(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 200125140 B2**
(10) Patent No. **780636**

(54) Title
Substituted glutarimides and use thereof IL-12 production inhibitors

(51)[7] International Patent Classification(s)
C07D 211/88 **A61P 037/02**
A61K 031/45

(21) Application No: **200125140** (22) Application Date: **2001.01.09**

(87) WIPO No: **WO01/53261**

(30) Priority Data

(31) Number	(32) Date	(33) Country
10002509	**2000.01.21**	**DE**

(43) Publication Date : **2001.07.31**
(43) Publication Journal Date : **2001.10.11**
(44) Accepted Journal Date : **2005.04.07**

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AU 200125140

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
26. Juli 2001 (26.07.2001)

PCT

(10) Internationale Veröffentlichungsnummer
WO 01/53261 A1

(51) Internationale Patentklassifikation[7]: C07D 211/88, A61K 31/45, A61P 37/02

(21) Internationales Aktenzeichen: PCT/EP01/00155

(22) Internationales Anmeldedatum:
9. Januar 2001 (09.01.2001)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
100 02 509.9 21. Januar 2000 (21.01.2000) DE

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(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:

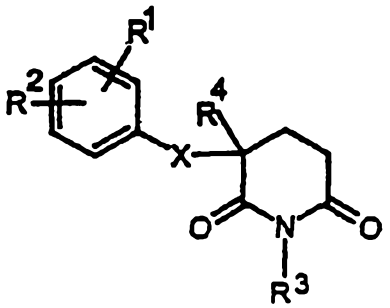
— *mit internationalem Recherchenbericht*

— *vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen*

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 GLUTARIMIDES AND USE THEREOF IL-12 PRODUCTION INHIBITORS

(54) Bezeichnung: SUBSTITUIERTE GLUTARIMIDE UND IHRE VERWENDUNG ALS INHIBITOREN DER IL-12 PRODUKTION



(I)

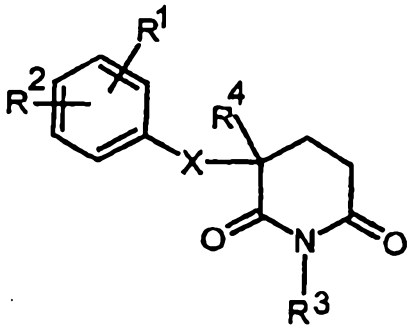
(57) Abstract: The invention relates to substituted glutarimides of formula (I), wherein x is a group of formula $(CH_2)_n$-$(CR^8R^9)_p$-Z-$(CR^8R^9)_m$, Z represents a sulphur or oxygen atom, the SO or SO_2 group, the radical NR^8 (optionally in the form of N oxide) or a CR^8R^9 group, m and p are 0 or 1, n is 0, 1, 2 or 3, m, n and p cannot simultaneously be 0. The invention also relates to the production and use thereof in medicaments, especially as immunomodulators and inhibitors of angiopathies and/or haematological//oncological diseases..

(57) Zusammenfassung: Es werden substituierte Glutarimide der Formel (I), in der X eine Gruppe der Formel $(CH_2)_n$-$(CR^8R^9)_p$-Z-$(CR^8R^9)_m$ bedeutet, Z für Schwefel- oder Sauerstoffatom, die SO- oder SO_2-Gruppe, den Rest NR^8 (gegebenenfalls in Form des N-oxids) oder eine CR^8R^9-Gruppe, m und p für 0 oder 1, n für 0, 1, 2 oder 3 stehen, wobei m, n und p nicht gleichzeitig 0 sein können, ihre Herstellung und Verwendung in Arzneimitteln, insbesondere als Immunmodulatoren sowie als Inhibitoren von Angiopathien und/oder hämatologisch/onkologischen Erkrankungen, beschrieben.

WO 01/53261 A1

Substituted glutarimides and their use as inhibitors of IL-12 production

The invention concerns substituted glutarimides having the general formula I



I

their production and their use in medicaments.

Autoimmune diseases arise as a result of a reactivity of the immune system against structures occurring naturally in the body. As part of this process, the normally existing tolerance towards the body's own tissue lapses. In addition to antibodies, T-lymphocytes and monocytes/macrophages in particular play a decisive role in the pathogenesis of the various autoimmune diseases. Activated monocytes/ macrophages secrete a number of different proinflammatory mediators that are directly or indirectly responsible for destroying tissue affected by the autoimmune disease. The activation of monocytes/macrophages occurs either in the interaction with T-lymphocytes or via bacterial products such as lipopolysaccharide (LPS).

IL-12 is a heterodimeric molecule consisting of a covalently bonded p35 and p40 chain. The molecule is formed by antigen-presenting cells (monocytes/macrophages, dendritic cells, B-lymphocytes). The formation of IL-12 by monocytes/macrophages is triggered either by various microbial products such as LPS, lipopeptides, bacterial DNA or in the interaction with activated T-lymphocytes (Trinchieri 1995. Ann.Rev.Immunol. 13: 251). IL-12 has a central immunoregulatory significance and is responsible for the development of proinflammatory TH1 reactivities. The presence of a TH1 immune reaction against self-antigens leads to the occurrence of serious diseases.

The significance of inflammatory cytokines such as IL-12 for the development and course of inflammations and autoimmune diseases has been clearly documented by numerous animal experimental and preliminary clinical trials. The pathophysiological importance of IL-12 has been demonstrated in various animal models for diseases such as rheumatoid arthritis, multiple sclerosis, diabetes mellitus and inflammatory diseases of the intestines, skin and mucous membranes (Trembleau et al. 1995. Immunol.Today 16: 383; Müller et al. 1995. J.Immunol. 155: 4661; Neurath et al. 1995. J.Exp.Med. 182: 1281; Segal et al. 1998. J.Exp.Med. 187: 537; Powrie et al. 1995. Immunity 3: 171; Rudolphi et al. 1996. Eur.J.Immunol. 26: 1156; Bregenholt et al. 1998. Eur.J.Immunol. 28: 379). Application of IL-12 could trigger the relevant disease and neutralisation of endogenic IL-12 led to the course of the disease being moderated through to the cure of the animals. The use of antibodies against IL-12 in humans is imminent.

It can be said in summary that an excess of IL-12 conditions the pathophysiology of a number of inflammatory diseases. Attempts to normalise the IL-12 level therefore have great therapeutic potential.

IL-12 is also involved in regulating the survival of cells. Uncontrolled cell growth is regulated by apoptosis (programmed cell death) amongst other things. Using T-lymphocytes it has been shown that IL-12 has an anti-apoptotic action and promotes the survival of T-cells (Clerici et al. 1994. Proc.Natl.Acad.Sci.USA 91: 11811; Estaquier et al. 1995. J.Exp.Med. 182: 1759). A local overproduction of IL-12 can therefore contribute to the survival of tumour cells.

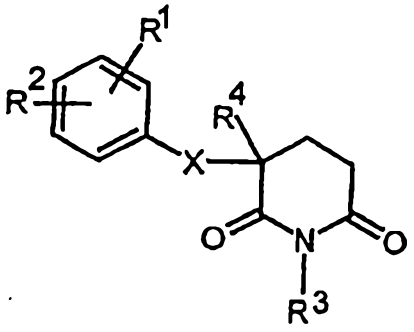
Inhibitors of IL-12 formation therefore possess great therapeutic potential.

DE 198 43 793.5 proposed substituted benzamides with immunomodulatory properties in which the ring-containing structural parts of the molecule are linked together by an amide bond. The disadvantage of the amide bond is its susceptibility to hydrolysis with an accompanying loss of action for the compound.

The object of the invention was therefore to develop new immunomodulators that are suitable for the treatment and/or prophylaxis of diseases caused by formation of the proinflammatory cytokine IL-12 and that at the same time display an improved hydrolytic stability.

These requirements made of the substances to be developed are met by certain substituted glutarimides.

In a first aspect, the invention accordingly provides substituted glutarimides having the formula I



I

in which X denotes a group having the formula $(CH_2)_n$-$(CR^8R^9)_p$-Z-$(CR^8R^9)_m$,

Z stands for a sulfur or oxygen atom, the SO or SO_2 group, the NR^8 radical (optionally in the form of N oxide) or a CR^8R^9 group,

m and p stand for 0 or 1,

n stands for 0, 1, 2 or 3,

whereby m, n and p cannot simultaneously be 0,

R^1 and R^2 are the same or different and stand for the carboxyl group, an ester group having the formula $COOR^5$ or an acyl group having the formula COR^5, in which R^5 in each case denotes an alkyl group (straight-chain or branched) with 1 to 6 C atoms (optionally substituted with the radical $COOR^5$ and/or a phenyl group), a C_3 to C_7 cycloalkyl group or a phenyl or benzyl radical, or an amide group having the formula $CONR^6R^7$, in which R^6 and

R^7 are the same or different and represent hydrogen, an alkyl group (straight-chain or branched) with 1 to 6 C atoms (optionally substituted with the radical $COOR^5$ and/or a phenyl group), the allyl radical, the phenyl radical or taken together with the N atom represent the hydrazide group, the pyrrolidine, piperidine, hexamethylene imine, morpholine, thiomorpholine, piperazine or N-methyl piperazine ring, for hydrogen, bromine, chlorine, fluorine, a mono-, di- or trifluoromethyl, trityl, hydroxyl, hydroxymethyl, trifluoromethoxy, nitro, amino (optionally substituted with the radical CH(=O) or COR^5 or an alkylsulfonyl group) or dimethylamino group, an alkyl or alkoxy radical (straight-chain or branched) with 1 to 6 C atoms, an amidine radical having the formula NH-CH(=NH) or NH-C(=NH)R^5, a phenyl radical or a fused benzene ring (optionally substituted in each case with above-mentioned atoms or groups), with the restriction that if $Z=CR^8R^9$ R^1 and R^2 cannot simultaneously be hydrogen and if Z = S and m = 0 they cannot represent the methoxy group,

R^3 stands for hydrogen, the hydroxy radical or a group having the formula $CH_2-NR^6R^7$, in which R^6 and R^7 are defined as above,

R^4 stands for hydrogen, a C_1 to C_3 alkyl group, a fluorine atom, the difluoro- or trifluoromethyl group,

R^8 stands for hydrogen, an alkyl group with 1 to 4 C atoms (straight-chain or branched), the benzyl or phenethyl radical (optionally substituted with above-mentioned atoms or groups),

and R^9 has the same meaning as R^8, stands for the ester group having the formula $COOR^5$, the phenyl radical, the hydroxyl group or an alkoxy radical (straight-chain or branched) with 1 to 4 C atoms, a fluorine or chlorine atom or the trifluoromethyl group,

and enantiomers, enantiomer blends, racemates, diastereomers or diastereomer blends thereof in the form of their bases or salts of physiologically compatible acids.

Preferred compounds according to the invention are those in which X stands for the groups CH_2-N and S-CH_2, R^1 stands for the carboxyl group, an ester group having the formula $COOR^5$ as defined above, an acyl group having the formula COR^5 as defined above or an amide group having the formula $CONR^6R^7$, in which R^6 and R^7 are the same or different and represent hydrogen, an alkyl group (straight-chain or branched) with 1 to 6 C atoms (optionally substituted as defined above), the phenyl radical or which taken together with the N atom represent the hydrazide group, the pyrrolidine or morpholidine ring, R^2 stands for hydrogen, the nitro or amino group, R^3 for hydrogen and R^4 for hydrogen, methyl or fluorine.

The following substituted glutarimides are particularly preferred:

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoic acid

2-[(3R)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoic acid

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl]-N,N-diethylbenzamide

(3S)-[2-morpholine-4-carbonyl)benzylamino] piperidine-2,6-dione

{2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoylamino} methyl acetate

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzamide

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl]-N-ethyl benzamide

(3S)-[2-pyrrolidine-1-carbonyl)benzylamino] piperidine-2,6-dione

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoic acid hydrazide

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl]-N-phenyl benzamide

2-[(3R)-(2,6-dioxopiperidin-3-ylamino)methyl]-N-phenyl benzamide

2-[(3R)-(2,6-dioxopiperidin-3-ylamino)methyl]-N,N-diethyl benzamide

2-[(3R)-(2,6-dioxopiperidin-3-ylamino)methyl] benzamide

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] methyl benzoate

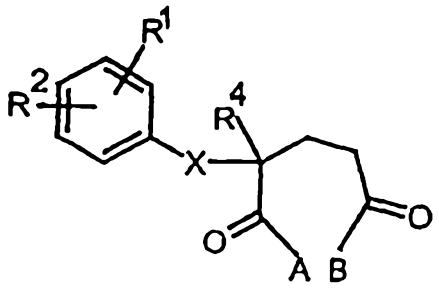
2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzyl benzoate

2-(2,6-dioxopiperidin-3-yl methyl sulfanyl) methyl benzoate

2-(2,6-dioxopiperidin-3-yl methyl sulfanyl)-6-methyl nitrobenzoate

The present invention also relates to methods for the production of compounds according to the invention having the general formula I.

According to a second aspect of the invention, compounds having the general formula I, in which R^3 stands for hydrogen or the hydroxy radical, can be obtained by cyclising glutaric acid derivatives having the general formula II



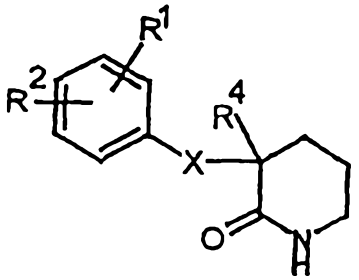
II

in which X, R^1, R^2 and R^4 have the same meaning as above, A stands for OH, B for NH_2 or NHOH or vice versa, in the presence of activating reagents such as carbonyl diimidazole, for example. If the radical Z within X in the compound having the formula I denotes an NH group, cyclisation is preferably performed with compounds having the formula II, in which the NH function is present in protected form, for example with a benzyl oxycarbonyl group. This is then expelled at temperatures of 20 to 40°C, e.g. with a solution of hydrogen bromide in acetic acid.

If A and B in formula II stand for OH, heating in acetic anhydride first produces a cyclisation to the cyclic anhydride, from which the compound having the formula I where R^3 = H is obtained by heating with urea or another nitrogen source.

According to a third aspect of the invention, compounds having the general formula I where $R^3 = CH_2\text{-}NR^6R^7$ can be produced by reaction with paraformaldehyde or an aqueous formaldehyde solution and a secondary amine having the formula HNR^6R^7, where R^6 and R^7 are defined as above.

According to a fourth aspect of the invention, compounds having the general formula I where R^3 = H can also be produced from lactams having the general formula III,

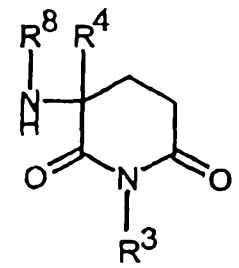


III

in which R^1, R^2, R^4 and X have the same meanings as above, by oxidising compound III to the imide, preferably with m-chloroperbenzoic acid or ruthenium(IV) oxide/sodium periodate.

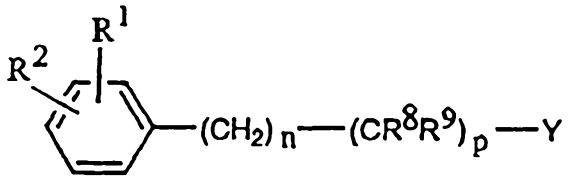
According to a fifth aspect of the invention in compounds having the general formula I, in which R^1 to R^3 and X have the same meanings as above and R^4 stands for hydrogen, this hydrogen can be exchanged for the conventional R^4 substituents in accordance with the definition by alkylation or halogenation reactions known per se.

According to a sixth aspect of the invention, if for the group X in the compounds having the formula I, m = 0 and if Z stands for the radical NR^8, in which R^8 and n and p have the same meanings as above, these can be obtained by alkylating α-aminoglutarimides having the general formula IV,



IV

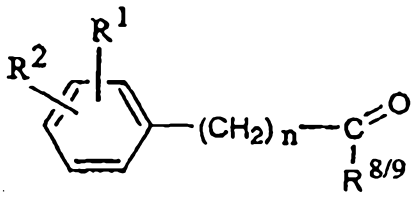
in which R^3, R^4 and R^8 have the same meanings as above, with compounds having the general formula V,



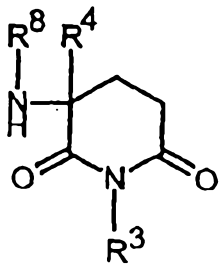
V

in which R^1, R^2, R^8, R^9, n and p have the same meanings as above and Y stands for a chlorine, bromine or iodine atom or the toluene-4-sulfonate radical.

According to a seventh aspect of the invention, compounds in which for the group X, p stands for 1 and R^8 or R^9 for hydrogen, can also be obtained by reductive amination from compounds having the general formulae VI and IV, in which R^1, R^2, R^4, R^8 and n have the same meanings as above and R^3 stands for hydrogen or the hydroxyl group.



VI

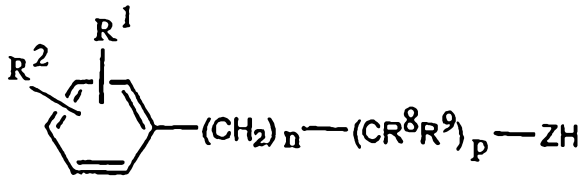


IV

Sodium boron hydride, sodium triacetoxyboron hydride, sodium cyanoboron hydride, the borane-pyridine complex or

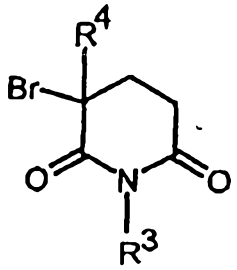
catalytically excited hydrogen are preferably used as the reducing agent.

According to an eighth aspect of the invention, if m stands for 0 and Z for O, S or NR^8 in the group X in the compound having the formula I and if R^8, n and p are defined as above, these compounds can also be obtained by alkylating a compound having the general formula VII,



VII

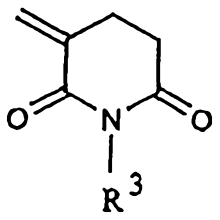
with α-bromoglutarimides having the general formula VIII,



VIII

in which R^3 and R^4 are defined as above.

According to a ninth aspect of the invention, compounds having the general formula I where R^4 = hydrogen, in which in the group X n and p are defined as above, m stands for 1, Z for O, S or NR^8 and in the group CR^8R^9 at least one of the radicals R^8 or R^9 stands for hydrogen, can be obtained by adding a compound having the general formula VII to a 3-methylene glutarimide having the general formula IX.



IX

The reaction is preferably performed in solvents such as acetonitrile or toluene with addition of tertiary amines such as triethylamine or diisopropyl ethylamine, for example, at temperatures of 80 to 110°C.

According to a tenth aspect of the invention, compounds having the formula I, in which R^1 and/or R^2 stand for an amino group, can generally be obtained by reduction of compounds having the formula I where R^1 and/or $R^2 = NO_2$. The reduction is performed, for example, by catalytically excited hydrogen in acid-containing organic solvents such as ethyl acetate, whereby palladium catalysts are preferably used. Alternatively, the reduction can be performed with metals such as tin or iron in acid solution.

According to an eleventh aspect of the invention, if Z in the group X stands for SO or SO_2, such compounds having the formula I can be obtained by stepwise oxidation of the corresponding dialkyl sulfide (Z = S). Hydrogen peroxide in acetic acid solution, m-chloroperbenzoic acid, tert-butyl hydroperoxide or oxones are available as oxidising agents, whereby the latter preferably serves for production of sulfones ($Z = SO_2$). The oxidation to sulfoxides (Z = SO) can also be structured asymmetrically, for example by using the Sharpless system or Davis reagent or by means of enzymatic methods.

According to a twelfth aspect of the invention, if Z in the group X stands for the radical NR^8, this can be converted to the corresponding N oxide, whereby hydrogen peroxide is preferably suitable as oxidising agent.

According to a thirteenth aspect the invention provides a substituted glutarimide prepared according to the process of any one of the second to the twelfth aspects of the invention.

According to a fourteenth aspect the invention provides a medicament containing as active agent at least one compound according to the first aspect of the invention.

According to a fifteenth aspect the invention provides the use of a substituted glutarimide having the formula I according to the first aspect of the invention for the production of a medicament.

According to a sixteenth aspect of the invention there is provided a method of treating angiopathies in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a compound according to the first aspect of the invention or a medicament according to the fourteenth aspect of the invention.

According to a seventeenth aspect of the invention there is provided a method of treating haematological/oncological diseases in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a compound according to the first aspect of the invention or a medicament according to the fourteenth aspect of the invention.

According to an eighteenth aspect of the invention there is provided a compound according to the first aspect of the invention or a medicament according to the fourteenth aspect of the invention, when used for treating angiopathies in a mammal.

According to a nineteenth aspect of the invention there is provided a compound according to the first aspect of the invention, or a medicament according to the fourteenth aspect of the invention, when used for treating haematological/oncological diseases in a mammal.

The compounds according to the invention possess immunomodulatory activity which is demonstrated by an inhibition of the production of IL-12 by LPS-activated monocytes. In comparison to compounds that have already been proposed, they also demonstrate an improved hydrolytic stability. They are suitable for the treatment and/or prophylaxis of inflammation and autoimmune diseases and also of haematological/oncological diseases.

The above groups of diseases include, amongst others, inflammation of the skin (e.g. atopic dermatitis, psoriasis, eczema), inflammations of the respiratory tracts (e.g. bronchitis, pneumonia, bronchial asthma, ARDS (adult respiratory distress syndrome), sarcoidosis, silicosis/fibrosis), inflammations of the gastrointestinal tract (e.g. gastroduodenal ulcers, Crohn's disease, ulcerative colitis), also diseases such as hepatitis, pancreatitis, appendicitis, peritonitis, nephritis, aphthosis, conjunctivitis, keratitis, uveitis, rhinitis.

The autoimmune diseases include, for example, arthritic diseases (e.g. rheumatoid arthritis, HLA-B27-associated diseases), Behcet's disease, also multiple sclerosis, juvenile diabetes or lupus erythematosus.

Further indications are sepsis, bacterial meningitis, cachexia, transplant rejection reactions, graft-versus-host reactions as well as reperfusion syndrome and

atherosclerosis along with angiopathies (such as macula degeneration, diabetic retinopathies).

The symptoms that can be inhibited by a reduction in IL-12 also include haematological diseases such as multiple myeloma and leukaemias along with other oncological diseases such as, e.g., glioblastoma, prostate cancer and mammary cancer.

Medicaments according to the invention contain, in addition to at least one compound having the general formula I, carriers, fillers, solvents, diluents, dyestuffs and/or binders. The choice of auxiliaries and the quantities to be used depend on whether the medicament is to be administered by oral, rectal, ophthalmic (intravitreal, intracameral), nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intratracheal and epidural) means.

Preparations in the form of tablets, chewable tablets, sugar-coated tablets, capsules, granules, drops, liquids or syrups are suitable for oral administration, solutions, suspensions, easily reconstituted dry preparations and sprays for administration by parenteral or topical means or by inhalation. Cutaneous administration forms are salves, gels, creams and pastes. Ophthalmic administration forms include drops, salves and gels. Compounds according to the invention contained in a reservoir in dissolved form, a carrier film or a plaster, optionally with the addition of skin-penetrating agents, are examples of suitable percutaneous administration forms. The compounds according

to the invention can be released on a delayed basis from oral or percutaneous forms of preparation.

The amount of active agent to be administered to patients varies according to the weight of the patient, the type of administration, the indication and the severity of the disease. 1 to 150 mg/kg of at least one compound according to the invention having the formula I are conventionally administered.

Examples

The following examples serve to describe the present invention in greater detail.

Silica gel 60 (0.040 - 0.063 mm) from E. Merck, Darmstadt, was used as stationary phase for the chromatographic separations. The mixing ratios of the eluents are always given as percentages by volume.

The substances were characterised by their melting point and/or the ^{1}H-NMR spectrum. The spectra were recorded at 300 MHz using a Gemini 300 device from Varian. The chemical shifts are given in ppm (δ-scale). Tetramethyl silane (TMS) was used as internal standard.

Example 1

3-(2-chlorobenzylamino) piperidine-2,6-dione; hydrochloride

Stage 1:

3-bromopiperidine-2,6-dione

4.5 ml bromine were added to 10.2 g glutarimide suspended in 20 ml chloroform and the mixture was stirred in a closed vessel for 90 minutes at a bath temperature of 110°C. After cooling, the vessel was opened and stirring was continued until no more hydrogen bromide escaped. The reaction mixture was evaporated in vacuo, the residue dissolved in ethanol and evaporated again. 17.1 g (99%) of the title compound remained in the form of practically white crystals, which melted at 76 to 83°C.

Stage 2:

3-(2-chlorobenzylamino) piperidine-2,6-dione; hydrochloride

A solution of 0.39 g of the product from stage 1 and 0.71 g 2-chlorobenzylamine in 8 ml N,N-dimethylformamide was stirred for 36 hours at 20°C. After evaporation in vacuo the oily residue was dissolved in 25 ml methanol and the solution stirred for two hours with 1 g Amberlyst A-21. It was filtered, 2 g silica gel were added to the filtrate and it was evaporated until dry. The adsorbed substance was placed in a chromatography column and the product was eluted with a mixture of ethyl acetate/cyclohexane (1/2 -> 1/1) containing 1 % triethylamine. The residue remaining after evaporation of the product fractions was dissolved in 10 ml methanol and 25 ml each of diethyl ether saturated with hydrogen chloride and diethyl ether were added to the solution. The precipitated hydrochloride was separated off and recrystallised out of methanol/diethyl ether. 0.24 g (41 % of theoretical) of the title compound were obtained in the form of crystals, which melted at 217°C with decomposition.

^{1}H-NMR (DMSO-d_6): 2.15 - 2.34 (1H, m); 2.40 - 2.56 (1H, m); 2.60 - 2.80 (2H, m); 4.35 (1H, t, J = 13.5 Hz); 4.45 (2H, d, J = 13.8 Hz); 7.40 - 7.94 (4H, m).

Example 2

Using the procedure described in Example 1, stage 2 and the corresponding benzylamines, the following were obtained in the same way:

2.1: 3-(2-trifluoromethyl benzylamino) piperidine-2,6-dione; hydrochloride

Melting point: > 250°C (decomposition)

2.2: 3-(2,4-dimethoxybenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 214°C (decomposition)

2.3: 3-(2,6-difluorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 208-215°C (decomposition)

2.4: 3-(2,5-difluorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 208°C (decomposition)

2.5: 3-(3,5-difluorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 230-236°C (decomposition)

2.6: 3-[(naphth-1-ylmethyl)amino] piperidine-2,6-dione; hydrochloride

Melting point: 188°C (decomposition)

2.7: 3-(2,3-difluorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 206-212°C (decomposition)

2.8: 3-(4-dimethylaminobenzylamino) piperidine-2,6-dione; base

2.9: 3-(4-nitrobenzylamino) piperidine-2,6-dione; hydrochloride

2.10: 3-(3-trifluoromethylbenzylamino) piperidine-2,6-dione; hydrochloride

2.11: 3-(3-trifluoromethoxybenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 199-201°C

2.12: 3-[naphth-2-ylmethyl)amino] piperidine-2,6-dione, base

Melting point: 120-125°C (decomposition)

2.13: 3-((2-chloro-4-fluorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 241-242°C

2.14: 3-(3-nitrobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: from 240°C with decomposition

2.15: 3-(2-chloro-6-methylbenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 238-240°C

2.16: 3-(2-methylbenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 235-240°C

2.17: 3-(3,5-dichlorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 234-238°C

2.18: 3-[3-fluoro-5-(trifluoromethyl) benzylamino] piperidine-2,6-dione; hydrochloride

Melting point: 241-243°C

2.19: 3-(3-fluorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 231-235°C

2.20: 3-(3-methylbenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 240-242°C

2.21: 3-(4-trifluoromethylbenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 252-255°C

2.22: 3-[4-fluoro-2-(trifluoromethyl) benzylamino] piperidine-2,6-dione; hydrochloride

Melting point: from 241°C with decomposition

2.23: 3-(4-fluorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 241-242°C

2.24: 3-(4-tert-butylbenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: from 239°C with decomposition

2.25: 3-(3,5-dimethylbenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: from 226°C with decomposition

2.26: 3-(3-chlorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 237-238°C

2.27: 3-(4-methoxybenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: from 227°C with decomposition

2.28: 3-(2,4-dichlorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 240-242°C

2.29: 3-(2-fluorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 245-247°C

2.30: 3-(2-bromobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 244-246°C

2.31: 3-[2-fluoro-5-(trifluoromethyl) benzylamino piperidine-2,6-dione; hydrochloride

Melting point: from 251°C with decomposition

2.32: 3-(2,3-dichlorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 246-248°C

2.33: 3-(3,4-dichlorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 252-254°C

2.34: 3-[3,5-bis(trifluoromethyl) benzylamino] piperidine-2,6-dione; hydrochloride

Melting point: 263-265°C

2.35: 3-(3-bromobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 229-232°C

2.36: 3-(4-trifluoromethoxybenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 253-255°C

2.37: 3-(4-chlorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 262-265°C

2.38: 3-(4-methylbenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 256°C with decomposition

2.39: 3-(2-ethoxybenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 208-212°C

2.40: 3-(2,5-dichlorobenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 242-246°C

2.41: 3-(3-methoxybenzylamino) piperidine-2,6-dione; hydrochloride

Melting point: 217-219°C

All compounds listed under 2.1 to 2.41 are in the form of the racemate.

Example 3

3-(3-aminobenzylamino) piperidine-2,6-dione; hydrochloride

0.56 g of the product from example 2.14 in a mixture consisting of 17 ml ethyl acetate and 0.85 ml 6N hydrochloric acid were hydrogenated at 20°C and a pressure of 4 bar over 0.17 g palladium on activated carbon (10 % Pd). After the theoretical amount of hydrogen had been recorded, the mixture was filtered off from the catalyst and the filtrate evaporated in vacuo. After recrystallisation of the residue from methanol, 0.25 g (50 % of theoretical) of the racemic title compound was obtained in the form of slightly coloured crystals, which melted at 236 - 239°C.

^{1}H-NMR (DMSO-d_6): 2.05 - 2.20 (m, 1H); 2.28 - 2.39 (m, 1H); 2.55 - 2.74 (m, 2H); 3.97 - 4.12 (q, 2H); 4.18 - 4.28 (m, 1H); 6.58 - 6.70 (m, 3H); 7.02 - 7.11 (m, 1H).

Example 4

Using the procedure described in Example 1, stage 2 and the corresponding arylalkylamines, the following were obtained in the same way:

4.1: 3-phenethylaminopiperidine-2,6-dione; hydrochloride

Melting point: from 220°C with decomposition

4.2: 3-[2-(2-chlorophenyl) ethylaminopiperidine-2,6-dione; hydrochloride

Melting point: 230°C (decomposition)

4.3: 3-(4-phenylbutylamino) piperidine-2,6-dione; hydrochloride

Melting point: from 231°C with decomposition

4.4: 3-(N-benzyl-N-methylamino) piperidine-2,6-dione; base

Melting point: 95-115°C

4.5: 3-(methylnaphth-1-yl methylamino) piperidine-2,6-dione; base

Melting point: 157-162°C

All compounds listed under 4.1 to 4.5 are in racemic form.

4.6: (2S)-[(3S) or (3R)-(2,6-dioxopiperidin-3-ylamino)] methyl phenylacetate; hydrochloride

Melting point: 200-207°C

4.7: (2R)-[(3S) or (3R)-(2,6-dioxopiperidin-3-ylamino)] methyl phenylacetate; hydrochloride

Melting point: 171-177°C (decomposition)

4.8: (2S)-[(3R,S)-(2,6-dioxopiperidin-3-ylamino)]-3-methyl phenylpropionate; hydrochloride

(blend of diastereomers)

Melting point: 146-150°C (decomposition)

Example 5

3-benzylaminopiperidine-2,6-dione

A) A solution of 0.50 g 3-aminopiperidine-2,6-dione [K. Fickentscher, Arch. Pharm. **1974**, 307, 840-844], 1.5 ml triethylamine and 0.4 ml benzyl bromide was stirred for 20 h at 20°C. It was then evaporated, the residue taken up in 50 ml aqueous potassium carbonate solution (10 % K_2CO_3) and the solution extracted twice with 40 ml ethyl acetate in each case. The organic phases were washed with 50 ml each of distilled water and saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuo. The residue was purified by flash chromatography on silica gel with a mixture of ethyl acetate/cyclohexane (2/1) containing 1 % triethylamine as eluent, whereby 0.21 g (26 % of theoretical) of the title compound was obtained as viscous oil.

The title compound could also be obtained in the form of the hydrobromide as pure S enantiomer in the following way:

B) Stage 1:

(2S)-(N-benzyl-N-benzyloxycarbonylamino)-4-carbamoyl butanoic acid

0.6 ml benzyl chloroformate were added dropwise to 0.95 g (2S)-benzylamino-4-carbamoyl butanoic acid [E. Davidov et al., Isr. J. Chem. **1969**, 7, 487-489] dissolved in 4 ml 2 M aqueous sodium hydroxide and 8 ml 1 M sodium hydrogen carbonate solution, over 2.5 h at 20°C whilst being stirred. The mixture was then

extracted twice with 20 ml diethyl ether in each case. The aqueous phase was acidified with conc. hydrochloric acid to pH 2-3 and extracted twice with 30 ml ethyl acetate in each case. The extracts were washed with distilled water, dried over sodium sulfate and evaporated in vacuo. After adding diethyl ether to the oily residue, 0.55 g (37 % of theoretical) of the title compound were obtained in the form of colourless crystals, which melted at 98-99°C.

Stage 2:

(3S)-(N-butyl-N-benzyloxycarbonylamino) piperidine-2,6-dione

A solution of 0.162 g N,N'-carbonyl diimidazole in 3 ml dry tetrahydrofuran was dripped into a solution of 0.37 g of the product from stage 1 in 2.5 ml dry tetrahydrofuran. It was refluxed for 3.5 h then stirred for a further 3 h at 20°C. The oil remaining after evaporation of the solvent in vacuo was dissolved in ethyl acetate and the solution washed successively with 20 ml each of 1 M aqueous sodium hydrogen carbonate solution, saturated sodium chloride solution and distilled water. It was then dried over sodium sulfate and evaporated in vacuo. 0.23 g (65 % of theoretical) of the title compound remained in the form of crystals, which melted at 51-52°C.

Stage 3:

(3S)-benzylaminopiperidine-2,6-dione; hydrobromide

The solution of 0.15 g of the product from stage 2 in 3 ml of a solution of hydrogen bromide in acetic acid

(33 % HBr) was stirred for 1 h at 20°C. The reaction mixture was then poured onto 50 ml diethyl ether. The deposit that was formed was separated off, washed with diethyl ether and dried in vacuo. 0.08 g (63 % of theoretical) of the title compound remained in the form of crystals, which melted at 228-230°C with decomposition.

^{1}H-NMR (DMSO-d_6): 2.01 - 2.43 (m, 2H); 2.60 - 2.80 (m, 2H); 4.20 - 4.45 (m, 3H); 7.40 - 7.60 (m, 5H).

Example 6

6.1 2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoic acid, hydrobromide

Stage 1:
2-[(1S)-(3-carbamoyl-1-carboxypropylamino)methyl] benzoic acid

A suspension of 1.65 g 2-formylbenzoic acid in 5 ml ethanol and 5 ml 2 M sodium hydroxide solution was added to a solution of 1.46 g L-glutamine in 5 ml of a 2 M aqueous sodium hydroxide solution. After stirring the mixture for 1 h at 20°C, it was cooled to 0°C and 0.25 g sodium boron hydride was added in portions over 15 min with vigorous stirring. After 90 min a further 0.33 g 2-formyl benzoic acid and 0.05 g sodium boron hydride were added. After stirring for 16 h at 20°C, the reaction mixture was acidified with conc. hydrochloric acid to pH 2 and cooled to 0°C. The deposit formed was separated off, washed with acetone and dried in vacuo. 0.87 g (31 % of theoretical) of

the title compound remained in the form of crystals, which melted at 132-133°C.

Stage 2:

2-{(1S)-[N-benzyloxycarbonyl-N-(3-carbamoyl-1-carboxypropyl)amino] methyl} benzoic acid

Using the procedure described in Example 5 B, stage 1, the title compound was obtained in the same way from the product from stage 1 in the form of crystals, which melted with decomposition at 103-104°C.

Stage 3:

2-{(3S)-[N-benzyloxycarbonyl-N-(2,6-dioxopiperidin-3-yl)amino] methyl} benzoic acid

Using the procedure described in Example 5 B, stage 2, the title compound was obtained in the same way from the product from stage 2 in the form of crystals, which melted at 71-73°C.

Stage 4:

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoic acid, hydrobromide

Using the procedure described in Example 5B, stage 3, the title compound was obtained in the same way from the product from stage 3 in the form of colourless crystals, which melted at 158-161°C.

^{1}H-NMR (DMSO-d_6): 2.00 - 2.25 (m, 1H); 2.35 - 2.95 (m, 1H); 2.60 - 2.80 (m, 2H); 4.35 - 4.50 (m, 1H); 4.50 - 4.70 (m, 2H); 7.50 - 7.75 (m, 3H); 8.00 - 8.10 (m, 1H).

6.2 2-[(3R)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoic acid; hydrobromide

Replacing L by D-glutamine in Example 6.1, stage 1, and using the procedure described in Example 6.1, the title compound was obtained in the same way in the form of crystals, which melted at 148-152°C.

Example 7

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl]-N,N-diethylbenzamide; hydrobromide

Stage 1:

(3S)-[N-(2-diethylcarbamoylbenzyl)-N-benzyloxycarbonyl] aminopiperidine-2,6-dione

A solution of 1.00 g of the product from Example 6.1, stage 3, 0.27 g N-methyl morpholine and 0.46 g 2-chloro-4,6-dimethoxy-1,3,5-triazine in 7 ml dry tetrahydrofuran was stirred for 1 h at 20°C. After adding 0.19 g diethylamine, stirring was continued for a further 7 h. The solution was then diluted with chloroform to a volume of 50 ml and washed successively with 25 ml 0.05 N hydrochloric acid, 25 ml 1 M aqueous sodium hydrogen carbonate solution and saturated sodium chloride solution. The organic phase was dried over sodium sulfate and evaporated in vacuo. After purifying the residue by flash chromatography on silica gel with ethyl acetate/cyclohexane (9/1) as eluent, 0.36 g (32 % of theoretical) of the title compound was obtained in the form of crystals, which melted at 65-66°C.

Stage 2:

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl]-N,N-diethylbenzamide; hydrobromide

0.30 g of the product from stage 1 were reacted as described under Example 5B, stage 3 with 3 ml of a solution of hydrogen bromide in acetic acid (33 % HBr). Once again, after processing and purification by recrystallisation from methanol/diethyl ether in the same way, 0.175 g (66 % of theoretical) of the title compound were obtained in the form of crystals, which melted at 119-120°C.

^{1}H-NMR (DMSO-d_6): 1.06 (t, J = 7.5 Hz, 3H); 1.21 (t, J = 6.9 Hz, 3H); 2.04 - 2.24 (m, 1H); 2.28 - 2.46 (m, 2H); 2.58 - 2.80 (m, 2H); 3.19 (dd, 2H); 3.51 (dd, 2H); 4.24 (s, 2H); 4.25 - 4.40 (m, 1H); 7.44 (d, 1H); 7.48 - 7.66 (m, 2H); 7.72 (d, 1H).

Example 8

By replacing diethylamine in Example 7, stage 1, by other amines, ammonia or hydrazine and using the additional procedure described in Example 7, the following were obtained in the same way:

8.1: (3S)-[2-morpholine-4-carbonyl)benzylamino] piperidine-2,6-dione; hydrobromide

Melting point: 133-135°C

8.2: {2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoylamino} methyl acetate; hydrobromide

Melting point: 121-123°C

8.3: 2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzamide; hydrobromide

Melting point: 155-156°C (decomposition)

8.4: 2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl]-N-ethyl benzamide; hydrobromide

Melting point: 144-146°C

8.5: (3S)-[2-pyrrolidine-1-carbonyl)benzylamino] piperidin-2,6-dione; hydrobromide

Melting point: 136-138°C

8.6: 2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoic acid hydrazide; hydrobromide

Melting point: 241-242°C

8.7: 2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl]-N-phenylbenzamide; hydrobromide

Melting point: 136-138°C

8.8: (2R)-{(3S)-2-[(2,6-dioxopiperidin-3-ylamino)methyl] benzoylamino} methyl phenylacetate; hydrobromide

Melting point: 149-151°C

8.9: (2S)-{(3S)-2-[(2,6-dioxopiperidin-3-ylamino)methyl] benzoylamino} methyl phenylacetate; hydrobromide

Melting point: 181-182°C

8.10: 2-[(3R)-(2,6-dioxopiperidin-3-ylamino)methyl]-N-phenyl benzamide; hydrobromide

Melting point: 168-171°C

8.11: 2-[(3R)-(2,6-dioxopiperidin-3-ylamino)methyl]-N,N-diethyl benzamide; hydrobromide

Melting point: 128-132°C

8.12: 2-[(3R)-(2,6-dioxopiperidin-3-ylamino)methyl] benzamide; hydrobromide

Melting point: 232-233°C

Example 9

9.1: 2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] methyl benzoate; hydrobromide

Stage 1:

2-{(3S)-[N-benzyloxycarbonyl-N-(2,6-dioxopiperidin-3-yl)amino]-methyl} methyl benzoate

A mixture consisting of 0.60 g of the product from Example 6.1, stage 3, and 0.25 g N,N'-carbonyl diimidazole in 5 ml dry tetrahydrofuran was stirred for 1.5 h at 20°C. 64 µl methanol were then added and stirring was continued for a further 40 h at 20°C. After evaporating off the solvent in vacuo the residue was taken up in 80 ml chloroform and the solution washed with 1 M sodium hydrogen carbonate solution and distilled water. It was dried over sodium sulfate and evaporated in vacuo. After purification of the residue by column chromatography on silica gel with chloroform/acetone (94/6) as eluent, 0.32 g (51 % of theoretical) of the title compound were obtained as a viscous oil.

Stage 2:

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] methyl benzoate; hydrobromide

By eliminating the benzyloxycarbonyl protective group in the product from stage 1 using the procedure described in Example 5B, stage 3, the title compound was obtained in the same way in the form of crystals, which melted at 187°C.

^{1}H-NMR (DMSO-d_6): 2.07 - 2.30 (m, 1H); 2.30 - 2.48 (m, 1H); 2.60 - 2.85 (m, 2H); 3.90 (s, 3H); 4.40 - 4.70 (m, 3H); 7.58 - 7.78 (m, 3H); 8.05 (d, J = 8 Hz, 1H).

9.2: 2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzyl benzoate; hydrobromide

By replacing methanol with benzyl alcohol in Example 9.1 and using the procedure described therein, the title compound was obtained in the same way in the form of white crystals, which melted at 175-177°C.

Example 10

3-phenylaminomethyl piperidine-2,6-dione

30 ml absolute triethylamine and 2.75 ml freshly distilled aniline were added to a solution of 1.25 g 3-methylene piperidine-2,6-dione [M.J. Wanner and G.-J. Koomen, Tetrahedron Lett. **1992**, 33, 1513-1516] in 100 ml acetonitrile and the mixture was stirred for 16 h at 80°C. After cooling, 10 g silica gel were added and the mixture was evaporated in vacuo. The residue was purified by flash chromatography on silica gel with tert-butyl methyl ether/cyclohexane (2/1) as eluent. 1.87 g (86 % of theoretical) of the title compound were obtained in the form of crystals, which melted at 137°C.

^{1}H-NMR ($CDCl_3$): 1.84 - 1.99 (m, 1H); 2.08 - 2.17 (m, 1H); 2.49 - 2.64 (m, 1H); 2.73 - 2.83 (m, 2H); 3.41 - 3.50 (m, 1H); 3.60 - 3.70 (m, 1H); 6.64 - 6.80 (m, 3H); 7.17 - 7.29 (m, 2H).

Example 11

By replacing aniline in Example 10 by other amines and using the procedure therein described, whereby optionally the mixture toluene/diisopropyl ethylamine was also used instead of the solvent system acetonitrile/triethylamine at a reaction temperature of 110°C, the following could be obtained in the same way:

11.1: 3-[(4-bromophenylamino)methyl] piperidine-2,6-dione
Melting point: 149-150°C

11.2: 3-[(3-trifluoromethyl phenylamino)methyl] piperidine-2,6-dione
Melting point: 135-138°C

11.3: 3-(naphth-1-ylaminomethyl) piperidine-2,6-dione
Melting point: 145-148°C

11.4: 3-(biphenyl-4-ylaminomethyl) piperidine-2,6-dione
Melting point: 135-138°C

11.5: 3-[(3-methoxyphenylamino)methyl] piperidine-2,6-dione
Viscous

11.6: 3-[(4-trityl phenylamino)methyl] piperidine-2,6-dione
Melting point: 221-225°C

11.7: 3-[(2,6-dioxopiperidin-3-ylmethyl)amino] ethyl benzoate

Viscous

11.8: 3-(benzylaminomethyl) piperidine-2,6-dione

Viscous

11.9: 3-[(3-acetyl phenylamino)methyl] piperidine-2,6-dione

Melting point: 129-132°C

11.10: 3-[(N-methyl-N-phenylamino)methyl] piperidine-2,6-dione

Melting point: 132-134°C

11.11: 3-{[(naphth-1-ylmethyl)amino]methyl} piperidine-2,6-dione

Viscous

11.12: 3-[(2-methoxyphenylamino)methyl] piperidine-2,6-dione

Viscous

11.13: 3-[(4-methoxyphenylamino)methyl] piperidine-2,6-dione

Melting point: 131-134°C

11.14: (2S)-[(2,6-dioxopiperidin-3-ylmethyl)amino]-3-methyl phenylpropionate

Viscous

11.15: 2-[(2,6-dioxopiperidin-3-ylmethyl)amino] benzamide

Melting point: 203-206°C

11.16: 3-[(4-acetylphenylamino)methyl] piperidine-2,6-dione

Melting point: 160°C

11.17: 3-[(3-benzoyl phenylamino)methyl] piperidine-2,6-dione

Melting point: 152-158°C

11.18: 4-[(2,6-dioxopiperidin-3-ylmethyl)amino] methyl benzoate

Melting point: 142-144°C

Example 12

3-[(2-hydroxymethyl phenylamino)methyl] piperidine-2,6-dione

Stage 1:

3-{[2-tert-butyl dimethyl silanyloxymethyl)phenylamino] methyl} piperidine-2,6-dione

By replacing aniline in Example 10 by 2-(tert-butyl dimethyl silanyloxymethyl) phenylamine and using the procedure therein described, the title compound was obtained in the form of white crystals, which melted at 85-87°C.

Stage 2:

3-[(2-hydroxymethyl phenylamino)methyl] piperidine-2,6-dione

5 ml of a 1 M solution of tetrabutyl ammonium fluoride trihydrate in tetrahydrofuran were added to a solution of 0.20 g of the product from stage 1 in 5 ml tetrahydrofuran.

It was stirred for 3 h at 20°C, evaporated in vacuo and the residue was purified by flash chromatography on silica gel with ethyl acetate as eluent. 0.12 g (85 % of theoretical) of the title compound were obtained in the form of a yellowish oil.

Example 13

By replacing aniline in Example 10 by thiophenols or mercaptans and using the procedure therein described, the following were obtained in the same way:

13.1: 3-phenylsulfanylmethyl piperidine-2,6-dione
Melting point: 98°C

13.2: 3-phenethylsulfanylmethyl piperidine-2,6-dione
Melting point: 78°C

13.3: 2-(2,6-dioxopiperidin-3-ylmethyl)sulfanyl) methyl benzoate
Melting point: 142-144°C

13.4: 3-benzylsulfanylmethyl piperidine-2,6-dione
Melting point: 105-107°C

13.5: 3-(3-aminophenylsulfanylmethyl) piperidine-2,6-dione
Melting point: 133-135°C

13.6: 2-(2,6-dioxopiperidin-3-ylmethylsulfanyl)-6-methyl nitrobenzoate
Melting point: 147-150°C

Example 14

2-amino-6-(2,6-dioxopiperidin-3-ylmethylsulfanyl) methyl benzoate

The title compound was obtained in the same way by catalytic hydrogenation of the product from Example 13.6 over palladium on activated carbon (10 % Pd) under the conditions described in Example 3.

Melting point: 164-167°C

Example 15

3-phenylsulfanylmethyl-1-piperidin-1-ylmethyl piperidine-2,6-dione

0.52 ml aqueous formaldehyde solution (35 %) and 0.43 ml piperidine were added to a solution of 1.20 g of the product from Example 13.1 in 30 ml ethanol. After being refluxed for 1 hour, the mixture was evaporated in vacuo. The residue was taken up in ethyl acetate and n-hexane added to the solution until a crystalline deposit formed. This was separated off and dried in vacuo. 1.23 g (74 % of theoretical) of the title compound were obtained, which displayed a melting point of 63-66°C.

^{1}H-NMR (DMSO-d_6): 1.37 - 1.47 (m, 6H), 1.72 - 1.88 (m, 1H), 2.08 - 2.16 (m, 1H), 2.21 - 2.33 (m, 4H), 2.49 - 2.57 (m, 1H), 2.70 - 2.82 (m, 1H), 3.07 - 3.18 (m, 1H), 3.28 - 3.33 (m, 1H), 3.47 - 3.56 (m, 1H), 4.56 - 4.69 (m, 2H), 7.17 - 7.25 (m, 1H), 7.28 - 7.39 (m, 4H).

Stimulation of human monocytes with lipopolysaccharide for secretion of IL-12

Human monocytes were isolated from peripheral blood mononuclear cells (PBMC) obtained by means of a Ficoll density-gradient centrifugation of heparinised whole blood. To this end, the PBMC were incubated with a monoclonal antibody directed against the monocyte-specific surface molecule CD14 and to which superparamagnetic microbeads (Miltenyi Biotech, Bergisch Gladbach) are coupled. In order for the marked monocytes to be positively selected from the mixture of cells in the PBMC, the total cell suspension was transferred to a column with a ferromagnetic carrier matrix and the column placed in a magnetic field. This caused the cells loaded with microbeads to be bonded to the carrier matrix, whilst unmarked cells passed through the column and were discarded. After removing the matrix from the magnetic field, the antibody-loaded cells were eluted by rinsing the now demagnetised column with buffer. The purity of this CD14-positive monocyte population thus obtained was around 95 to 98%. These monocytes were incubated in a density of 10^6 cells/ml culture medium (RPMI, supplemented with 10% foetal calf serum) with the test substances dissolved in DMSO for one hour at 37°C and 5% CO_2. 20 µg/ml LPS from E. coli were then added. After 24 hours, cell-free culture supernatants were taken and tested for their IL-12 content.

The concentration of IL-12 in the cell culture supernatants was determined by means of sandwich ELISA using two anti-IL-12 monoclonal antibodies (Biosource Europe, Fleurus, Belgium). A reference standard curve with human IL-12 was included. The detection limit of the IL-12 ELISA was 10 pg/ml.

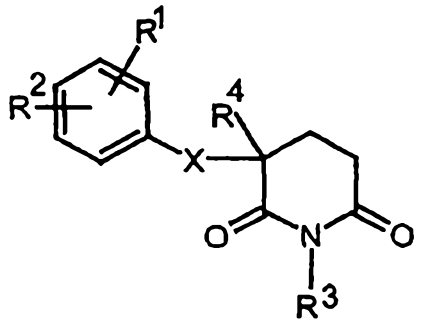
Table 1. Influence of the test substances on IL-12 production by LPS-activated monocytes.

Example no.	Inhibition of IL-12 production	
	Maximum (%)	IC50 (µg/ml)
6.1	85	1.0
6.2	75	1.0
9.1	90	0.1
9.2		
8.3	90	0.15
8.12	84	1.0
7	90	1.5
8.11	90	0.2
8.1	90	1.8
8.5	80	2.0
8.4	80	0.9
8.7	55	0.7
8.10	50	-
8.6	90	0.04
8.2	70	1.8
13.3	50	6.0
13.6	57	3.0

The results set out in Table 1 show that the substituted glutarimides have an immunomodulatory action. They exert a potent inhibitory effect on the synthesis of IL-12 by LPS-activated monocytes.

The claims defining the invention are as follows:

1) Substituted glutarimides having the general formula I



I

in which X denotes a group having the formula $(CH_2)_n$-$(CR^8R^9)_p$-Z-$(CR^8R^9)_m$,

Z stands for a sulfur or oxygen atom, the SO or SO_2 group, the NR^8 radical (optionally in the form of N oxide) or a CR^8R^9 group,

m and p stand for 0 or 1,

n stands for 0, 1, 2 or 3,

whereby m, n and p cannot simultaneously be 0,

R^1 and R^2 are the same or different and stand for the carboxyl group, an ester group having the formula $COOR^5$ or an acyl group having the formula COR^5, in which R^5 in each case denotes an alkyl group (straight-chain or branched) with 1 to 6 C atoms (optionally substituted with the radical $COOR^5$ and/or a phenyl

group), a C_3 to C_7 cycloalkyl group or a phenyl or benzyl radical, or an amide group having the formula $CONR^6R^7$, in which R^6 and R^7 are the same or different and represent hydrogen, an alkyl group (straight-chain or branched) with 1 to 6 C atoms (optionally substituted with the radical $COOR^5$ and/or a phenyl group), the allyl radical, the phenyl radical or taken together with the N atom represent the hydrazide group, the pyrrolidine, piperidine, hexamethylene imine, morpholine, thiomorpholine, piperazine or N-methyl piperazine ring, for hydrogen, bromine, chlorine, fluorine, a mono-, di- or trifluoromethyl, trityl, hydroxyl, hydroxymethyl, trifluoromethoxy, nitro, amino (optionally substituted with the radical CH(=O) or COR^5 or an alkylsulfonyl group) or dimethylamino group, an alkyl or alkoxy radical (straight-chain or branched) with 1 to 6 C atoms, an amidine radical having the formula NH-CH(=NH) or NH-C(=NH)R^5, a phenyl radical or a fused benzene ring (optionally substituted in each case with above-mentioned atoms or groups), with the restriction that if $Z=CR^8R^9$ R^1 and R^2 cannot simultaneously be hydrogen and if Z = S and m = 0 they cannot represent the methoxy group,

R^3 stands for hydrogen, the hydroxy radical or a group having the formula $CH_2-NR^6R^7$, in which R^6 and R^7 are defined as above,

R^4 stands for hydrogen, a C_1 to C_3 alkyl group, a fluorine atom, the difluoro- or trifluoromethyl group

R^8 stands for hydrogen, an alkyl group with 1 to 4 C atoms (straight-chain or branched), the benzyl or phenethyl radical (optionally substituted with above-mentioned atoms or groups),

and R^9 has the same meaning as R^8, stands for the ester group having the formula $COOR^5$, the phenyl radical, the hydroxyl group or an alkoxy radical (straight-chain or branched) with 1 to 4 C atoms, a fluorine or chlorine atom or the trifluoromethyl group,

and enantiomers, enantiomer blends, racemates, diastereomers or diastereomer blends thereof in the form of their bases or salts of physiologically compatible acids.

2) Substituted glutarimides having the general formula I according to claim 1, characterised in that X stands for the groups CH_2-N and S-CH_2, R^1 stands for the carboxyl group, an ester group having the formula $COOR^5$ as defined above, an acyl group having the formula COR^5 as defined above or an amide group having the formula $CONR^6R^7$, in which R^6 and R^7 are the same or different and represent hydrogen, an alkyl group (straight-chain or branched) with 1 to 6 C atoms (optionally substituted as defined above), the phenyl radical or which taken together with the N atom represent the

hydrazide group, the pyrrolidine or morpholidine ring, R^2 stands for hydrogen, the nitro or amino group, R^3 for hydrogen and R^4 for hydrogen, methyl or fluorine.

3) Compounds according to claim 1:

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoic acid

2-[(3R)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoic acid

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl]-N,N-diethylbenzamide

(3S)-[2-morpholine-4-carbonyl)benzylamino] piperidine-2,6-dione

{2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoylamino} methyl acetate

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzamide

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl]-N-ethyl benzamide

(3S)-[2-pyrrolidine-1-carbonyl)benzylamino] piperidine-2,6-dione

2-[(3S)-(2,6-dioxopiperidin-3-ylamino)methyl] benzoic acid hydrazide

2-[(3S)-(2,6-dioxopiperidin-3-ylamino) methyl]-N-phenyl benzamide

2-[(3R)-(2,6-dioxopiperidin-3-ylamino) methyl]-N-phenyl benzamide

2-[(3R)-(2,6-dioxopiperidin-3-ylamino) methyl]-N,N-diethyl benzamide

2-[(3R)-(2,6-dioxopiperidin-3-ylamino) methyl] benzamide

2-[(3S)-(2,6-dioxopiperidin-3-ylamino) methyl] methyl benzoate

2-[(3S)-(2,6-dioxopiperidin-3-ylamino) methyl] benzyl benzoate

2-(2,6-dioxopiperidin-3-ylmethylsulfanyl) methyl benzoate

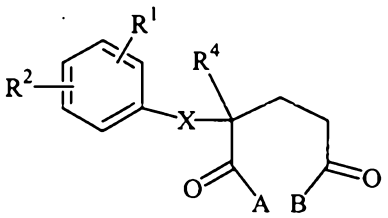
2-(2,6-dioxopiperidin-3-ylmethylsulfanyl)-6-methyl nitrobenzoate.

4. A substituted glutarimide, substantially as hereinbefore described with reference to any one of examples 1-15.

5. A medicament containing as active agent at least one compound according to any one of claims 1 to 4.

6. The medicament according to claim 5, with immunomodulatory action and/or for the treatment of angiopathies and/or haematological/oncological diseases.

7. A process for the production of substituted glutarimides having the general formula I according to claim 1, in which R^3 stands for hydrogen or a hydroxy radical, wherein glutaric acid derivatives having the general formula II,



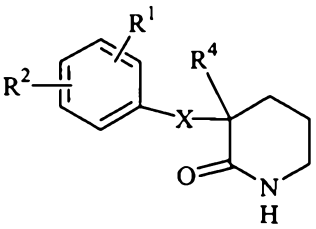
II

in which X, R^1, R^2 and R^4 have the same meanings as above, are either, if A stands for OH and B for NH_2 or NHOH or vice versa, cyclised in the presence of activating reagents, or,

if A and B are both OH, heated in acetic anhydride and the anhydrides obtained by cyclisation are reacted to form compounds having the formula I where R^3 = H by further heating with urea or another nitrogen source.

8. The process according to claim 7, wherein said activating agent is carbonyl diimidazole.

9. A process for the production of substituted glutarimides having the general formula I according to claim 1, in which R^3 = H, wherein lactams having the general formula III



III

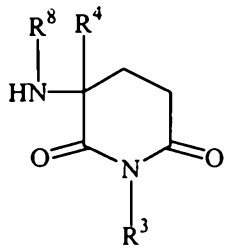
in which R^1, R^2, R^4 and X have the same meanings as above, are oxidised to the corresponding imide.

10. The process according to claim 9, wherein said lactams are oxidised with m-chloroperbenzoic acid or ruthenium (IV) oxide/sodium periodate.

11. A process for the production of substituted glutarimides having the general formula I according to claim 1, in which R^3 stands for CH_2-NR^6R^7, wherein compounds having the formula I where R^3 = H are reacted with paraformaldehyde or an aqueous formaldehyde solution and a secondary amine having the formula HNR^6R^7, where R^6 and R^7 are defined as above.

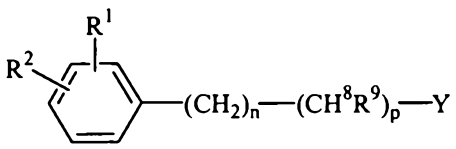
12. A process for the production of substituted glutarimides having the general formula I according to claim 1, in which R^4 denotes a C_1 to C_3 alkyl group, a fluorine atom, a difluoro- or trifluoromethyl group, wherein in compounds having the general formula I where R^4 = H, this hydrogen is exchanged for a C_1 to C_3 alkyl group or the difluoro- or trifluoromethyl group by means of alkylation reactions known per se or for a fluorine atom by means of halogenation reactions known per se.

13. A process for the production of substituted glutarimides having the general formula I according to claim 1, in which for the group X, m = 0 and Z = NR^8, whereby R^8 and n and p have the same meanings as above, wherein -aminoglutarimides having the general formula IV,



IV

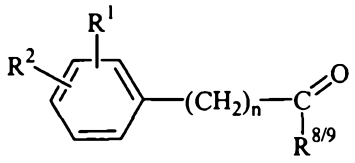
in which R^3, R^4 and R^8 have the same meanings as above, are alkylated with compounds having the general formula V,



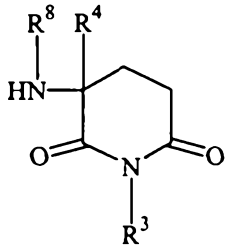
V

in which R^1, R^2, R^8, R^9, n and p have the same meanings as above and Y stands for a chlorine, bromine or iodine atom or a toluene-4-sulfonate radical.

14. A process for the production of substituted glutarimides having the general formula I according to claim 1, in which for the group X, p = 1 and R^8 or R^9 is hydrogen, characterised in that they are produced by reductive amination from compounds having the general formulae VI and IV,



VI

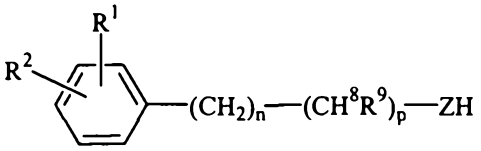


IV

in which R^1, R^2, R^4, R^8, R^9 and n have the same meanings as defined above and R^3 stands for hydrogen or a hydroxyl group.

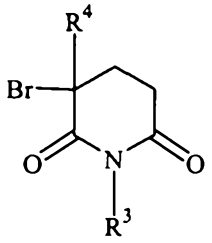
15. The process according to claim 14, wherein the reducing agent is selected from sodium borohydride, sodium triacetoxyborohydride, sodium cyanoborohydride, borane-pyridine complex, or catalytically excited hydrogen.

16. A process for the production of substituted glutarimides having the general formula I according to claim 1, in which for the group X, m = 0, and Z stands for O, S or NR^8 and R^8, n and p are defined as above, characterised in that a compound having the general formula VII,



VII

in which R^1, R^2 have the same meanings as above, is alkylated with -bromoglutarimides having the general formula VIII,

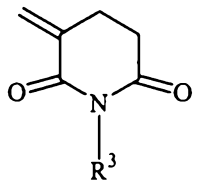


VIII

in which R^3 and R^4 are defined as above.

17. A process for the production of substituted glutarimides having the general formula I according to claim 1, in which R^4 = H and in the group X, n and p are defined as above, m stands for 1, Z for O, S or NR^8 and in the group CR^8R^9 at least one of the

radicals R^8 or R^9 stands for hydrogen, characterised in that a compound having the general formula VII is added to a 3-methylene glutarimide having the general formula IX,



IX

whereby the reaction is performed in a solvent with addition of tertiary amines at temperatures of 80 to 110°C.

18. The process according to claim 17, wherein said solvent is acetonitrile or toluene.

19. The process according to claim 17, wherein said tertiary amine is triethylamine or diisopropyl ethylamine.

20. A process for the production of substituted glutarimides having the general formula I according to claim 1, in which R^1 and/or R^2 stand for an amino group, characterised in that they are obtained by reduction of compounds having the formula I where R^1 and/or $R^2 = NO_2$, whereby the reduction is performed by catalytically excited hydrogen in acid-containing organic solvents, or with metals in acid solution.

21. The process according to claim 20, wherein said organic solvent is ethyl acetate.

22. The process according to claim 20 or 21, wherein the reduction is performed by catalytically excited hydrogen in acid-containing organic solvents using palladium catalysts.

23. The process according to claim 20, wherein said metal is tin or iron.

24. A process for the production of substituted glutarimides having the general formula I according to claim 1, in which Z in the group X stands for SO or SO_2, characterised in that they are obtained by stepwise oxidation of the corresponding dialkyl sulfide (Z = S), whereby hydrogen peroxide in acetic acid solution, m-chloroperbenzoic acid, tert-butyl hydroperoxide or oxones are used as oxidising agents, or the oxidation to sulfoxides (Z = SO) is alternatively structured asymmetrically by using the Sharpless system or Davis reagent or by means of enzymatic methods.

25. The process according to claim 24, wherein said oxidation is carried out with oxones for production of sulfones ($Z = SO_2$).

26. A process for the production of substituted glutarimides having the general formula I according to claim 1, in which Z in the group X stands for the radical NR^8, characterised in that this radical can be converted to the corresponding N-oxide by an oxidising agent.

27. The process according to claim 25, wherein the oxidising agent is hydrogen peroxide.

28. A process for the production of substituted glutarimides having the general formula I as defined in claim 1, substantially as hereinbefore described with reference to any one of examples 1 to 23.

29. A substituted glutarimide prepared according to the process of any one of claims 7 to 28.

30. Use of a substituted glutarimide having the formula I according to any one of claims 1 to 4 or 29 for the production of a medicament.

31. The use according to claim 30 for the production of a medicament having an immunomodulatory action.

32. The use according to claim 30 for the production of a medicament for the treatment of angiopathies.

33. The use according to claim 30 for the production of a medicament for the treatment of haematological/oncological diseases.

34. A method of treating angiopathies in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a compound according to any one of claims 1 to 4 or 29 or a medicament according to claim 5.

35. A method of treating haematological/oncological diseases in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a compound according to any one of claims 1 to 4 or 29 or a medicament according to claim 5.

36. A compound according to any one of claims 1 to 4 or 29 or a medicament according to claim 5, when used for treating angiopathies in a mammal.

37. A compound according to any one of claims 1 to 4 or 29, or a medicament according to claim 5, when used for treating haematological/oncological diseases in a mammal.

Dated 3 February, 2005
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