cardiovascular diseases or depression (Von Geldern et al, *J. Med. Chem.* 2004, Vol 47 (17), pp 4213-4230; Hu et al, *Drug Develop. Res.* 2006, Vol. 67, pp 871-883; Andrews, *Handbook of the stress and the brain* 2005, Vol. 15, pp 437-450). This approach might also improve peripheral insulin sensitivity (Zinker et al, *Meta. Clin. Exp.* 2007, Vol. 57, pp 380-387) and protect pancreatic beta cells (Delauney et al, *J. Clin. Invest.* 1997, Vol. (100, pp 2094-2098).

Diabetic patients have an increased level of fasting blood glucose which has been correlated in clinic with an impaired control of gluconeogenesis (DeFronzo, *Med. Clin. N. Am.* 2004, Vol. 88 pp 787-835). The hepatic gluconeogenesis process is under the control of glucocorticoids. Clinical administration of a non-specific GR antagonist (RU486 / mifepristone) leads acutely to a decrease of fasting plasma glucose in normal volunteers (Garrel et al, *J. Clin. Endocrinol. Metab.* 1995, Vol. 80 (2), pp 379-385) and chronically to a decrease of plasmatic HbA1c in Cushing's patients (Nieman et al, *J. Clin. Endocrinol. Metab.* 1985, Vol. 61 (3), pp 536-540). Moreover, this drug given to leptin deficient animals normalizes fasting plasma glucose (ob/ob mice, Gettys et al, *Int. J. Obes.* 1997, Vol. 21, pp 865-873) as well as the activity of gluconeogenic enzymes (db/db mice, Friedman et al, *J. Biol. Chem.* 1997, Vol. 272 (50) pp 31475-31481). Liver-specific knockout mice have been produced and these animals display a moderate hypoglycemia when they are fasted for 48h excluding the risk of severe hypoglycemia (Opherk et al, *Mol. Endocrinol.* 2004, Vol. 18 (6), pp 1346-1353).

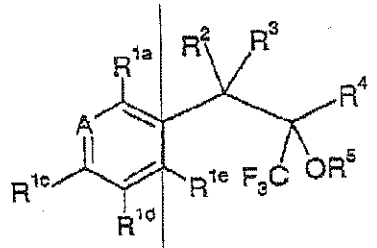
Mifepristone is also known to stimulate the Hypothalamus-Pituitary gland- Adrenal gland (HPA) axis via the activation of a feed-back mechanism which leads to an increase of endogenous corticosteroids circulating in the blood (Gaillard et al, *Pro. Natl. Acad. Sci.* 1984, Vol. 81, pp 3879-3882). Mifepristone also induces some adrenal insufficiency symptoms after long term treatment (up to 1 year, for review see: Sitruk-Ware et al, 2003, *Contraception*, Vol. 68, pp 409-420).

For GR modulators to be used in indications such as diabetes, dyslipidemia, obesity, hypertension and cardiovascular diseases it is necessary to limit the risk to activate or inhibit the HPA axis. Several strategies can be used to achieve this goal like to have a drug with a moderate to high liver selectivity or to get a drug which would not penetrate brain. Liver selectivity can be obtained by introducing liver targeting vectors in the molecule or by limiting the volume of distribution of the substance in the body. On the opposite for GR modulators to be used in indications such as adrenal/HPA imbalance, insomnia or depression it will be necessary to obtain a drug with a moderate to high brain selectivity.

It is therefore an object of the ~~present invention~~embodiments disclosed herein to provide potent and highly selective modulators of the glucocorticoid receptor (GR), preferably GR antagonists, with various tissue selectivities. Such GR modulators are useful as therapeutically active substances, particularly in

the treatment and/or prevention of diseases which are associated with modulation of the glucocorticoid receptors.

In a first aspect, there is provided compounds of the general formula



I

wherein

A is C-R^{1b} or N;

R^{1a}, R^{1b} and R^{1c} independently from each other are selected from the group consisting of

hydrogen, C_{1-7}-alkyl, C_{2-7}-alkenyl, C_{3-7}-cycloalkyl-C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, halogen-C_{1-7}-alkoxy, halogen-C_{1-7}-alkyl-sulfonyloxy, hydroxy, hydroxy-C_{1-7}-alkyl, C_{1-7}-alkoxy, C_{1-7}-alkoxy-C_{1-7}-alkoxy, hydroxy-C_{1-7}-alkoxy, amino-C_{1-7}-alkoxy, cyano, carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkoxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy, C_{1-7}-alkoxycarbonylamino-C_{1-7}-alkoxy, C_{1-7}-alkylcarbonyloxy-C_{1-7}-alkoxy, aminocarbonyl-C_{1-7}-alkoxy, di-C_{1-7}-alkylamino, di-C_{2-7}-alkenylamino, C_{1-7}-alkylsulfonyl-amino, carboxyl-C_{1-7}-alkylaminocarbonyl,

phenyl, said phenyl being substituted by a group selected from carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkoxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy and aminocarbonyl, and, in addition, optionally substituted by one or two substituents selected from the group consisting of C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy and halogen-C_{1-7}-alkoxy;

phenyloxy, wherein the phenyl ring is unsubstituted or substituted by one, two or three substituents selected from the group consisting of C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy, halogen-C_{1-7}-alkoxy; carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkoxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy and aminocarbonyl,

heteroaryl selected from the group consisting of pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl, said heteroaryl being unsubstituted or substituted by one, two or three substituents selected from the group consisting of C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy, halogen-C_{1-7}-alkoxy, carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-

alkoxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy and aminocarbonyl;

heteroaryloxy, wherein heteroaryl is selected from the group consisting of pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl, and is unsubstituted or substituted by one, two or three substituents selected from the group consisting of C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy, halogen-C_{1-7}-alkoxy; carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkoxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy and aminocarbonyl,

phenyl-C_{1-7}-alkoxy, wherein the phenyl ring is unsubstituted or substituted by one, two or three substituents selected from the group consisting of C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkyl, hydroxy, cyano, C_{1-7}-alkylsulfonyl, C_{1-7}-alkoxy, halogen-C_{1-7}-alkoxy; carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkoxy, C_{1-7}-alkoxy-carbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl and C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy; and

heterocyclyl or heterocyclylcarbonyl, wherein heterocyclyl is selected from the group consisting of pyrrolidine, piperidine and azepine and is substituted by carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkoxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl and C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy;

R^2 is selected from the group consisting of C_{1-7}-alkyl, C_{3-7}-cycloalkyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl, triazolyl-C_{1-7}-alkyl and phenyl, said phenyl being unsubstituted or substituted by one, two or three halogen groups;

R^3 is hydrogen or C_{1-7}-alkyl;

or R^2 and R^3 together with the carbon atom they are attached to form a C_3-C_5-cycloalkyl ring;

R^4 is a heteroaryl ring selected from the group consisting of
3-oxo-3,4-dihydro-2H-benzo[1,4]oxazinyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl,
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazinyl, 4-oxo-4H-quinolizinyl,
2-oxo-2,3-dihydro-1H-benzoimidazoyl, 2-oxo-2,3-dihydro-benzooxazolyl,
benzo[1,3]dioxolyl, 2-oxo-1,2-dihydro-quinolinyl and
1,3-dimethyl-2,2-dioxo-2,3-dihydro-1H-2λ6-benzo[1,2,5]thiadiazolyl,
said heteroaryl ring being unsubstituted or substituted by one, two or three substituents selected from the group consisting of C_{1-7}-alkyl, C_{2-7}-alkenyl and halogen, or

R^4 is phenyl substituted by cyano and, in addition, optionally substituted by one or two substituents selected from the group consisting of halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkyl, C_{1-7}-alkoxy and halogen-C_{1-7}-alkoxy; and

R^5 is hydrogen or methyl;

wherein one of R^{1c} and R^{1d} is selected from the group consisting of

phenyl, said phenyl being substituted by a group selected from carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkoxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy and aminocarbonyl, and, in addition, optionally substituted by one or two substituents selected from the group consisting of C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy and halogen-C_{1-7}-alkoxy;

phenyloxy, wherein the phenyl ring is unsubstituted or substituted by one, two or three substituents selected from the group consisting of C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy, halogen-C_{1-7}-alkoxy; carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkoxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy and aminocarbonyl,

heteroaryl selected from the group consisting of pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl, said heteroaryl being unsubstituted or substituted by one, two or three substituents selected from the group consisting of C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy, halogen-C_{1-7}-alkoxy, carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkoxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy and aminocarbonyl;

heteroaryloxy, wherein heteroaryl is selected from the group consisting of pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl, and is unsubstituted or substituted by one, two or three substituents selected from the group consisting of C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy, halogen-C_{1-7}-alkoxy; carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkoxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy and aminocarbonyl,

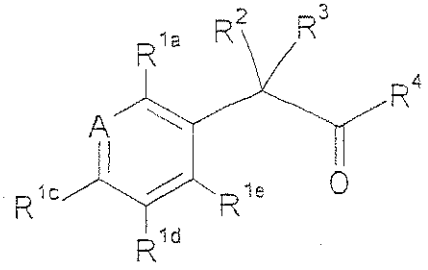
phenyl-C_{1-7}-alkoxy, wherein the phenyl ring is unsubstituted or substituted by one, two or three substituents selected from the group consisting of C_{1-7}-alkyl, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkyl, hydroxy, cyano, C_{1-7}-alkylsulfonyl, C_{1-7}-alkoxy and halogen-C_{1-7}-alkoxy; carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkoxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl and C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy; and

heterocyclyl or heterocyclylcarbonyl, wherein heterocyclyl is selected from the group consisting of pyrrolidine, piperidine and azepine and is substituted by carboxyl, carboxyl-C_{1-7}-alkyl, carboxyl-C_{1-7}-alkoxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkoxycarbonyl-C_{1-7}-alkyl and C_{1-7}-alkoxycarbonyl-C_{1-7}-alkoxy;

or pharmaceutically acceptable salts thereof.

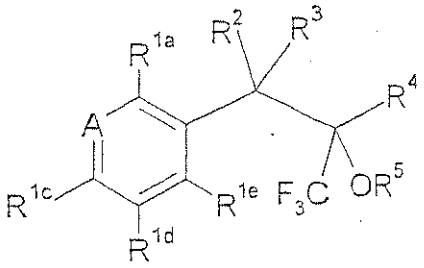
In a second aspect, there is provided a process for the manufacture of a compound of formula I as defined above, which process comprises

treating a compound of the formula II



II

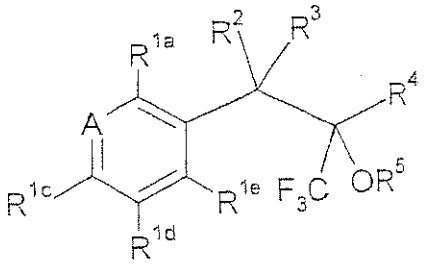
wherein A, R^{1a} to R^{1e}, R^2, R^3 and R^4 are as defined above, with trifluoromethyltrimethylsilane and a suitable fluoride, to obtain a compound of the formula Ia



Ia

,

wherein R^5 is hydrogen, and, if desired, alkylating the compound of formula Ia with methyliodide in the presence of a base such as NaH to obtain a compound of formula Ib



Ib

,

wherein R^5 is methyl, and, if desired, converting the compound obtained into a pharmaceutically acceptable salt.

In a third aspect, there is provided pharmaceutical compositions comprising a compound as defined above as well as a pharmaceutically acceptable carrier and/or adjuvant.

In a fourth aspect, there is provided compounds as defined above for use as therapeutically active substances.

In a fifth aspect, there is provided compounds as defined above for use as therapeutically active substances for the treatment and/or prevention of diseases which are associated with glucocorticoid receptor modulation, wherein such disease is selected from the group consisting of diabetes and other disorders such, as dyslipidemia, obesity, hypertension, cardiovascular diseases, adrenal imbalance and depression.

In a sixth aspect, there is provided compounds as defined above for use as therapeutically active substances in combination with another antidiabetic drug.

In a seventh aspect, there is provided the use of compounds as defined above for the preparation of medicaments for the treatment and/or prevention of diseases which are associated with glucocorticoid receptor modulation, wherein such disease is selected form the group consisting of diabetes and other disorders such as dyslipidemia, obesity, hypertension, cardiovascular diseases, adrenal imbalance and depression.

In the present description the term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms.

The term "lower alkyl" or "C_{1-7}-alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 7 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 C_{1-7} alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls and the isomeric heptyls, preferably methyl and ethyl and most preferred methyl.

The term "lower alkenyl" or "C_{2-7}-alkenyl" signifies a straight-chain or branched chain hydrocarbon residue comprising an olefinic bond and 1 to 7, preferably 1 to 6, particularly preferred 1 to 4 carbon atoms. Examples of alkenyl groups are ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl and isobutenyl. A preferred example is 2-propenyl.

The term "cycloalkyl" or "C_{3-7}-cycloalkyl" denotes a saturated carbocyclic group containing from 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Especially preferred are cyclobutyl and cyclopentyl.

The term "lower cycloalkylalkyl" or "C_{3-7}-cycloalkyl-C_{1-7}-alkyl" refers to lower alkyl groups as defined above wherein at least one of the hydrogen atoms of the lower alkyl group is replaced by cycloalkyl. A preferred example is cyclopropylmethyl.

The term "lower alkoxy" or "C_{1-7}-alkoxy" refers to the group R'-O-, wherein R' is lower alkyl and the term "lower alkyl" has the previously given significance. Examples of lower alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.-butoxy and tert.-butoxy, preferably methoxy and ethoxy and most preferred ethoxy.

The term "lower alkoxyalkoxy" or "C_{1-7}-alkoxy -C_{1-7}-alkoxy" refers to lower alkoxy groups as defined above wherein at least one of the hydrogen atoms of the lower alkoxy group is replaced by another alkoxy group. Also included are groups wherein the second alkoxy group is substituted by a further alkoxy group. Among the preferred lower alkoxyalkoxy groups are 1-methoxymethoxy, 2-methoxyethoxy, 3-methoxypropyloxy and 2-(2-methoxyethoxy)-ethoxy.

The term "lower hydroxyalkyl" or "hydroxy-C_{1-7}-alkyl" refers to lower alkyl groups as defined above wherein at least one of the hydrogen atoms of the lower alkyl group is replaced by