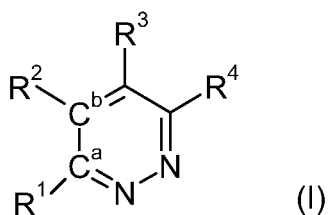


ALKYL-PYRIDAZINE DERIVATIVES AS INHIBITORS OF 11 BETA HYDROXYSTEROID
DEHYDROGENASE TYPE 1 (11B-HSD 1)

The present invention is concerned with novel pyridazine derivatives useful as 11b-HSD1 inhibitors (T2D).

The invention is concerned particularly with compounds of formula I

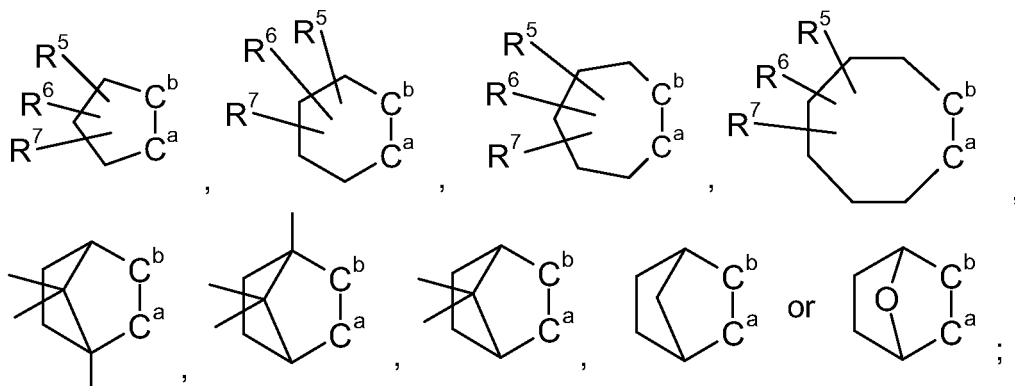


wherein

R¹ is cycloalkyl, arylalkyl or aryloxyalkyl;

R² is cyclalkyl, arylalkyl or aryloxyalkyl; or

R¹ and R² together with the carbon atoms C^a and C^b to which they are attached form



R³ is hydrogen, alkyl, cycloalkyl or trifluoromethyl;

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R⁴ is 2,2-dimethyl-propyl, 3-methyl-butyl, iso-propyl, tert-butyl, cyclopropylmethyl, cyclopentylmethyl, 3,3-dimethyl-butyl or 1-cyclopropyl-1-methyl-ethyl;

R⁵ is hydrogen, alkyl, cycloalkyl or alkoxy;

R⁶ is hydrogen, alkyl, cycloalkyl or alkoxy;

5 R⁷ is hydrogen, alkyl, cycloalkyl or alkoxy;

and pharmaceutically acceptable salts and esters thereof.

Glucocorticoids (cortisol in humans, corticosterone in mice and rats) are an important class of adrenocorticosteroids that regulate many metabolic and homeostatic processes and form a key component of the response to stress. Glucocorticoids act via
10 intracellular glucocorticoid receptors and, in some tissues, mineralocorticoid receptors; both being nuclear transcription factors. Glucocorticoid action on target tissues depends not only on circulating steroid concentrations and the cellular expression of receptors, but also on intracellular enzymes that critically determine to which extent glucocorticoids gain access to receptors in an active forms. 11beta-hydroxysteroid dehydrogenases (11beta-
15 HSD's) catalyze the interconversion of the principal active 11-hydroxy-glucocorticoid (Cortisol in men) and their inactive 11-keto metabolites (cortisone in men).

The enzyme 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1) inter-converts inactive into active glucocorticoids, thereby playing a major role in local modulation of cellular agonist concentration and thus activation of corticosteroid
20 receptors in target tissues. In a recent study made by F. Hoffmann-La Roche differences in gene expression in lean and obese men were analyzed using gene array technology in order to identify specific changes in gene expression that might be associated with insulin resistance or altered metabolism. This study revealed that the mRNA for 11beta-HSD1 is approximately two-fold up regulated in adipose tissue in obese individuals. Moreover,
25 overexpressing 11beta-HSD1 in adipocytes of mice led to visceral obesity and to a syndrome-X like phenotype (Masuzaki H. et al., Science. 2001 Dec 7; 294(5549):2166-70.). Taken together, these data very strongly support an important role of 11beta-HSD1 in the induction of obesity and the impairment of glucose homeostasis and lipid parameters. Thus, selective inhibition of this enzyme could lower blood glucose levels in Type 2
30 diabetic patients, normalize elevated lipid parameters and/or reduce weight in obese subjects .

The first pharmacological indication that 11 β -HSD1 inhibition in men might have beneficial effects were obtained by using carbenoxolone, an anti-ulcer drug which inhibits both 11 β -HSD1 and the related enzyme 11 β -HSD2. Treatment with carbenoxolone led to an increase in insulin sensitivity indicating that that inhibition of 11 β -HSD1 may
5 reduce cellular cortisol levels and therefore minimizing some of its deleterious effects. (Walker et al. 1995; J. Clin. Endocrinol. Metab. 80, 31155-3159).

11 β -HSD1 is expressed in many tissues including liver, adipose tissue, vascular smooth muscles, pancreas and brain. Its activity is dependent on NADP(H) and it has a relatively low affinity for its substrate (compared to 11 β -HSD2). 11 β -HSD1 in tissue
10 homogenates and when purified is bidirectional, exhibiting both 11 β -dehydrogenase and 11 β -reductase reactions, with greater stability of the dehydrogenase activity (P.M. Stewart and Z.S. Krozowski, Vitam. Horm. 57 (1999), pp. 249–324). However, when the enzyme activity is tested in intact cells, the 11 β -reductase activity predominates, which regenerates active glucocorticoids from inert 11-keto forms. Such glucocorticoid
15 regeneration will increase effective intracellular glucocorticoid levels and thereby amplifying glucocorticoid activity. It is this elevated cellular cortisol concentration that might lead to increased hepatic glucose production, adipocyte differentiation and insulin resistance.

Inhibition of 11 β -HSD1 should not only reduce the typical Syndrome-X /
20 Diabetes associated symptoms, but it should also be save and without major side effect. Studies with the unspecific inhibitor carbenoxolone highlight the importance of developing specific 11 β -HSD1 inhibitors. The inhibition of the 11 β -HSD2 enzyme is badly tolerated and results in increased blood pressure. In contrast inhibition of 11 β -HSD1 should be well tolerated since 11 β -HSD1 knockout mice were found be healthy
25 and to resist hyperglycemia provoked by obesity or stress (Kotelevtsev Y. et al., Proc Natl Acad Sci U S A. 1997 Dec 23;94(26):14924-9). Similar upon starvation these mice had attenuated activation of key hepatic enzymes that are involved in gluconeogenesis. In addition, these mice had improved lipid and lipoprotein profiles suggesting that inhibition of HSD1 might be highly efficacious and safe. Recent reports indicate that 11 β -HSD1
30 inhibitors might also be beneficial to reduce high blood pressure (Masuzaki H. et al., J Clin Invest. 2003 July;112(1):83-90; Rauz S. et al., QJM. 2003 July;96(7):481-90) to improve cognition (Sandeep TC. et al., Proc Natl Acad Sci U S A. 2004 Apr. 27;101(17):6734-9) or to improve Alzheimer associated deficits. Taken together 11 β -HSD1 inhibition might

be a save and efficacious approach to treat symptoms of diabetes, obesity and other diseases.

The compounds of formula I and their pharmaceutically acceptable salts and esters are novel and have valuable pharmacological properties. In particular they are 11b-HSD1 inhibitors (T2D) and they display selectivity against the related 11beta-HSD2 enzyme. Therefore the compounds which are specific 11beta-HSD1 inhibitors (T2D) represent an approach to e.g. lower blood glucose levels and normalize lipid parameters in Type 2 diabetic patients by modulating the local concentration of the active glucocorticoid cortisol in target tissue (liver, adipose tissue).

10 The compounds of the present invention can be used in the prophylaxis and/or treatment of metabolic disorders, obesity, dyslipidemiae, hypertension and/or diabetes, particularly diabetes Type II.

The compounds of this invention can further be used in the prophylaxis and/or treatment of high ocular eye pressure, cognition, Alzheimer and/or neurodegeneration.

15 Further, the compounds of this invention can be used for promoting wound healing, particularly by topical application. Moreover, the compounds of the present invention can be used to improve cognitive impairment, particularly impairment developed with age, and improvement of memory.

Objects of the present invention are the compounds of formula I and their
20 aforementioned salts and esters per se and their use as therapeutically active substances, a process for the manufacture of the said compounds, intermediates, pharmaceutical compositions, medicaments containing the said compounds, their pharmaceutically acceptable salts and esters, the use of the said compounds, esters and salts for the prophylaxis and/or therapy of illnesses, especially in the treatment or prophylaxis of eating
25 disorders, obesity, dyslipidemiae, hypertension and/or diabetes, particularly diabetes Type II, and the use of the said compounds, salts and esters for the production of medicaments for the treatment or prophylaxis of metabolic disorders, obesity, dyslipidemiae, hypertension and/or diabetes, particularly diabetes Type II.

The compounds of the present invention can further be combined with PPAR
30 (alpha, gamma, delta) agonists, DHEA (dehydroepiandrosterone), DPPIV inhibitors, insulin and/or lipase inhibitors, particularly orlistat.

In the present description the term "alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, preferably a straight or branched-chain alkyl group with 1 to 6 carbon atoms and particularly preferred a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched C₁-C₈ alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl and ethyl and most preferred methyl.

The term "cycloalkyl", alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and preferably a cycloalkyl ring with 3 to 6 carbon atoms. Examples of C₃-C₈ cycloalkyl are cyclopropyl, methyl-cyclopropyl, dimethylcyclopropyl, cyclobutyl, methyl-cyclobutyl, cyclopentyl, methyl-cyclopentyl, cyclohexyl, methyl-cyclohexyl, dimethyl-cyclohexyl, cycloheptyl and cyclooctyl. Preferred cycloalkyl are methyl-cyclopropyl and particularly 1-methyl-cyclopropyl. Particularly preferred is cyclopropyl.

The term "alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec. butoxy and tert.butoxy, preferably methoxy and ethoxy and most preferred methoxy.

The term "hydroxyalkyl", alone or in combination, signifies an alkyl group as defined before, wherein one or more hydrogen atoms, preferably one hydrogen atom is replaced by a hydroxy group. Examples of hydroxyalkyl are hydroxymethyl and hydroxyethyl.

The term "aryl", alone or in combination, signifies a phenyl or naphthyl group, preferably a phenyl group which optionally carries one or more substituents, preferably one to three, each independently selected from halogen, trifluoromethyl, trifluoromethoxy, amino, alkyl, alkoxy, alkylcarbonyl, cyano, carbamoyl, alkoxycarbamoyl, methylendioxy, carboxy, alkoxycarbonyl, aminocarbonyl, alkyaminocarbonyl, dialkylaminocarbonyl, hydroxy, nitro, alkyl-SO₂-, amino-SO₂-, cycloalkyl and the like. Examples are phenyl or naphthyl, particularly phenyl optionally substituted with one to three, preferably one or two substituents independently selected from alkyl, halogen, alkoxy, trifluoromethoxy, nitro and trifluoromethyl.

The term "aryloxy", alone or in combination, signifies a aryl-O- group in which the term "aryl" has the previously given significance.

The term "amino", alone or in combination, signifies a primary, secondary or tertiary amino group bonded via the nitrogen atom, with the secondary amino group carrying an
5 alkyl or cycloalkyl substituent and the tertiary amino group carrying two similar or different alkyl or cycloalkyl substituents or the two nitrogen substituents together forming a ring, such as, for example, -NH₂, methylamino, ethylamino, dimethylamino, diethylamino, methyl-ethylamino, pyrrolidin-1-yl or piperidino etc., preferably primary amino, dimethylamino and diethylamino and particularly dimethylamino.

10 The term "halogen", alone or in combination, signifies fluorine, chlorine, bromine or iodine and preferably fluorine, chlorine or bromine.

The term "carbonyl", alone or in combination, signifies the -C(O)- group.

The term "oxy", alone or in combination, signifies the -O- group.

The term "nitro", alone or in combination signifies the -NO₂ group.

15 The term "cyano", alone or in combination signifies the group -CN.

The term "pharmaceutically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the
20 like, preferably hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein and the like. In addition these salts may be prepared from addition of an inorganic base or an
25 organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine,
30 trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine,

arginine, N-ethylpiperidine, piperidine, polyimine resins and the like. The compound of formula I can also be present in the form of zwitterions. Particularly preferred pharmaceutically acceptable salts of compounds of formula I are the hydrochloride salts.

5 The compounds of formula I can also be solvated, e.g. hydrated. The solvation can be effected in the course of the manufacturing process or can take place e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of formula I (hydration). The term pharmaceutically acceptable salts also includes physiologically acceptable solvates.

10 "Pharmaceutically acceptable esters" means that compounds of general formula (I) may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compounds in vivo. Examples of such compounds include physiologically acceptable and metabolically labile ester derivatives, such as methoxymethyl esters, methylthiomethyl esters and pivaloyloxymethyl esters. Additionally, any physiologically acceptable equivalents of the compounds of general formula (I),
15 similar to the metabolically labile esters, which are capable of producing the parent compounds of general formula (I) in vivo, are within the scope of this invention.

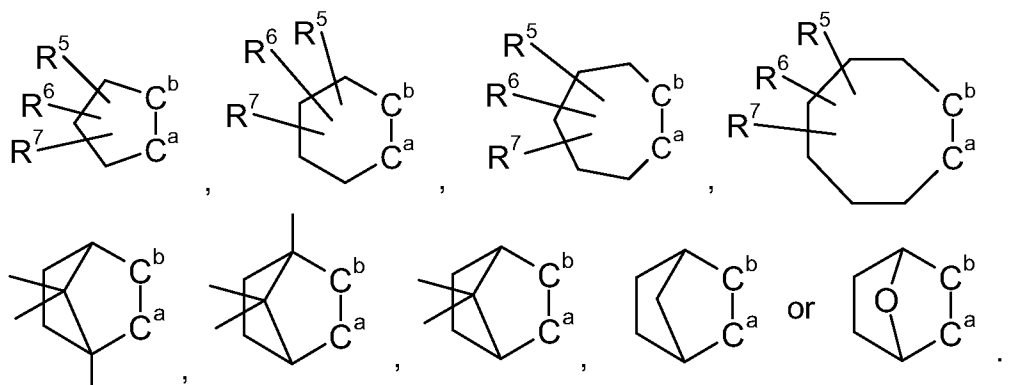
The compounds of formula I can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers,
20 diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

The term "asymmetric carbon atom" (C^*) means a carbon atom with four different substituents. According to the Cahn-Ingold-Prelog Convention the asymmetric carbon atom can be of the "R" or "S" configuration.

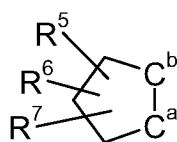
Preferred are the compounds of formula I and pharmaceutically acceptable salts
25 thereof, particularly the compounds of formula I.

Preferred are compounds of formula I, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form

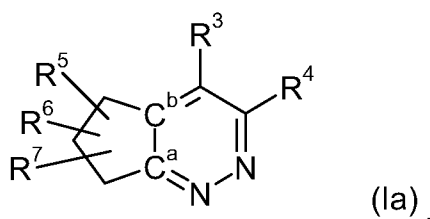
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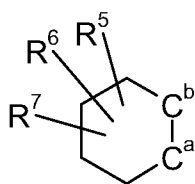
Further preferred are compounds of formula I, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form



5 have the following formula

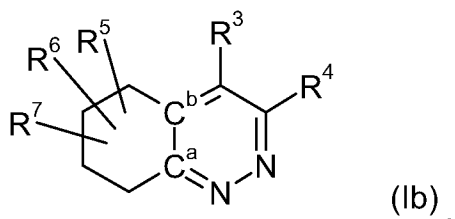


Also preferred are compounds of formula I, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form

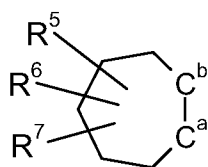


10 have the following formula

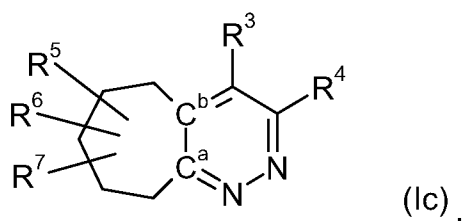
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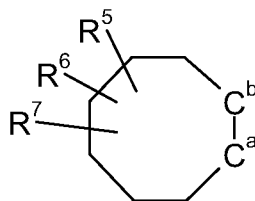
Preferred are compounds of formula I, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form



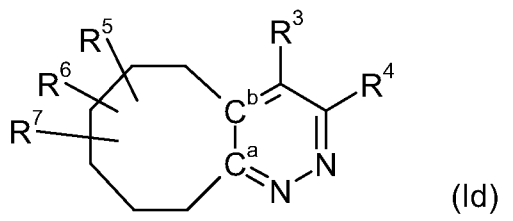
5 have the following formula



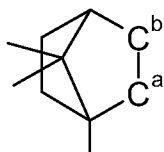
Further preferred are compounds of formula I, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form



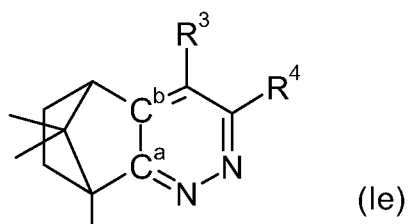
10 have the following formula



Further preferred are compounds of formula I, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form

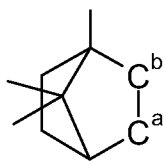


have the following formula

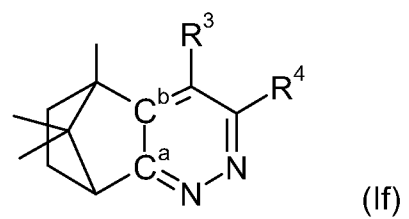


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Further preferred are compounds of formula I, wherein R^1 and R^2 form together with the carbon atoms C^a and C^b to which they are attached

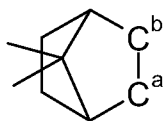


have the following formula

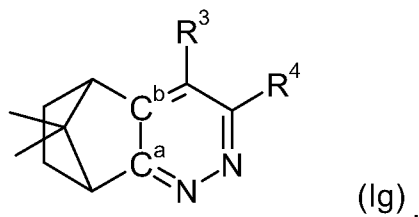


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Further preferred are compounds of formula I, wherein R^1 and R^2 form together with the carbon atoms C^a and C^b to which they are attached

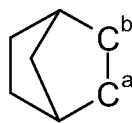


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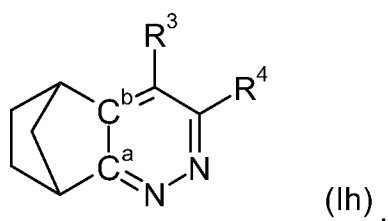


Also preferred are compounds according to formula I, wherein R^1 and R^2 form together with the carbon atoms C^a and C^b to which they are attached

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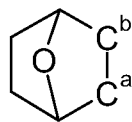


have the following formula

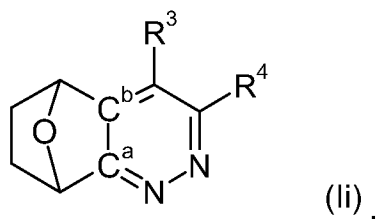


Preferred are compounds of formula I, wherein R^1 and R^2 form together with the carbon atoms C^a and C^b to which they are attached

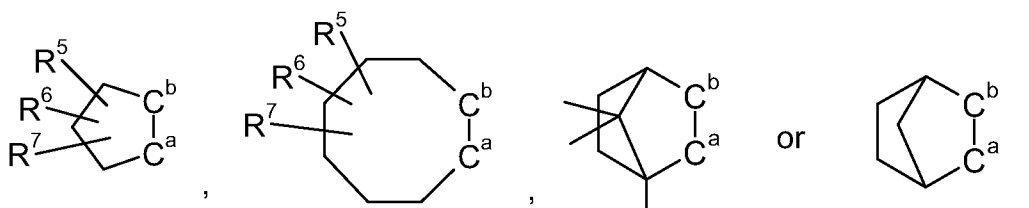
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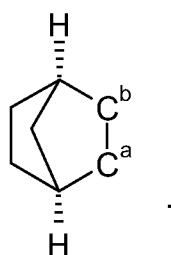
have the following formula



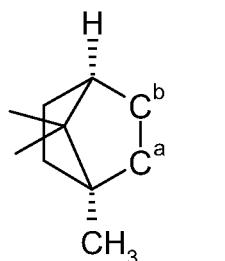
Further preferred are compounds of formula I, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form



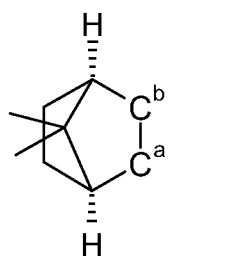
Particularly preferred are those compounds of formula I, wherein R^1 and R^2 together
5 with the carbon atoms C^a and C^b to which they are attached form



Further particularly preferred are those compounds of formula I, wherein R^1 and R^2
together with the carbon atoms C^a and C^b to which they are attached form



10 Also particularly preferred are those compounds of formula I, wherein R^1 and R^2
together with the carbon atoms C^a and C^b to which they are attached form



Also particularly preferred are those compounds of formula I, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form



Further preferred are the compounds of formula I, wherein R^3 is hydrogen. Also
 5 preferred are the compounds of formula I, wherein R^3 is methyl.

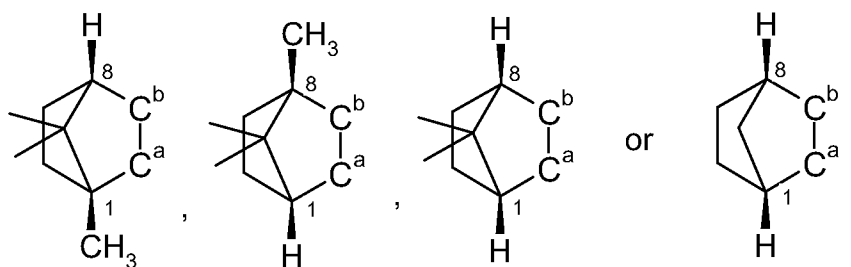
Preferred are compounds according to formula I, wherein R^4 is 2,2-dimethyl-propyl, 3-methyl-butyl, iso-propyl, tert-butyl, cyclopropylmethyl or cyclopentylmethyl.

Preferred are those compounds of formula I, wherein R^4 is 2,2-dimethyl-propyl, 3-methyl-butyl, iso-propyl or tert-butyl. Particularly preferred are the compounds of
 10 formula I, wherein R^4 is 2,2-dimethyl-propyl or tert-butyl. Further particularly preferred are those compounds of formula I, wherein R^4 is 3-methyl-butyl.

A further preferred aspect of the present invention are the compounds of formula I, wherein R^5 , R^6 and R^7 are independently selected from hydrogen and methyl. Particularly preferred are those compounds of formula I, wherein R^5 , R^6 and R^7 are hydrogen.

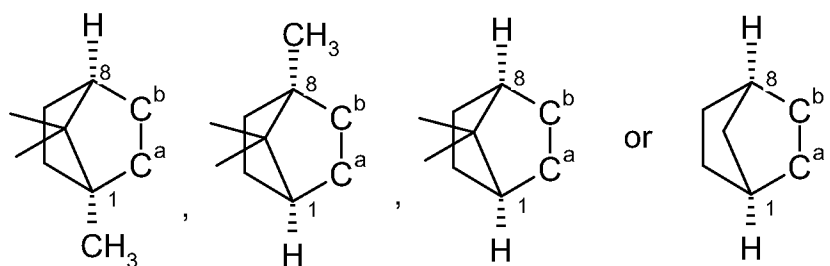
15 Preferred are chiral compounds of formula I.

Preferred are those compounds of formula I, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form



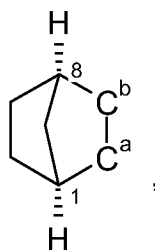
wherein the carbon atom of the 1 position is of the R configuration and the carbon atom
 20 of the 8 position is of the S configuration.

Particularly preferred are those compounds of formula I, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form



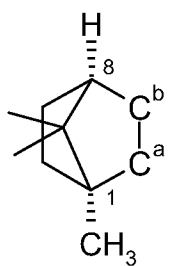
wherein the carbon atom of the 1 position are of the S configuration and the carbon atom of the 8 position is of the R configuration.

Further particularly preferred are those compounds of formula I, wherein R¹ and R²
 5 together with the carbon atoms C^a and C^b to which they are attached form



wherein the carbon atom of the 1 position is of the R configuration and the carbon atom of the 8 position is of the S configuration.

Further particularly preferred are the compounds according to formula I, wherein R¹
 10 and R² together with the carbon atoms C^a and C^b to which they are attached form



According to the above formula the carbon atom of the 1 position is of the S configuration and the carbon atom of the 8 position is of the R configuration.

Examples of preferred compounds of formula (I) are:

15 1. 3-(2,2-Dimethyl-propyl)-5,6,7,8,9,10-hexahydro-cycloocta[c]pyridazine;

2. (1SR,8RS)-5-(2,2-Dimethyl-propyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
3. (1S,8R)-5-(2,2-Dimethyl-propyl)-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 5 4. (1S,8R)-5-tert-Butyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
5. 3-(2,2-Dimethyl-propyl)-6,6-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridazine;
6. (1SR,8RS)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 10 7. 3-tert-Butyl-6,6-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridazine;
8. (1SR,8RS)-5-(3-Methyl-butyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene;
9. (1SR,8RS)-5-tert-Butyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
10. (1S,8R)-1,11,11-Trimethyl-5-(3-methyl-butyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 15 11. (1S,8R)-5-Isopropyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
12. (1SR,8RS)-5-Cyclopropylmethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene;
- 20 13. (1S,8R)-5-Cyclopropylmethyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene;
14. 3-Cyclopropylmethyl-6,6-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridazine;
and
- 25 15. (1S,8R)-5-Cyclopentylmethyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene.

Examples of particularly preferred compounds of formula (I) are:

(1SR,8RS)-5-(2,2-Dimethyl-propyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;

- (1S,8R)-5-(2,2-Dimethyl-propyl)-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1S,8R)-5-tert-Butyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1SR,8RS)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 5 3-tert-Butyl-6,6-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridazine; and
- (1S,8R)-1,11,11-Trimethyl-5-(3-methyl-butyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene.
- 10 Further preferred examples of the present invention are
- (1S,8R)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1S,8R)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 15 (1S,8R)-5-(3,3-Dimethyl-butyl)-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1SR,8RS)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1S,8R)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1R,8S)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 20 (1SR,8RS)-5-(2,2-Dimethyl-propyl)-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1SR,8RS)-5-(2,2-Dimethyl-propyl)-6,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1SR,8RS)-5-(1-Cyclopropyl-1-methyl-ethyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 25 (1SR,8RS)-5-Cyclopentylmethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;

(1R,8S)-5-(2,2-Dimethyl-propyl)-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene;

(1S,8R)-5-(2,2-Dimethyl-propyl)-8,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene;

5 (1R,8S)-5-tert-Butyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene; and

(1S,8R)-5-tert-Butyl-8,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene.

10 Further examples of particularly preferred compounds of formula (I) are:

(1S,8R)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;

(1S,8R)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;

15 (1S,8R)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;

(1R,8S)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;

(1SR,8RS)-5-(2,2-Dimethyl-propyl)-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;

20 (1S,8R)-5-(2,2-Dimethyl-propyl)-8,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene; and

(1S,8R)-5-tert-Butyl-8,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene.

Processes for the manufacture of compounds of formula I are an object of the invention.

25 The preparation of compounds of formula I of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the invention are shown in

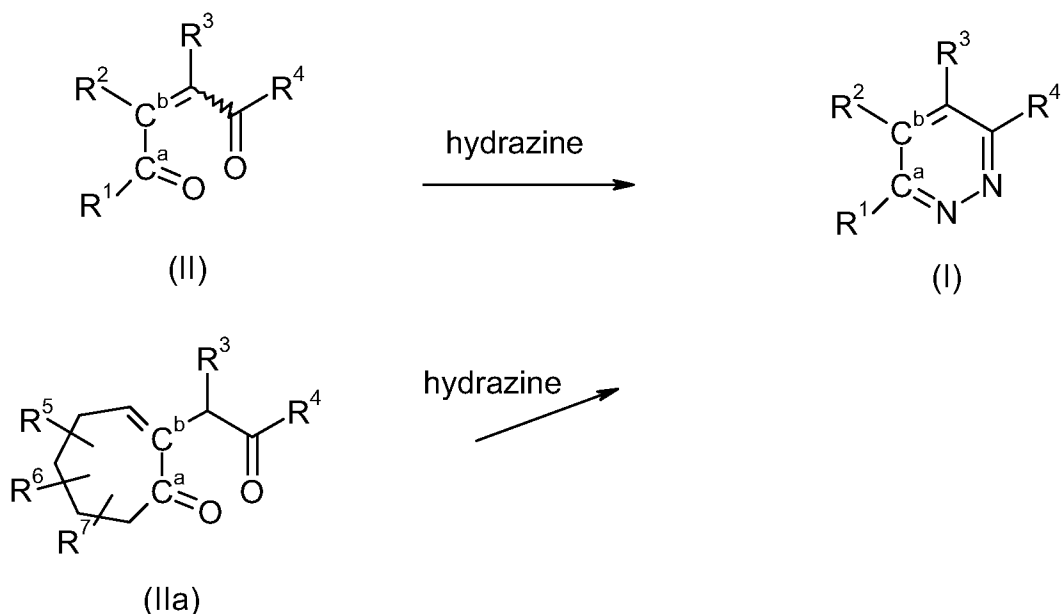
the following Schemes. The skills required for carrying out the reaction and purification of the resulting products are known to those persons skilled in the art. The substituents and indices used in the following description of the processes have the significance given above unless indicated to the contrary.

- 5 In general, compounds of type I are readily accessible by treatment of compounds of formula II with hydrazine: different reaction conditions can be used to perform the condensation reaction, e.g.: heating II with hydrazine monohydrate in toluene in the presence of an acid such as p-toluene sulfonic acid, (ii) heating II and hydrazine monohydrate in a mixture of water / acetic acid at reflux temperature, (iii) heating II and
10 hydrazine monohydrate in a mixture of water / acetic acid at reflux temperature which is then followed, after work-up, by a basic treatment with NaOMe in n-butanol at reflux temperature to complete the ring closing reaction to pyridazine.

- The application of the different conditions depends on the respective starting materials used and is outlined in the experimental part. The geometries of the double bond of
15 compounds of type II can be E or Z, or mixtures of E and Z. Independent of the double bond geometry, they can be converted to I by choosing the most appropriate reaction conditions outlined above, and as exemplified in the experimental part.

- In cases where R1 and R2 form 5 to 8 membered rings, the synthesis of these analogues of formula II via a Horner-Wittig reaction (chapter below) can give rise to isomeric
20 compounds, with the double bond migrated into the ring system, and as exemplified in formula IIa for the 7 membered ring system. Also these isomers can be directly converted to II by employing the reaction conditions outlined above.

Scheme 1



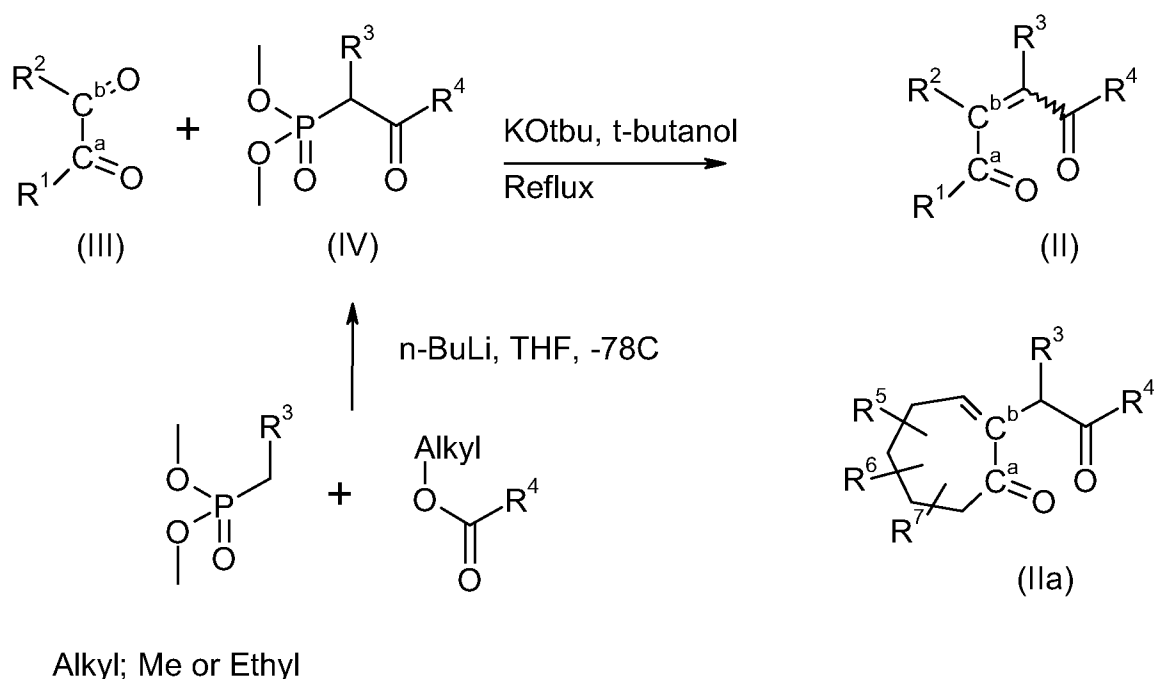
The compound of type II, employed in scheme 1 as starting materials, can be prepared as summarized in scheme 2:

- Thus, on reacting a 1,2-diketone of formula III with a phosphonate of formula IV in a Horner-Emmons (or Wittig-Horner) reaction, this gives rise to compounds of formula II. The conditions that can be used are, e.g.: potassium tert-butoxide as a base in tert-butanol as solvent under reflux conditions. Depending on the starting material, double bond migration can occur were possible, as shown in formula IIa for compounds were R¹, R² form a 7 membered ring, and as exemplified in the experimental part.
- The double bond geometries of the compounds of formula II can be E, Z or a mixture of E and Z depending on the R¹, R²; R³, R⁴ groups. In many cases only one isomer (the thermodynamically more stable E isomer) is predominantly formed. In cases were mixtures are obtained these can be separated by chromatography or used as mixtures in the ring forming reaction. The stereochemistry of the double bond can be assigned by NMR for the compounds of formula II (experimental part). Instead of a phosphonate of type IV it is also possible to use a corresponding alpha-halo ketone analogue and performing a Reformatsky reaction followed by water elimination (for an example of this type of reaction: Huang, J. Chem. Soc., Perkin Trans. 1, 1989, 2397).

For compounds of formula III that are not symmetric, compounds of formula II are directly obtained in cases where the C^b carbonyl group is more reactive then C^a carbonyl. In cases were the two carbonyl groups can react, mixtures can be obtained, which can be separated by chromatography and processed further accordingly.

In cases where the Ca carbonyl group is the more reactive in regard to the Horner-Emmons (or Wittig-Horner) reaction - compounds of formula II can be obtained via several routes, e.g. : (i) conversion of the Ca carbonyl into a cyclic ketal group on reaction with, for example, ethane-1,2-diol (analogues to: Boeckman, J. Am. Chem. Soc., 1986, 5549),
 5 performing the Wittig-Horner reaction at Cb followed by Ca ketal cleavage; or alternatively: (ii) reduction of the Ca carbonyl group to hydroxy and protection, for example, as a t-butyl-dimethyl-silyl ether (for an example: Boeckman, J. Am. Chem. Soc., 1986, 5549), performing then the Horner-Wittig reaction at Cb, de-protection and final
 10 oxidation of hydroxy back to carbonyl - using, for example, the Swern oxidation conditions (for an example of the reaction: Albright, J. Org. Chem., 1965 30, 1107).

Scheme 2



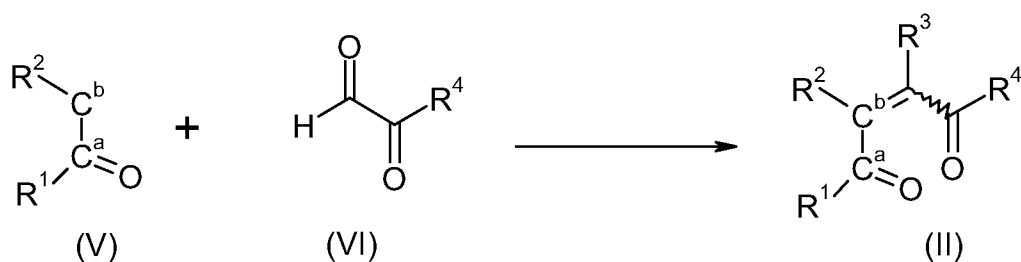
The 1,2-diketones III used in scheme II are either commercial, known in the literature or can be prepared by combination of methods known in the art.

15 The phosphonates of formula IV are either known in the literature or can be prepared by standard procedures. An example of preparing compounds IV consists of treatment of an alkyl-phosphonic acid dimethyl ester with a base such as N-butyllithium, in THF as solvent at -78°C and subsequent reaction with an alkyl carboxylate to give IV. Alternatively, methyl-phosphonic acid dimethyl ester (R³=H) can be used in the reaction,
 20 with an subsequent alkylation step to introduce R³ - reacting IV (R=H) with an alkylating reagent (R³-hal) in the presence of a base such as potassium t-butoxide or N-butyllithium

or potassium carbonate (for an analogous reaction: B. Kirschberger, *Synthesis*, 1986, 11, 926).

Alternative ways to prepare compounds of formula II consists of reaction a ketone of formula V with compounds of formula VI according to Scheme 3. The reaction can be achieved in analogy to a method described by Mukaiyama (*J. Am. Chem. Soc.*, 1974, 96, 7503) via a cross aldol reaction, reacting V, via its pre-formed silyl enol-ether, with a formyl carbonyl of formula IV, in the presence of titanium tetrachloride, to give II after dehydration of the primary coupling product. Compounds VI are either commercial available ore prepared in analogy to methods described in the literature, e.g. from corresponding methyl ketones and SeO_2 oxidation (for a literature example: K.C. Joshi, *Heterocycles*, 1981, 16, 1545), or from alpha-halo ketones and Swern oxidation (for an example; D. Swern, *Synthesis*, 1981, 165).

Scheme 3



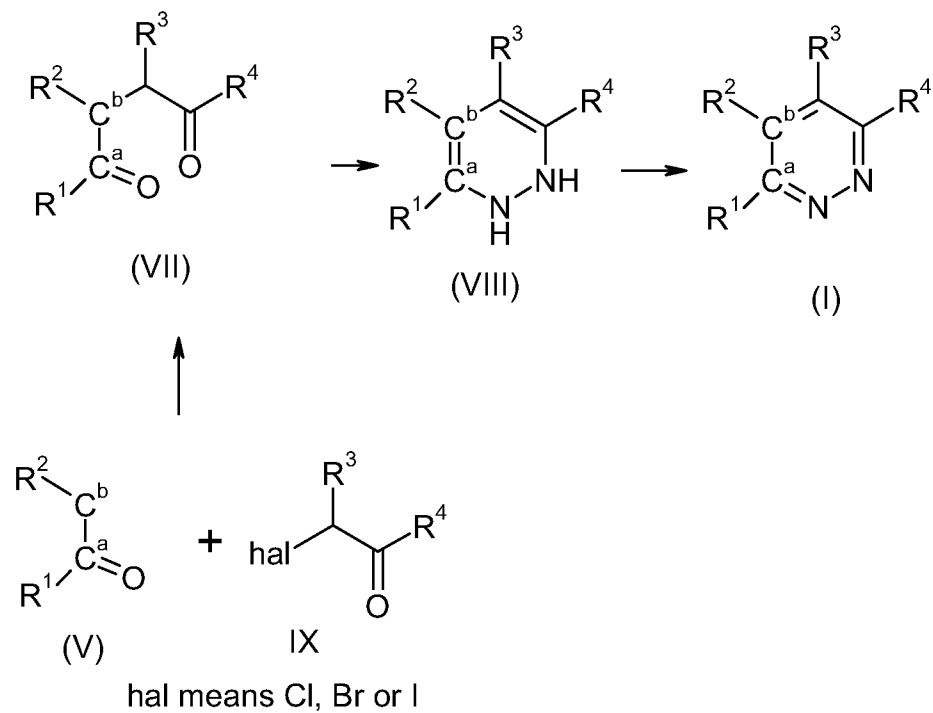
R^3 means hydrogen

The compounds of formula V are either commercial, described in the literature or can be prepared by applying known procedures.

An further alternative way to prepare compounds of formula I is outlined in scheme 4: It consists to react 1,4-diketones of formula VII with hydrazine under conditions discussed above to give the dihydropyridazines of formula VIII (one of several possible isomeric forms drawn). These can then be aromatized with, for example, Pd on charcoal or another oxidation reagent such as Br_2 (for analogues procedures: Baumgarten, *J. Am. Chem. Soc.* 1958, 80, 6609) to give compounds of formula I. The 1,4 diketones of formula VII are widely used synthetic building blocks and numerous methods for their preparation are known in the literature (for example: Corey *J. Am. Chem. Soc.* 1969, 91, 4926; Katritzky, *J. Org. Chem.* 1991, 56, 6917). A more recent example to prepare these compounds is to use the procedure published by A. Baba (*J. Org. Chem.*, 1997, 62, 8282): It consists to react

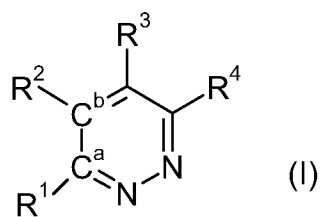
ketone V, via prior conversion to the corresponding tin enolate, with the alpha-halo ketone IX in the presence of catalytic amounts of ZnCl_2 (Scheme 4).

Scheme 4

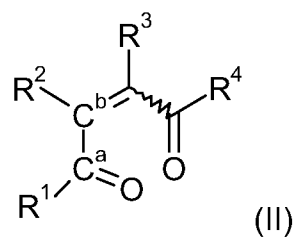


5

A preferred process for the preparation of a compound of formula



comprises the reaction of a compound according to formula



10

with hydrazine in order to obtain a compound according to formula I;

wherein R^1 to R^4 are defined as before.

The compounds of formula I described above for use as therapeutically active substance are a further object of the invention.

- 5 Also an object of the present invention are compounds as described above for the preparation of medicaments for the prophylaxis and therapy of illnesses which are caused by disorders associated with the enzyme 11 β -hydroxysteroid dehydrogenase1 (11 β HSD1).

- 10 Likewise an object of the invention are pharmaceutical compositions comprising a compound of the formula I as described above and a therapeutically inert carrier.

A further preferred embodiment of the present invention is the use of a compound of the formula I as described above for the preparation of medicaments for the treatment and prophylaxis of diabetes, obesity, eating disorders, dyslipidemiae and hypertension.

- 15 Particularly preferred is the use of a compound according to formula I as described above for the preparation of medicaments for the treatment and prophylaxis of diabetes Type II.

A further object of the present invention comprises a compound according to formula I as described above, when manufactured according to any one of the described processes.

- 20 Also an object of the invention is a method for the treatment and prophylaxis of diabetes, obesity, eating disorders, dyslipidemiae and hypertension, which method comprises administering an effective amount of a compound of formula I as described above.

- 25 Particularly preferred is a method for the treatment and prophylaxis of diabetes Type II, which method comprises administering an effective amount of a compound according to formula I as described above.

Assay Procedures

Transient expression and partial Purification:

The cDNA encoding the human 11beta-HSD1 protein was cloned into the expression
5 vector pcDNA3 (Stratagene). This construct (for details see Alex Odermatt et al.; J Biol
Chem.,1999, Vol. 274, Issue 40, 28762-28770) was used to transiently express the protein
in HEK293 cells (ATCC number: CRL-1573, described in Graham, F.L., Smiley, J., Russell,
W.C., Nairn, R.; (1977)) using lipofectamine. 48h after transfection cells were washed
10 twice with ice-cold PBS (Phosphate buffered Saline). To 1 volume of cell suspension in
PBS 2 volumes of ice-cold lysis buffer (50mM Tris; pH7.5; 1mM EDTA; 100mM NaCl)
were added. The cells were lysed by Potter-homogenization (20 strokes). The resulting
homogenate was sonicated with a tip sonicator (10% output; 2 x 30 sec.) and cleared by a
low speed centrifugation (10min x 9000g; 4°C). The microsomal fraction was collected by
15 a high speed centrifugation (60 min x 110'000g). The resulting pellet was resuspended in
storage buffer (20mM Tris pH 7.5; 1 mM EDTA; 10% Glycerol) and the centrifugation was
repeated. The resulting pellet containing the microsomal fraction was again taken up into
storage buffer and aliquots were kept frozen in liquid Nitrogen until use.

Generation of stable cell lines expressing 11beta-HSD1:

20 The same construct used for transient expression of human 11beta-HSD1 was also used to
establish cell lines stably expressing the protein. Briefly, (HEK293) cells were transfected
with 11beta-HSD1 construct using the lipofectamine reagent (Gibco BRL) according to the
manufacturer's instruction. Two days after transfection, geneticin selection (0.8 mg/ml)
was initiated and several stable clones were isolated. One clone was further used for
25 pharmacological characterization.

Microsome Assay

Microsomes isolated from HEK293 cells transiently expressing human 11beta-HSD1 (for
details see above) were incubated in assay buffer (100 mM NaCl; 1mM EDTA; 1mM

EGTA; 1mM MgCl; 250 mM Sucrose; 20 mM Tris pH 7.4; Cortisone 50-200nM and NADPH 1mM) together with different concentrations of test substances. After 60 min. of incubation at 37°C the assay was stopped by heating to 80°C (5 min.) and by addition of the inhibitor Carbenoxolone (1 uM). The amount of Cortisol produced in this assay was
5 determined using a commercially available, ELISA-based Cortisol-detection kit (Distributed by Assay Design, Inc.). Inhibitors were characterized by there IC50 values, e.g. the concentration at which the production of cortisol was 50% reduced.

In this test preferred compounds as described above have IC50 values below 1000 nM; more preferred compounds have IC50 values below 100 nM. Most preferred compounds
10 have IC50 values below 10nM.

Cellular Assay

To measure the effect of inhibitors in intact cells HEK293 cells stably expressing human 11beta-HSD1 (see above) were cultivated in 96 well plates in DMEM. First inhibitors and
15 60 min later Cortisone was added to the cells. After 60 min of incubation at 37°C in a 5% CO2 atmosphere part of the medium was removed and the conversion from Cortisone to Cortisol was measured using a commercially available ELISA kit (Distributed by Assay Design, Inc.).

Results obtained in the microsome assay using representative compounds of the
20 invention as the test compounds are shown in the following table:

Results obtained in the microsome assay using representative compounds of the invention as the test compounds are shown in the following table:

<u>Compound</u>	<i>h</i> 11-beta-HSD 1 IC ₅₀ (nM)
Example 1	6
Example 3	14

Compounds as described above have IC_{50} values below 1000 nM; preferred compounds have IC_{50} values below 100 nM. More preferred compounds have IC_{50} values below 10 nM. These results have been obtained by using the foregoing test.

The compounds of formula I and their pharmaceutically acceptable salts and esters
5 can be used as medicaments (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parentally, such as
10 intramuscularly or intravenously (e.g. in the form of injection solutions).

The compounds of formula I and their pharmaceutically acceptable salts and esters can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées and hard gelatin capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as
15 such adjuvants for tablets, dragées and hard gelatin capsules.

Suitable adjuvants for soft gelatin capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

20 Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers,
25 viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

In accordance with the invention the compounds of formula I and their pharmaceutically acceptable salts can be used for the prophylaxis and treatment of

arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity. The dosage can vary in wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 20 mg per kg body weight, preferably
5 about 0.5 mg to 4 mg per kg body weight (e.g. about 300 mg per person), divided into preferably 1-3 individual doses, which can consist, for example, of the same amounts, should be appropriate. It will, however, be clear that the upper limit given above can be exceeded when this is shown to be indicated.

The invention is illustrated hereinafter by Examples, which have no limiting
10 character.

Examples

Example 1: 3-(2,2-Dimethyl-propyl)-5,6,7,8,9,10-hexahydro-cycloocta[c]pyridazine

Step A]: (4,4-Dimethyl-2-oxo-pentyl)-phosphonic acid dimethyl ester

5 A solution of methyl-phosphonic acid dimethyl ester (9.53 g) in THF (50 mL) under an argon atmosphere was cooled to -65°C and treated dropwise with 48 mL of a 1.6 M solution of N-butyllithium in hexane keeping the temperature of the reaction mixture below -65°C. After stirring for 15 minutes 3,3-dimethyl-butyric acid methyl ester (5 g in 5 ml THF) were added slowly and the mixture was stirred for 30 minutes (temperature
10 below -65°C). The reaction mixture was allowed to warm to 0°C, quenched with 1N aqueous HCl, and then partitioned between ACOEt and water. The layers were separated, the organic layer was washed with water, dried over MgSO₄, filtered and evaporated to give 4,4-dimethyl-2-oxo-pentyl)-phosphonic acid dimethyl ester (9.21 g) as a light yellow liquid that was used in the next reaction without further purification. MS (ESI): 223.2 (MH⁺).

15 Step B]: (Z)-2-(4,4-Dimethyl-2-oxo-pentyl)-cyclooct-2-enone

A solution of potassium tert-butoxide (0.192 g) in tert-butanol (10 mL) under an argon atmosphere was treated at 50 °C with (4,4-dimethyl-2-oxo-pentyl)-phosphonic acid dimethyl ester (0.38 g) and cyclooctane-1,2-dione (0,2 g), and the mixture was then heated at reflux for 12 h under an argon atmosphere. The reaction mixture was partitioned
20 between water and AcOEt, the layers were separated, the aqueous layer extracted twice with AcOEt. The combined organic layers were washed with water, dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography (heptane/AcOEt 100% to 95%) to give (Z)-2-(4,4-dimethyl-2-oxo-pentyl)-cyclooct-2-enone (0.076 g) as a light yellow oil. MS (ESI): 237.0 (MH⁺).

25 Step C]: 3-(2,2-Dimethyl-propyl)-5,6,7,8,9,10-hexahydro-cycloocta[c]pyridazine

(i) A solution of (Z)-2-(4,4-Dimethyl-2-oxo-pentyl)-cyclooct-2-enone (0.07 g) in ethanol (6 ml) was treated at RT with water (1.5ml), hydrazine monohydrate (0.07ml) and acetic acid (1.5 ml), and the mixture was then heated to reflux for 12 h (oil bath temperature: 105 °C). The reaction mixture was partitioned between water and AcOEt. The combined
30 organic layers were washed with 2M aqueous KHCO₃, dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography (heptane/AcOEt 100% to

85%) to give 3-(2,2-dimethyl-propyl)-5,6,7,8,9,10-hexahydro-cycloocta[c]pyridazine, (0.018 g) as an amorphous white solid. MS (ESI): 233.2 (MH⁺).

Further compounds that were prepared according to example 1, steps A] to C]:

Example 2 (1SR,8RS)-5-(2,2-Dimethyl-propyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-
5 2,4,6-triene

light-yellow solid. MS (ESI): 217.2 (MH⁺). Prepared from bicyclo[2.2.1]heptan-2,3-dione, (4,4-dimethyl-2-oxo-pentyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 3: (1S,8R)-5-(2,2-Dimethyl-propyl)-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

10 light-yellow solid. MS (ESI): 258.9 (MH⁺). Prepared from (1S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2,3-dione, (4,4-dimethyl-2-oxo-pentyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 4: (1S,8R)-5-tert-Butyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

15 MS (EI): 244.3 (M⁺), light-yellow crystalline solid. Prepared from (1S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2,3-dione, (3,3-dimethyl-2-oxo-butyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 5: 3-(2,2-Dimethyl-propyl)-6,6-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridazine

20 off-white solid. MS (ESI): 219.3 (MH⁺). Prepared from 4,4-dimethyl-cyclopentane-1,2-dione, (4,4-dimethyl-2-oxo-pentyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 6: (1SR,8RS)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

25 light-yellow oil. MS (ESI): 297.1 (MH⁺). Prepared from bicyclo[2.2.1]heptane-2,3-dione, (1,4,4-trimethyl-2-oxo-pentyl)-phosphonic acid diethyl ester, hydrazine monohydrate.

Example 6a,b:

(1S,8R)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene and (1R,8S)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

Submission of compound of example 6 to preparative HPLC, using a chiral column Chiralpak AD, with 5% isopropanol/heptane as eluant gave the two enantiomers, in optically pure form. Off-white solids.

Example 7: 3-tert-Butyl-6,6-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridazine

white crystalline solid. MS (ESI): 205.0 (MH⁺). Prepared from 4,4-dimethyl-cyclopentane-1,2-dione, (3,3-dimethyl-2-oxo-butyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 8: (1SR,8RS)-5-(3-Methyl-butyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene

yellow solid. MS (ESI): 217.4 (MH⁺). Prepared from bicyclo[2.2.1]heptane-2,3-dione, (5-methyl-2-oxo-hexyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 9: (1SR,8RS)-5-tert-Butyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

off-white crystalline solid. MS (EI): 245.2 (M⁺). Prepared from bicyclo[2.2.1]heptane-2,3-dione, (3,3-dimethyl-2-oxo-butyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 10: (1S,8R)-1,11,11-Trimethyl-5-(3-methyl-butyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

yellow solid. MS (ESI): 259.0 (MH⁺). Prepared from (1S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2,3-dione, (5-methyl-2-oxo-hexyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 11: (1S,8R)-5-Isopropyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

off-white crystalline solid. MS (ESI): 231.0 (MH⁺). Prepared from (1S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2,3-dione, (3-methyl-2-oxo-butyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 12: (1SR,8RS)-5-Cyclopropylmethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-
5 2(7),3,5-triene

light brow oil. MS (ESI): 201.1 (MH⁺). Prepared from bicyclo[2.2.1]heptane-2,3-dione, (3-cyclopropyl-2-oxo-propyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 13 (1S,8R)-5-Cyclopropylmethyl-1,11,11-trimethyl-3,4-diaza-
tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene

10 Yellow solid. MS (ESI): 243.2 (MH⁺). Prepared from (1S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2,3-dione, [(3-cyclopropyl-2-oxo-propyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 14: 3-Cyclopropylmethyl-6,6-dimethyl-6,7-dihydro-5H-
cyclopenta[c]pyridazine

15 Prepared from 4,4-dimethyl-cyclopentane-1,2-dione, (3-cyclopropyl-2-oxo-propyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 15 (1S,8R)-5-Cyclopentylmethyl-1,11,11-trimethyl-3,4-diaza-
tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

20 off-white crystalline solid. MS (ESI): 271.4 (MH⁺). Prepared from (1S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2,3-dione, [(3-cyclopentyl-2-oxo-propyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 16 (1S,8R)-5-(3,3-Dimethyl-butyl)-1,11,11-trimethyl-3,4-diaza-
tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

25 light yellow viscous oil MS (ESI): 273.2 (MH⁺). Prepared from (1S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2,3-dione, (5,5-dimethyl-2-oxo-hexyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 17 (1SR,8RS)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-
tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

white solid MS (ESI): 231 (MH⁺). Prepared from 7,7-dimethyl-bicyclo[2.2.1]heptane-2,3-dione (Childs, Ronald F.; Rogerson, Carol V.; J. Am. Chem. Soc.; EN; 102; 12; 1980; 4159), 3,3-dimethyl-2-oxo-butyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

- 5 **Example 17a,b** (1S,8R)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene and (1R,8S)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

Submission of compound of example 17 to preparative HPLC, using a chiral column Chiralpak AD, with 2% isopropanol/heptane as eluant gave the two enantiomers, in
10 optically pure form. White solids.

Example 18 (1SR,8RS)-5-(2,2-Dimethyl-propyl)-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

light yellow solid. MS (ESI): 245.2 (MH⁺). Prepared from 7,7-dimethyl-bicyclo[2.2.1]heptane-2,3-dione, (4,4-dimethyl-2-oxo-pentyl)-phosphonic acid dimethyl
15 ester, hydrazine monohydrate.

Example 19 (1SR,8RS)-5-(2,2-Dimethyl-propyl)-6,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

yellow solid. MS (ESI): 259.3 (MH⁺). Prepared from 7,7-dimethyl-bicyclo[2.2.1]heptane-2,3-dione, (1,4,4-trimethyl-2-oxo-pentyl)-phosphonic acid diethyl ester, hydrazine
20 monohydrate.

Example 20 (1SR,8RS)-5-(1-Cyclopropyl-1-methyl-ethyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

white solid. MS (ESI): 229.2 (MH⁺). Prepared from bicyclo[2.2.1]heptan-2,3-dione, (3-cyclopropyl-3-methyl-2-oxo-butyl)-phosphonic acid dimethyl ester, hydrazine
25 monohydrate.

Submission of the racemate to preparative HPLC, using a chiral column, Chiralpak AD, with 5% isopropanol/ heptane as eluant gave the two enantiomers, in optically pure form.

Example 21 (1SR,8RS)-5-Cyclopentylmethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene

light yellow gum. MS (ESI): 229.2 (MH⁺). Prepared from bicyclo[2.2.1]heptan-2,3-dione, [(3-cyclopentyl-2-oxo-propyl)-phosphonic acid dimethyl ester, hydrazine monohydrate.

Example 22 (1R,8S)-5-(2,2-Dimethyl-propyl)-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene

- 5 off-white solid. MS (ESI): 259.1 (MH⁺). Prepared from (1R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2,3-dione, (4,4-dimethyl-2-oxo-pentyl)-phosphonic acid dimethyl ester, hydrazine monohydrate. Main product, isolated and purified by silica gel chromatography.

Example 23 (1S,8R)-5-(2,2-Dimethyl-propyl)-8,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene

white solid. MS (ESI): 259.1 (MH⁺). Prepared from (1R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2,3-dione, (4,4-dimethyl-2-oxo-pentyl)-phosphonic acid dimethyl ester, hydrazine monohydrate. Minor product, regioisomer of compound of example 22, isolated and purified by silica gel chromatography.

15 **Example 24** (1R,8S)-5-tert-Butyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene

- light yellow oil. MS (ESI): 245.2 (MH⁺). Prepared from (1R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2,3-dione, (3,3-dimethyl-2-oxo-butyl)-phosphonic acid dimethyl ester, hydrazine monohydrate. Main product isolated and purified by silica gel
20 chromatography.

Example 25 (1S,8R)-5-tert-Butyl-8,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene

- light yellow oil. MS (ESI): 245.2 (MH⁺). Prepared from (1R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2,3-dione, (3,3-dimethyl-2-oxo-butyl)-phosphonic acid dimethyl
25 ester, hydrazine monohydrate. Minor product, regioisomer of compound of example 24, isolated and purified by silica gel chromatography.

Example A

- A compound of formula I can be used in a manner known per se as the active
30 ingredient for the production of tablets of the following composition:

- 34 -

Per tablet

	Active ingredient	200 mg
	Microcrystalline cellulose	155 mg
	Corn starch	25 mg
5	Talc	25 mg
	Hydroxypropylmethylcellulose	<u>20 mg</u>
		425 mg

Example B

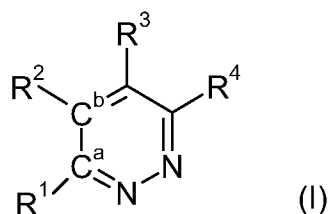
- A compound of formula I can be used in a manner known per se as the active
- 10 ingredient for the production of capsules of the following composition:

Per capsule

	Active ingredient	100.0 mg
	Corn starch	20.0 mg
	Lactose	95.0 mg
15	Talc	4.5 mg
	Magnesium stearate	<u>0.5 mg</u>
		220.0 mg

CLAIMS

1. Compounds of formula

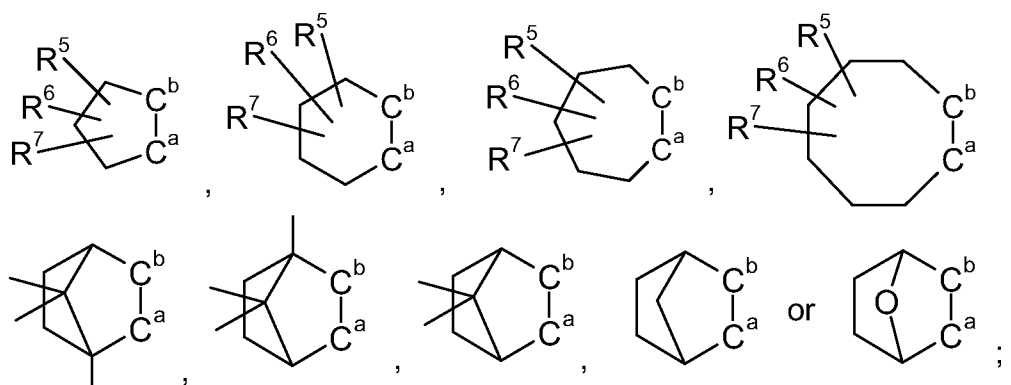


5 wherein

R^1 is cycloalkyl, arylalkyl or aryloxyalkyl;

R^2 is cyclalkyl, arylalkyl or aryloxyalkyl; or

R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form



10 R^3 is hydrogen, alkyl, cycloalkyl or trifluoromethyl;

R^4 is 2,2-dimethyl-propyl, 3-methyl-butyl, iso-propyl, tert-butyl, cyclopropylmethyl, cyclopentylmethyl, 3,3-dimethyl-butyl or 1-cyclopropyl-1-methyl-ethyl;

R^5 is hydrogen, alkyl, cycloalkyl or alkoxy;

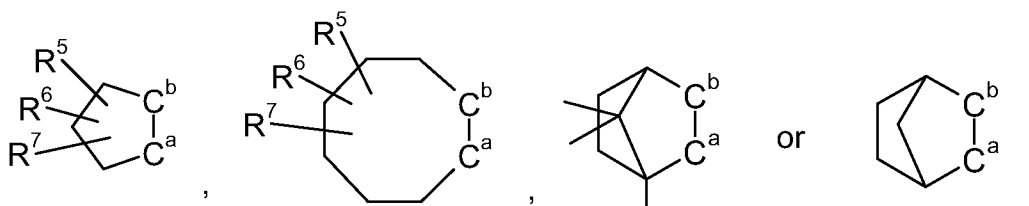
R^6 is hydrogen, alkyl, cycloalkyl or alkoxy;

15 R^7 is hydrogen, alkyl, cycloalkyl or alkoxy;

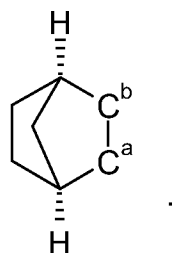
and pharmaceutically acceptable salts and esters thereof.

2. Compounds according to claim 1, wherein R^4 is 2,2-dimethyl-propyl, 3-methyl-butyl, iso-propyl, tert-butyl, cyclopropylmethyl or cyclopentylmethyl.
3. Compounds according to any one of claims 1 or 2, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form

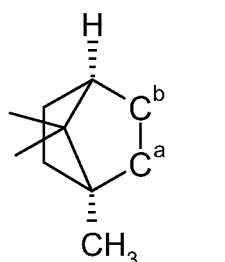
5



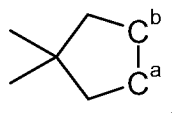
4. Compounds according to any one of claims 1 to 3, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form



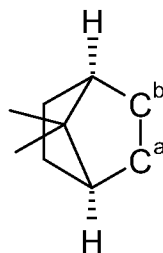
- 10 5. Compounds according to any one of claims 1 to 3, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form



6. Compounds according to any one of claims 1 to 3, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form



7. Compounds according to claims 1 to 3, wherein R^1 and R^2 together with the carbon atoms C^a and C^b to which they are attached form

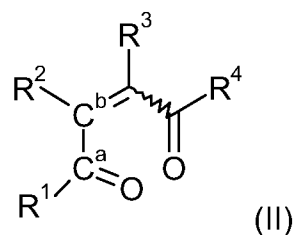


8. Compounds according to any one of claims 1 to 7, wherein R^3 is hydrogen.
- 5 9. Compounds according to any one of claims 1 to 7, wherein R^3 is methyl.
10. Compounds according to any one of claims 1 to 9, wherein R^4 is 2,2-dimethyl-propyl or tert-butyl.
11. Compounds according to any one of claims 1 to 9, wherein R^4 is 3-methyl-butyl.
12. Compounds according to any one of claims 1 to 11, wherein R^5 , R^6 and R^7 are independently selected from hydrogen and methyl.
- 10 13. Compounds according to any one of claims 1 to 12, wherein R^5 , R^6 and R^7 are hydrogen.
14. Compounds according to any one of claims 1 to 13 selected from
- 3-(2,2-Dimethyl-propyl)-5,6,7,8,9,10-hexahydro-cycloocta[c]pyridazine;
- 15 (1SR,8RS)-5-(2,2-Dimethyl-propyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1S,8R)-5-(2,2-Dimethyl-propyl)-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1S,8R)-5-tert-Butyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 20 3-(2,2-Dimethyl-propyl)-6,6-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridazine;
- (1SR,8RS)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;

- 3-tert-Butyl-6,6-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridazine;
 (1SR,8RS)-5-(3-Methyl-butyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene;
 (1SR,8RS)-5-tert-Butyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
 (1S,8R)-1,11,11-Trimethyl-5-(3-methyl-butyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-
 5 2,4,6-triene;
 (1S,8R)-5-Isopropyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-
 triene;
 (1SR,8RS)-5-Cyclopropylmethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene;
 (1S,8R)-5-Cyclopropylmethyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-
 10 2(7),3,5-triene;
 3-Cyclopropylmethyl-6,6-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridazine; and
 (1S,8R)-5-Cyclopentylmethyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-
 2,4,6-triene.
15. Compounds according to any one of claims 1 to 14 selected from
 15 (1SR,8RS)-5-(2,2-Dimethyl-propyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
 (1S,8R)-5-(2,2-Dimethyl-propyl)-1,11,11-trimethyl-3,4-diaza-
 tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
 (1S,8R)-5-tert-Butyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-
 triene;
 20 (1SR,8RS)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-
 2,4,6-triene;
 3-tert-Butyl-6,6-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridazine; and
 (1S,8R)-1,11,11-Trimethyl-5-(3-methyl-butyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-
 2,4,6-triene.
- 25
16. Compounds according to any one of claims 1 to 13 selected from
 (1S,8R)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-
 2,4,6-triene;

- (1S,8R)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1S,8R)-5-(3,3-Dimethyl-butyl)-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 5 (1SR,8RS)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1S,8R)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 10 (1R,8S)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1SR,8RS)-5-(2,2-Dimethyl-propyl)-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1SR,8RS)-5-(2,2-Dimethyl-propyl)-6,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 15 (1SR,8RS)-5-(1-Cyclopropyl-1-methyl-ethyl)-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1SR,8RS)-5-Cyclopentylmethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1R,8S)-5-(2,2-Dimethyl-propyl)-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene;
- 20 (1S,8R)-5-(2,2-Dimethyl-propyl)-8,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene;
- (1R,8S)-5-tert-Butyl-1,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene; and
- (1S,8R)-5-tert-Butyl-8,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene.
- 25
17. Compounds according to any one of claims 1 to 13 and 16 selected from

- (1S,8R)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 5 (1S,8R)-5-(2,2-Dimethyl-propyl)-6-methyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1S,8R)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1R,8S)-5-tert-Butyl-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- 10 (1SR,8RS)-5-(2,2-Dimethyl-propyl)-11,11-dimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene;
- (1S,8R)-5-(2,2-Dimethyl-propyl)-8,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene; and
- 15 (1S,8R)-5-tert-Butyl-8,11,11-trimethyl-3,4-diaza-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene.
18. A process for the preparation of a compound according to any one of claims 1 to 17 comprising the reaction of a compound according to formula



with hydrazine; wherein R¹ to R⁴ are defined as in claim 1.

- 20 19. Compounds according to any one of claims 1 to 17 for use as therapeutically active substance.
20. Compounds according to any one of claims 1 to 17 for the preparation of medicaments for the prophylaxis and therapy of illnesses which are caused by disorders associated with the enzyme 11beta-hydroxysteroid dehydrogenase 1.

21. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 17 and a therapeutically inert carrier.
22. The use of a compound according to any one of claims 1 to 17 for the preparation of medicaments for the treatment and prophylaxis of diabetes, obesity, eating disorders,
5 dyslipidemiae and hypertension.
23. The use of a compound according to any one of claims 1 to 17 for the preparation of medicaments for the treatment and prophylaxis of diabetes Type II.
24. A compound according to any one of claims 1 to 17, when manufactured according to a process of claim 18.
- 10 25. A method for the treatment and prophylaxis of diabetes, obesity, eating disorders, dyslipidemiae and hypertension, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 17.
26. A method for the treatment and prophylaxis of diabetes Type II, which method comprises administering an effective amount of a compound as defined in any one of
15 claims 1 to 17.
27. The invention as hereinbefore described.
