyanate of formula III is added to the mixture with cooling. The reaction may then be completed for example at a low or a slightly elevated temperature, advantageously at a temperature of from -5°C to ambient temperature.

The compounds of general formula I obtained may, if desired be converted into an alkali metal salt thereof.

The sulfonamides of general formula II are also new and in order to prepare those wherein R₁ represents hydrogen or a chlorine or bromine atom, a benzenesulfonamide of formula



(wherein R₃ represents a hydrogen atom or an acetyl group) is initially reacted with homophthalic acid, a homophthalic acid derivative having an activated carboxy group or a 4-halohomophthalic acid. The reaction is advantageously effected as a melt or, if desired, in solution in an inert organic solvent, con-

veniently at a temperature of from 150° to 200°C. The sulfonamides thus obtained are then methylated by a conventional method, for example using a methyl halide advantageously in the presence of an inorganic base such as sodium hydroxide or a sodium alcoholate. However, if desired, the corresponding methyl substituted homophthalic acid may be used as starting material.

The sulfonamides of formula II (wherein R₁ represents an alkoxy group) may be prepared for example by condensation of 2-(4-amino-sulfonylphenyl)-ethylamine with a 1,2,3,4-tetrahydro - 4,4 - dimethyl - 7 - alkoxyisochromane - 1,3 - dione. The reaction is preferably effected in a solvent, for example in xylene advantageously at the boiling point of the solvent with separation of the water formed.

The 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 7 - alkoxyisochromane - 1,3 - diones may be prepared, for example by alkylation of 2,4,4 - trimethyl - 7 - hydroxyisoquinoline - 1,3 - dione followed by refluxing with aqueous sodium hydroxide solution and acidification. 2,4,4 - Trimethyl - 7 - hydroxyisoquinoline - 1,3 - dione may be prepared for example by nitration of 2,4,4 - trimethylisoquinoline - 1,3 - dione followed by reduction of the nitro group conveniently using catalytically activated hydrogen, followed by diazotisation and refluxing of the resulting diazonium compound in water.

The isocyanates of formula III used as starting material are known and may be prepared from the corresponding amines for example using phosgene.

According to a yet further feature of the invention there are provided pharmaceutical compositions comprising at least one compound according to the invention as herein defined in association with a pharmaceutical carrier or excipient. The compositions may be presented in a form suitable for oral, rectal or parenteral administration, oral forms being particularly preferred. Thus, for example, compositions for oral administration may be solid or liquid and may take the form of granules, tablets, coated tablets, capsules, syrups, emulsions, suspensions or drops, such compositions comprising carriers or excipients conventionally used in the pharmaceutical art. Tablets and capsules are the preferred form for oral administration. Thus, for example, suitable tableting excipients include lactose, potato and soluble starches and magnesium stearate.

For parenteral administration, the carrier may be a sterile, parenterally acceptable liquid such as sterile water, or a parenterally acceptable oil e.g. arachis oil, contained in ampoules. Compositions for rectal administration may take the form of suppositories, the carrier comprising a suppository base.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Tablets, coated tablets, capsules, suppositories and ampoules are examples of suitable dosage unit forms. Each dosage unit preferably contains 1 to 10 mg, and especially 2.5 to 5 mg, of active ingredient.

The following examples illustrate the preparation of compounds according to the invention, and also pharmaceutical compositions containing such compounds as active ingredients:—

EXAMPLE 1

a) 1,2,3,4-Tetrahydro-4,4-dimethyl-2-[2-(4-aminosulfonylphenyl)ethyl]-7-methoxyisoquinoline-1,3-dione

45 4 g of 1,2,3,4 - tetrahydro - 4,4 - dimethyl-7 - methoxyisochromane - 1,3 - dione (m.p.: 95—97°C) and 2.53 g of 2 - (4 - aminosulfonylphenyl) - ethylamine in 150 ml of xylene were refluxed for 2 hours, the water formed being removed in a separating funnel. After cooling, the reaction mixture was sucked off and the residue recrystallized from n-propanol with the addition of charcoal.

50 Yield: 2.9 g (58% of theory), m.p.: 203—205°C.

b) N-Cyclohexyl-N'-{4-[2-(7-methoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)ethyl]-benzenesulfonyl}-urea

32.2 g of 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - 7 - methoxyisoquinoline - 1,3 - dione were dissolved in 700 ml of dimethylformamide. 9.1 g of potassium tert.-butoxide were added to the mixture and 14.9 g of cyclohexylisocyanate were then added dropwise with ice cooling. Subsequently, the reaction mixture was stirred for 5 hours with ice cooling and left to stand over night at -2°C. The mixture was mixed with water, the precipitate formed was sucked off and the filtrate was acidified with 2N hydrochloric acid after more water had been added. A greasy product was precipitated and this became crystalline on being refluxed in methanol.

Yield: 26 g (85% of theory), m.p.: 180—182°C.

10.5 g of N - cyclohexyl - N' - {4 - [2 - (7 - methoxy - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl} - urea were dissolved in 500 ml of acetone and the stoichiometric quantity of sodium ethoxide, dissolved in 20 ml of ethanol, was added dropwise and slowly at a temperature between -5° and 0°C. 10.1 g (91% of theory) of the sodium salt of N - cyclohexyl - N' - {4 - [2 - (7 - methoxy - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl} - urea were obtained in the form of colourless crystals which sinter above 160°C.

EXAMPLE 2

N-Adamant-1-yl-N'-{4-[2-(7-methoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

Prepared from 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - 7 - methoxyisoquinoline - 1,3 - dione and adamantylisocyanate analogously to Example 1b.

M.p. of the sodium salt: 235—238°C.

EXAMPLE 3

N-Cyclohexyl-N'-{4-[2-(7-ethoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

Prepared from 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - 7 - ethoxyisoquinoline - 1,3 - dione [m.p.: 149°C, prepared from 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 7 - ethoxyisochromane - 1,3 - dione and 2 - (4 - aminosulfonylphenyl) - ethylamine analogously to Example 1a] and cyclohexylisocyanate analogously to Example 1b.

M.p.: 90°C

M.p. of the sodium salt: 175°C.

EXAMPLE 4

N-Adamant-1-yl-N'-{4-[2-(7-ethoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

Prepared from 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - 7 - ethoxyisoquinoline - 1,3 - dione and adamantylisocyanate analogously to Example 1b.

M.p.: 107°C

M.p. of the sodium salt: 225°C.

EXAMPLE 5

N-Cyclohexyl-N'-{4-[2-(7-isopropoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

Prepared from 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - 7 - isopropoxyisoquinoline - 1,3 - dione [m.p.: 154°C, prepared from 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 7 - isopropoxyisochromane - 1,3 - dione and 2 - (4 - aminosulfonylphenyl) - ethylamine analogously to Example 1a] and cyclohexylisocyanate analogously to Example 1b.

M.p.: 124°C

M.p. of the sodium salt: 183°C.

EXAMPLE 6

N-Cyclohexyl-N'-{4-[2-(7-n-butoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

Prepared from 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - 7 - n - butoxyisoquinoline - 1,3 - dione [m.p.: 107°C, prepared from 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 7 - n - butoxyisochromane - 1,3 - dione and 2 - (4 - aminosulfonylphenyl) - ethylamine analogously to Example 1a] and cyclohexylisocyanate analogously to Example 1b.

M.p.: 95°C

M.p. of the sodium salt: 225°C.

EXAMPLE 7

a) 1,2,3,4-Tetrahydro-4,4-dimethyl-2-[2-(4-aminosulfonylphenyl)-ethyl]-isoquinoline-1,3-dione

26.7 g of 1,2,3,4 - tetrahydro - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - isoquinoline - 1,3 - dione (m.p.: 246°C) in 170 ml of ethanol and 30 ml of water were refluxed with 22 g of methyl iodide. A solution of 155 mMole of sodium ethoxide in 70 ml of ethanol was simultaneously dropped in. After the addition of the sodium ethoxide the reaction mixture was still refluxed for 2 to 4 hours. The solvents were distilled off and the residue was mixed with ice water. The insoluble crude product was recrystallized from chlorobenzene.

Yield 22.7 g (78.5% of theory)

M.p.: 213—214°C.

b) N-Cyclohexyl-N'-{4-[2-(1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

5 g of 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - isoquinoline - 1,3 - dione were dissolved in 28 ml of dimethylformamide and the sodium salt was formed with 0.64 g of sodium hydride (50% oil suspension). After the latter had been completely dissolved, 1.83 g of cyclohexylisocyanate were added at 5°C. To complete the reaction, the mixture was stirred for 1 to 2 hours at room temperature. The reaction mixture was then mixed with 100 ml of water and acidified with glacial acetic acid. The precipitated product was recrystallized from methanol.

Yield: 2.6 g (39.1% of theory)

M.p. 179—181°C

M.p. of the sodium salt: from 205°C (decomp.)

EXAMPLE 8

N-Adamant-1-yl-N'-{4-[2-(7-bromo-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

Prepared from 7 - bromo - 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - isoquinoline - 1,3 - dione [m.p.: 186°C, prepared from 7 - bromo - 1,2,3,4 - tetrahydro - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - isoquinoline - 1,3 - dione (m.p.: 238°C) and methyl iodide analogously to Example 7a] and adamantylisocyanate analogously to Example 7b.

Yield: 14.4% of theory

M.p.: 119°C (methanol)

M.p. of the sodium salt: 226°C (decomp)

EXAMPLE 9

N-Cyclohexyl-N'-{4-[2-(7-chloro-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

Prepared from 7 - chloro - 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - isoquinoline - 1,3 - dione [m.p.: 193°C, prepared from 7 - chloro - 1,2,3,4 - tetrahydro - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - isoquinoline - 1,3 - dione (m.p.: 252°C) and methyl iodide analogously to Example 7a] and adamantylisocyanate analogously to Example 7b.

Yield: 40% of theory

M.p.: 177°C (methanol).

EXAMPLE 10

N-Adamant-1-yl-N'-{4-[2-(1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

Prepared from 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - aminosulfonylphenyl)-

ethyl] - isoquinoline - 1,3 - dione and adamantyl isocyanate analogously to Example 7b.

Yield: 10.4% of theory

M.p.: 199°C (methanol)

- 5 M.p. of the sodium salt: 232—235°C (decomp).

EXAMPLE 11

N-Adamant-1-yl-N'-{4-[2-(7-chloro-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

10

Prepared from 7 - chloro - 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - isoquinoline - 1,3 - dione and adamantylisocyanate analogously to Example 7b.

Yield: 10% of theory

M.p.: 184°C (ethanol).

EXAMPLE 12

N-Cyclohexyl-N'-{4-[2-(7-bromo-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

20

Prepared from 7 - bromo - 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - aminosulfonylphenyl) - ethyl] - isoquinoline - 1,3 - dione and cyclohexylisocyanate analogously to Example 7b.

Yield: 50% of theory

- 30 M.p.: 179°C (ethanol).

EXAMPLE 13

Tablets containing

N-Cyclohexyl-N'-{4-[2-(7-methoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

35

Composition:

1 tablet contains:

40	N-cyclohexyl-N'-{4-[2-(7-methoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea	2.5 mg
	lactose	87.5 mg
45	corn starch	26.0 mg
	polyvinylpyrrolidone	3.0 mg
	magnesium stearate	1.0 mg
		120.0 mg

Compounding procedure:

- 50 The active substance was intensively mixed with lactose and corn starch and evenly moistened with a 12.5% (g/g) solution of the polyvinylpyrrolidone in ethanol. The mass was passed through a 1.5mm-mesh screen, dried at 45°C and again passed through a screen of 1.0 mm. The granulate obtained was mixed

with magnesium stearate and pressed into tablets.

Weight of tablet: 120 mg

Die: 7 mm, flat, with facet and notch.

60

EXAMPLE 14

Capsules containing

N-Cyclohexyl-N'-{4-[2-(7-methoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

65

Composition:

1 capsule contains:

	N-cyclohexyl-N'-{4-[2-(7-methoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea	2.5 mg
	corn starch (dried)	97.5 mg
		100.0 mg

75

Compounding procedure:

The ingredients were intensively mixed and the mixture was granulated through a 0.75 mm-mesh screen and filled into gelatine-capsules of appropriate size.

Contents of capsule: 100 mg.

According to the same method tablets and gelatine capsules may also be produced with 2.5 mg of each one of the following substances:

85

N - Cyclohexyl - N' - {4 - [2 - (7 - bromo - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl} - urea

N - Adamant - 1 - yl - N' - {4 - [2 - (1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl} - urea

90

N - Adamant - 1 - yl - N' - {4 - [2 - (7 - chloro - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl} - urea

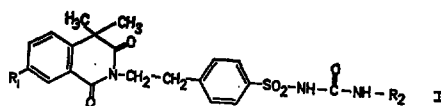
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N - Adamant - 1 - yl - N' - {4 - [2 - (7 - methoxy - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl} - urea.

100

WHAT WE CLAIM IS:—

1. Compounds of the general formula



(wherein R₁ represents a hydrogen, chlorine 105

ethyl] - isoquinoline - 1,3 - dione and adamantyl isocyanate analogously to Example 7b.
Yield: 10.4% of theory
M.p.: 199°C (methanol)
5 M.p. of the sodium salt: 232—235°C (decomp).

EXAMPLE 11

10 N-Adamant-1-yl-N'-{4-[2-(7-chloro-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea
Prepared from 7 - chloro - 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - amino-sulfonylphenyl) - ethyl] - isoquinoline - 1,3 -
15 dione and adamantylisocyanate analogously to Example 7b.
Yield: 10% of theory
M.p.: 184°C (ethanol).

EXAMPLE 12

20 N-Cyclohexyl-N'-{4-[2-(7-bromo-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea
Prepared from 7 - bromo - 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 2 - [2 - (4 - amino-sulfonylphenyl) - ethyl] - isoquinoline - 1,3 -
25 dione and cyclohexylisocyanate analogously to Example 7b.
Yield: 50% of theory
30 M.p.: 179°C (ethanol).

EXAMPLE 13

Tablets containing

35 N-Cyclohexyl-N'-{4-[2-(7-methoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

Composition:

1 tablet contains:

40	N-cyclohexyl-N'-{4-[2-(7-methoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea	2.5 mg
	lactose	87.5 mg
45	corn starch	26.0 mg
	polyvinylpyrrolidone	3.0 mg
	magnesium stearate	1.0 mg
		120.0 mg

Compounding procedure:

50 The active substance was intensively mixed with lactose and corn starch and evenly moistened with a 12.5% (g/g) solution of the polyvinylpyrrolidone in ethanol. The mass was passed through a 1.5mm-mesh screen, dried
55 at 45°C and again passed through a screen of 1.0 mm. The granulate obtained was mixed

with magnesium stearate and pressed into tablets.

Weight of tablet: 120 mg

Die: 7 mm, flat, with facet and notch.

60

EXAMPLE 14

Capsules containing

N-Cyclohexyl-N'-{4-[2-(7-methoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea

65

Composition:

1 capsule contains:

N-cyclohexyl-N'-{4-[2-(7-methoxy-1,2,3,4-tetrahydro-1,3-dioxo-4,4-dimethylisoquinol-2-yl)-ethyl]-benzenesulfonyl}-urea	2.5 mg	70
corn starch (dried)	97.5 mg	
	100.0 mg	75

Compounding procedure:

The ingredients were intensively mixed and the mixture was granulated through a 0.75 mm-mesh screen and filled into gelatine-capsules of appropriate size.

80

Contents of capsule: 100 mg.

According to the same method tablets and gelatine capsules may also be produced with 2.5 mg of each one of the following substances:

85

N - Cyclohexyl - N' - {4 - [2 - (7 - bromo - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl} - urea

N - Adamant - 1 - yl - N' - {4 - [2 - (1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl} - urea

90

N - Adamant - 1 - yl - N' - {4 - [2 - (7 - chloro - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl} - urea

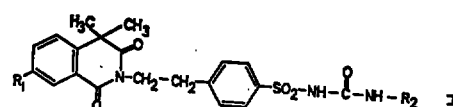
95

N - Adamant - 1 - yl - N' - {4 - [2 - (7 - methoxy - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl} - urea.

100

WHAT WE CLAIM IS:—

1. Compounds of the general formula



(wherein R₁ represents a hydrogen, chlorine 105



or bromine atom or an alkoxy group containing from 1 to 4 carbon atoms and R_2 represents a cyclohexyl or adamant-1-yl group) and non-toxic salts thereof.

5 2. Compounds of the formula I, as defined in claim 1, wherein R_1 represents a hydrogen, chlorine or bromine atom and alkali metal salts thereof.

10 3. Compounds of the formula I, as defined in claim 1, wherein R_1 represents an alkoxy group containing from 1 to 4 carbon atoms and alkali metal salts thereof.

15 4. Compounds as claimed in claim 3 wherein R_1 represents a methoxy, ethoxy, isopropoxy or n-butoxy group.

20 5. N - cyclohexyl - N' - { 4 - [2 - (7 - bromo - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl } - urea and alkali metal salts thereof.

25 6. N - Adamant - 1 - yl - N' - { 4 - [2 - (1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl } - urea and alkali metal salts thereof.

30 7. N - Adamant - 1 - yl - N' - { 4 - [2 - (7 - bromo - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl } - urea and alkali metal salts thereof.

35 8. N - Cyclohexyl - N' - { 4 - [2 - (7 - methoxy - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl } - urea and alkali metal salts thereof.

40 9. N - Adamant - 1 - yl - N' - { 4 - [2 - (7 - methoxy - 1,2,3,4 - tetrahydro - 1,3 - dioxo - 4,4 - dimethylisoquinol - 2 - yl) - ethyl] - benzenesulfonyl } - urea and alkali metal salts thereof.

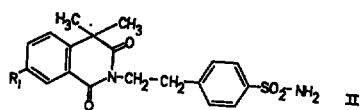
45 10. Compounds as claimed in any of claims 2, 5, 6 and 7 wherein the alkali metal salt is the sodium salt.

50 11. Compounds as claimed in any of claims 3, 4, 8 and 9 wherein the alkali metal salt is the sodium salt.

55 12. Compounds as claimed in claim 2, with the exception of those as claimed in any of claims 5 to 7, as herein specifically described.

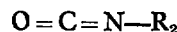
13. Compounds as claimed in claim 3, with the exception of those as claimed in either of claims 8 and 9, as herein specifically described.

14. A process for the preparation of compounds as claimed in claim 1 wherein a sulfonamide of formula



(wherein R_1 represents a hydrogen, chlorine or

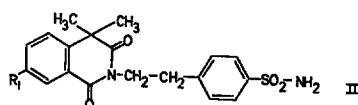
bromine atom or an alkoxy group containing from 1 to 4 carbon atoms) or an alkali metal salt thereof is reacted with an isocyanate of formula



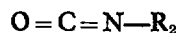
III

(wherein R_2 is as defined in claim 1) and the compound of formula I thus produced is, if desired, converted into a non-toxic salt thereof.

15. A process for the preparation of compounds as claimed in claim 2 wherein a sulfonamide of formula



(wherein R_1 represents a hydrogen, chlorine or bromine atom) or an alkali metal salt thereof is reacted with an isocyanate of formula



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(wherein R_2 is as defined in claim 1) and the compound of formula I thus produced is, if desired, converted into an alkali metal salt thereof.

16. A process as claimed in claim 15 wherein the reaction is effected in an inert solvent.

17. A process as claimed in claim 16 wherein the solvent comprises a dipolar aprotic solvent.

18. A process as claimed in claim 17 wherein the solvent comprises dimethylformamide, acetone or N-methylpyrrolidone.

19. A process as claimed in any of claims 16 to 18 wherein an alkali metal salt of a compound of formula II is used and is prepared in the solution by reacting a compound of formula II with a strong anhydrous basic alkali metal compound.

20. A process as claimed in claim 19 wherein the basic alkali metal compound comprises an alkali metal alcoholate, an alkali metal hydride or an alkali metal hydroxide.

21. A process as claimed in claim 20 wherein the alkali metal alcoholate is potassium tert.-butoxide.

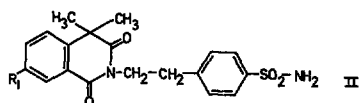
22. A process as claimed in any of claims 15 to 21 wherein the reaction is effected at a temperature of from -5°C to ambient temperature.

23. A process as claimed in claim 15 substantially as herein described.

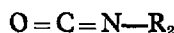
24. A process for the preparation of compounds as claimed in claim 2, substantially as herein described in any of Examples 7 to 12.

25. A process for the preparation of compounds as claimed in claim 3 wherein a sulfonamide of formula





(wherein R_1 represents an alkoxy group containing from 1 to 4 carbon atoms) or an alkali metal salt thereof is reacted with an isocyanate of formula



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(wherein R_2 is as defined in claim 1), and the compound of formula I thus produced is if desired converted into an alkali metal salt thereof.

26. A process as claimed in claim 25 wherein the reaction is effected in an inert solvent.

27. A process as claimed in claim 26 wherein the solvent comprises a dipolar aprotic solvent.

28. A process as claimed in claim 27 wherein the solvent comprises dimethylformamide, acetone or N-methylpyrrolidone.

29. A process as claimed in any of claims 26 to 28 wherein an alkali metal salt of a compound of formula II is used and is prepared in the solution by reacting a compound of formula II with a strong anhydrous basic alkali metal compound.

30. A process as claimed in claim 29 wherein the basic alkali metal compound comprises an alkali metal alcoholate, an alkali metal hydride or an alkali metal hydroxide.

31. A process as claimed in claim 30 wherein the alkali metal alcoholate is potassium tert.-butoxide.

32. A process as claimed in any of claims 25 to 31 wherein the reaction is effected at a temperature of from -5°C to ambient temperature.

33. A process as claimed in claim 25 substantially as herein described.

34. A process for the preparation of compounds as claimed in claim 3, substantially as

herein described in any of Examples 1 to 6.

35. Compounds as claimed in claim 2 when prepared by a process as claimed in any of claims 15 to 24.

36. Compounds as claimed in claim 3 when prepared by a process as claimed in any of claims 25 to 34.

37. Pharmaceutical compositions comprising as active ingredient at least one compound as claimed in claim 1 in association with a pharmaceutical carrier or excipient.

38. Pharmaceutical compositions comprising as active ingredient at least one compound as claimed in claim 2 in association with a pharmaceutical carrier or excipient.

39. Pharmaceutical compositions comprising as active ingredient at least one compound as claimed in claim 3 in association with a pharmaceutical carrier or excipient.

40. Compositions as claimed in any of claims 37 to 39 in the form of granules, tablets, coated tablets, capsules, syrups, emulsions, suspensions or drops.

41. Compositions as claimed in any of claims 37 to 40 in the form of dosage units.

42. Compositions as claimed in claim 41 wherein each dosage unit contains from 1 to 10 mg. of active ingredient.

43. Compositions as claimed in claim 42 wherein each dosage unit contains from 2.5 to 5 mg of active ingredient.

44. Compositions as claimed in claim 37 substantially as herein described.

45. Compositions as claimed in claim 38 substantially as herein described.

46. Compositions as claimed in claim 39 substantially as herein described.

47. Pharmaceutical compositions substantially as herein described in either of Examples 13 and 14.

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