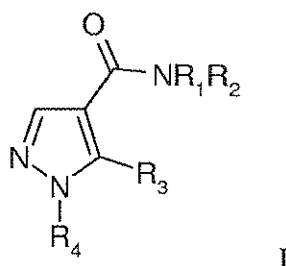


1H-PYRAZOLE 4-CARBOXYLAMIDES, THEIR PREPARATION AND THEIR USE AS 11BETA-HYDROXYSTEROID DEHYDROGENASE

The invention relates to inhibitors of 11 β -hydroxysteroid dehydrogenase. The inhibitors include, for example, pyrazoles and derivatives thereof and are useful for the treatment of diseases such as type II diabetes mellitus and metabolic syndrome. The compounds according to the present invention can be characterized by formula I:

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wherein:

10 one of R₁ or R₂ is hydrogen or alkyl and the other is lower alkyl or (CH₂)_pY, wherein Y is a substituted or unsubstituted, saturated, partially unsaturated, or unsaturated mono-, bi- or tri-cyclic 5-10 membered cycloalkyl ring and p is 0 or 1, and wherein substituents on Y are lower alkyl, lower alkoxy, hydroxy, hydroxy-alkyl, alkyl-phenyl, phenyl-alkyl, pyridine or halogen,

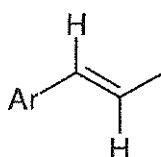
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or R₁ and R₂, together with the N atom to which they are attached, form a substituted or unsubstituted ring Z, wherein Z is a 5- to 7-membered monocyclic or 7- to 10-membered bicyclic saturated, partially unsaturated or unsaturated substituted or unsubstituted heterocyclic ring which contains the N atom to which R₁ and R₂ are attached, and optionally another hetero atom which is selected from N, O and S, wherein the substituted heterocyclic ring is mono- or di- substituted with lower alkyl, hydroxy, hydroxy-alkyl, alkyl-phenyl, phenyl-alkyl, pyridine or halogen;

20

R₃ is an aromatic ring system selected from the group consisting of [2,2']bithiophenyl, 1-methyl-indole, 2,3-dihydro-benzo[1,4]dioxin, benzo[1,3]dioxole, benzo[b]thiophene, benzothienophene, dibenzofuran, furane, naphthalene, phenyl, biphenyl, quinoline, thianthrene and thiophene, wherein said aromatic ring may be unsubstituted or substituted with one or
5 more amino, cyano, formyl, halo, hydroxy, hydroxymethyl, lower-acyl, lower-acyl-amino, lower-alkoxy, lower-alkoxy-carbonyl, 2-(lower-alkoxy-carbonyl)-ethenyl, lower-alkyl, lower-alkyl-thio, nitro, trifluoromethoxy or trifluoromethyl, wherein said phenyl ring may additionally be substituted with phenoxy or benzyloxy,

10 or R₃ is:



wherein Ar is a carbocyclic or heterocyclic aryl group which may be unsubstituted or substituted with one or more groups selected from the group consisting of halogen, lower alkyl,
15 lower alkoxy, trifluoromethyl, cyano and nitro; and

R₄ is lower alkyl;

and pharmaceutically acceptable salts thereof.

20

All documents cited or relied upon below are expressly incorporated herein by reference. Diabetes mellitus is a serious illness that affects an increasing number of people across the world. Its incidence is increasing along with the increasing trend to obesity in many countries. The serious consequences of the disease include increased risk of stroke, heart disease, kidney damage, blindness, and amputation. Diabetes is characterized by decreased
25 insulin secretion and/or an impaired ability of peripheral tissues to respond to insulin, resulting in increased plasma glucose levels. There are two forms of diabetes: insulin-dependent and non-insulin-dependent, with the great majority of diabetics suffering from the non-insulin-dependent form of the disease, known as type 2 diabetes or non-insulin-dependent diabetes mellitus (NIDDM). Because of the serious consequences, there is an
30 urgent need to control diabetes.

Treatment of NIDDM generally starts with weight loss, a healthy diet and an exercise program. These factors are especially important in addressing the increased cardiovascular risks associated with diabetes, but they are generally ineffective in controlling the disease itself. There are a number of drug treatments available, including insulin, metformin, sulfonylureas, acarbose, and thiazolidinediones. However, each of these treatments has disadvantages, and there is an ongoing need for new drugs to treat diabetes.

Metformin is an effective agent that reduces fasting plasma glucose levels and enhances the insulin sensitivity of peripheral tissue. Metformin has a number of effects *in vivo*, including an increase in the synthesis of glycogen, the polymeric form in which glucose is stored [R. A. De Fronzo *Drugs* **1999**, 58 Suppl. 1, 29]. Metformin also has beneficial effects on lipid profile, with favorable results on cardiovascular health—treatment with metformin leads to reductions in the levels of LDL cholesterol and triglycerides [S. E. Inzucchi *JAMA* **2002**, 287, 360]. However, over a period of years, metformin loses its effectiveness [R. C. Turner et al. *JAMA* **1999**, 281, 2005] and there is consequently a need for new treatments for diabetes.

Thiazolidinediones are activators of the nuclear receptor peroxisome-proliferator activated receptor-gamma. They are effective in reducing blood glucose levels, and their efficacy has been attributed primarily to decreasing insulin resistance in skeletal muscle [M. Tadayyon and S. A. Smith *Expert Opin. Investig. Drugs* **2003**, 12, 307]. One disadvantage associated with the use of thiazolidinediones is weight gain.

Sulfonylureas bind to the sulfonylurea receptor on pancreatic beta cells, stimulate insulin secretion, and consequently reduce blood glucose levels. Weight gain is also associated with the use of sulfonylureas [S. E. Inzucchi *JAMA* **2002**, 287, 360] and, like metformin, efficacy decreases over time [R. C. Turner et al. *JAMA* **1999**, 281, 2005]. A further problem often encountered in patients treated with sulfonylureas is hypoglycemia [M. Salas and J. J. Caro *Adv. Drug React. Tox. Rev.* **2002**, 21, 205-217].

Acarbose is an inhibitor of the enzyme alpha-glucosidase, which breaks down disaccharides and complex carbohydrates in the intestine. It has lower efficacy than metformin or the sulfonylureas, and it causes intestinal discomfort and diarrhea which often lead to the discontinuation of its use [S. E. Inzucchi *JAMA* **2002**, 287, 360]

The metabolic syndrome is a condition where patients exhibit more than two of the following symptoms: obesity, hypertriglyceridemia, low levels of HDL-cholesterol, high blood pressure, and elevated fasting glucose levels. This syndrome is often a precursor of type 2 diabetes, and has high prevalence in the United States with an estimated prevalence of 24% (E. S. Ford et al. *JAMA* **2002**, 287, 356). A therapeutic agent that ameliorates the metabolic syndrome would be useful in potentially slowing or stopping the progression to type 2 diabetes.

10 In the liver, glucose is produced by two different processes: gluconeogenesis, where new glucose is generated in a series of enzymatic reactions from pyruvate, and glycolysis, where glucose is generated by the breakdown of the polymer glycogen.

Two of the key enzymes in the process of gluconeogenesis are phosphoenolpyruvate carboxykinase (PEPCK) which catalyzes the conversion of oxalacetate to phosphoenolpyruvate, and glucose-6-phosphatase (G6Pase) which catalyzes the hydrolysis of glucose-6-phosphate to give free glucose. The conversion of oxalacetate to phosphoenolpyruvate, catalyzed by PEPCK, is the rate-limiting step in gluconeogenesis. On fasting, both PEPCK and G6Pase are upregulated, allowing the rate of gluconeogenesis to increase. The levels of these enzymes are controlled in part by the corticosteroid hormones (cortisol in human and corticosterone in mouse). When the corticosteroid binds to the corticosteroid receptor, a signaling cascade is triggered which results in the upregulation of these enzymes.

The corticosteroid hormones are found in the body along with their oxidized 11-dehydro counterparts (cortisone and 11-dehydrocorticosterone in human and mouse, respectively), which do not have activity at the glucocorticoid receptor. The actions of the hormone depend on the local concentration in the tissue where the corticosteroid receptors are expressed. This local concentration can differ from the circulating levels of the hormone in plasma, because of the actions of redox enzymes in the tissues. The enzymes that modify the oxidation state of the hormones are 11beta-hydroxysteroid dehydrogenases forms I and II. Form I (11 β -HSD1) is responsible for the reduction of cortisone to cortisol *in vivo*, while form II (11 β -HSD2) is responsible for the oxidation of cortisol to cortisone. The enzymes have low homology and are expressed in different tissues. 11 β -HSD1 is highly expressed in a number of tissues including liver, adipose tissue, and brain, while 11 β -HSD2

is highly expressed in mineralocorticoid target tissues, such as kidney and colon. 11 β -HSD2 prevents the binding of cortisol to the mineralocorticoid receptor, and defects in this enzyme have been found to be associated with the syndrome of apparent mineralocorticoid excess (AME).

5

Since the binding of the 11 β -hydroxysteroids to the corticosteroid receptor leads to upregulation of PEPCK and therefore to increased blood glucose levels, inhibition of 11 β -HSD1 is a promising approach for the treatment of diabetes. In addition to the biochemical discussion above, there is evidence from transgenic mice, and also from small clinical studies in humans, that confirm the therapeutic potential of the inhibition of 11 β -HSD1.

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Experiments with transgenic mice indicate that modulation of the activity of 11 β -HSD1 could have beneficial therapeutic effects in diabetes and in the metabolic syndrome. For example, when the 11 β -HSD1 gene is knocked out in mice, fasting does not lead to the normal increase in levels of G6Pase and PEPCK, and the animals are not susceptible to stress- or obesity-related hyperglycemia. Moreover, knockout animals which are rendered obese on a high-fat diet have significantly lower fasting glucose levels than weight-matched controls (Y. Kotolevtsev et al. *Proc. Natl. Acad. Sci. USA* **1997**, 94, 14924). 11 β -HSD1 knockout mice have also been found to have improved lipid profile, insulin sensitivity, and glucose tolerance (N. M. Morton et al. *J. Biol. Chem.* **2001**, 276, 41293). The effect of overexpressing the 11 β -HSD1 gene in mice has also been studied. These transgenic mice displayed increased 11 β -HSD1 activity in adipose tissue and exhibited visceral obesity which is associated with the metabolic syndrome. Levels of the corticosterone were increased in adipose tissue, but not in serum, and the mice had increased levels of obesity, especially when on a high-fat diet. Mice fed on low-fat diets were hyperglycemic and hyperinsulinemic, and also showed glucose intolerance and insulin resistance (H. Masuzaki et al. *Science*, **2001**, 294, 2166).

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The effects of the non-selective 11 β -hydroxysteroid dehydrogenase inhibitor carbenoxolone have been studied in a number of small trials in humans. In one study, carbenoxolone was found to lead to an increase in whole body insulin sensitivity, and this increase was attributed to a decrease in hepatic glucose production (B. R. Walker et al. *J. Clin. Endocrinol. Metab.* **1995**, 80, 3155). In another study, decreased glucose production and glycogenolysis in response to glucagon challenge were observed in diabetic but not

healthy subjects (R. C. Andrews et al. *J. Clin. Endocrinol. Metab.* **2003**, 88, 285). Finally, carbenoxolone was found to improve cognitive function in healthy elderly men and also in type 2 diabetics (T. C. Sandeep et al. *Proc. Natl. Acad. Sci USA* **2004**, 101, 6734).

5 A number of non-specific inhibitors of 11 β -HSD1 and 11 β -HSD2 have been identified, including glycyrrhetic acid, abietic acid, and carbenoxolone. In addition, a number of selective inhibitors of 11 β -HSD1 have been found, including chenodeoxycholic acid, flavanone and 2'-hydroxyflavanone (S. Diederich et al. *Eur. J. Endocrinol.* **2000**, 142, 200 and R. A. S. Schweizer et al. *Mol. Cell. Endocrinol.* **2003**, 212, 41).

10

WO 2004089470, WO 2004089416 and WO 2004089415 (Novo Nordisk A/S); and WO 0190090, WO 0190091, WO 0190092, WO 0190093, WO 03043999, WO 0190094, WO 03044000, WO 03044009, and WO 2004103980 (Biovitrum AB) disclose compounds as inhibitors of 11 β -HSD1. These compounds are different in structure from the compounds
15 of the current invention. WO 2004112781 and WO 2004112782 disclose the method of use of some of these compounds for the promotion of wound healing.

WO 03065983, WO 03075660, WO 03104208, WO 03104207, US20040133011, WO 2004058741, WO2005016877 and WO 2004106294 (Merck & Co., Inc.) disclose com-
20 pounds as inhibitors of 11 β -HSD1. These compounds are different in structure from the compounds of the current invention.

US2004122033 discloses the combination of an appetite suppressant with inhibitors of 11 β -HSD1 for the treatment of obesity, and obesity-related disorders.

25

WO 2004065351 (Novartis) discloses compounds as inhibitors of 11 β -HSD1. These compounds are different in structure from the compounds of the current invention.

WO 2004089415 (Novo Nordisk A/S) discloses the use of an inhibitor of 11 β -HSD1 in
30 combination with an agonist of the glucocorticoid receptor for the treatment of diseases including cancer and diseases involving inflammation. Several different classes of 11 β -HSD1 inhibitors are disclosed including amino-ketones, benzimidazoles, carboxamides, 2,3-dihydrobenzofuran-7-carboxamides, indoles, methylenedioxyphenyl-carboxamides,

oxazole-4-carboxamides, oxazole-5-carboxamides pyrazolo[1,5-a]pyrimidines, pyrazole-4-carboxamides, thiazole-4-carboxamides, thiazole-5-carboxamides, and 1,2,4-triazoles.

5 WO 2004089416 (Novo Nordisk A/S) discloses the use of an inhibitor of 11 β -HSD1 in combination with an antihypertensive agent for the treatment of diseases including insulin resistance, dyslipidemia and obesity. WO 2004089470 (Novo Nordisk A/S) discloses substituted amides as inhibitors of 11 β -HSD1.

10 WO 2004089471 (Novo Nordisk A/S) discloses pyrazolo[1,5-a]pyrimidines as inhibitors of 11 β -HSD1. WO 2004089896 (Novo Nordisk A/S) discloses compounds as inhibitors of 11 β -HSD1. These compounds are different in structure from the compounds of the current invention.

15 WO 2004011410, WO 2004033427, and WO 2004041264 (AstraZeneca UK Limited) disclose compounds as inhibitors of 11 β -HSD1. These compounds are different in structure from the compounds of the current invention.

20 WO 02076435A2 (The University of Edinburgh) claims the use of an agent which lowers levels of 11 β -HSD1 in the manufacture of a composition for the promotion of an atheroprotective lipid profile. Agents mentioned as inhibitors of 11 β -HSD1 include carbenoxolone, 11-oxoprogesterone, 3 α ,17,21-trihydroxy-5 β -pregnan-3-one, 21-hydroxy-pregn-4-ene-3,11,20-trione, androst-4-ene-3,11,20-trione and 3 β -hydroxyandrost-5-en-17-one. None of these compounds is similar in structure to the compounds of the current invention.

25 WO 03059267 (Rhode Island Hospital) claims a method for treating a glucocorticoid-associated state by the administration of a 11 β -HSD1 inhibitor such as 11-ketotestosterone, 11-keto-androsterone, 11-keto-pregnenolone, 11-keto-dehydro-epiandrostenedione, 3 α ,5 α -reduced-11-ketoprogesterone, 3 α ,5 α -reduced-11-ketotestosterone, 3 α ,5 α -reduced-11-keto-androstenedione, or 3 α ,5 α -tetrahydro-11 β -dehydro-corticosterone. None of these compounds is similar in structure to the compounds of the current invention.

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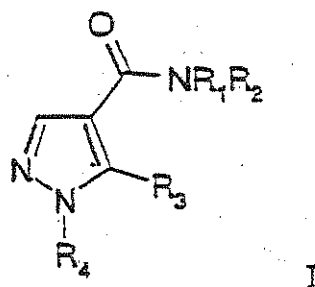
WO 2001070671 (E. I. Du Pont de Nemours & Co.) discloses compounds as insecticides. These compounds are different in structure from the compounds of the current invention.

EP 360701 (Rhone-Poulenc Agrochimie) discloses compounds as agrochemical fungicides. These compounds are different in structure from the compounds of the current invention.

DE 3713774 (Mitsui Toatsu Chemicals, Inc.) discloses compounds as an agrochemical fungicide. These compounds are different in structure from the compounds of the current invention.

A need exists in the art, however, for 11β -HSD1 inhibitors that have efficacy for the treatment of diseases such as type II diabetes mellitus and metabolic syndrome. Further, a need exists in the art for 11β -HSD1 inhibitors having IC50 values less than about 1 μ M.

In a first aspect, there is provided a compound of the formula I:



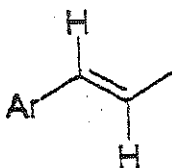
wherein:

one of R₁ or R₂ is hydrogen or unsubstituted alkyl and the other is unsubstituted lower alkyl or (CH₂)_pY, wherein Y is a substituted or unsubstituted, saturated, partially unsaturated, or unsaturated mono-, bi- or tri-cyclic 5-10 membered cycloalkyl ring and p is 0 or 1, and wherein substituents on Y are lower alkyl, lower alkoxy, hydroxy, hydroxy-alkyl, alkyl-phenyl, phenyl-alkyl, pyridine or halogen,

or R₁ and R₂, together with the N atom to which they are attached, form a substitute or unsubstituted ring Z, wherein Z is selected from the group consisting of 2-ethyl-piperidine, 3-phenyl-pyrrolidine, 3-(pyridin-3-yl)-pyrrolidine, 4-chloro-decahydro-quinoline, 4a-bromo-decahydro-isoquinoline, 6-bromo-octahydro-isoquinoline, 3-cyclohexyl-piperidine, 3-benzyl-piperidine, decahydro-quinoline and decahydro-isoquinoline;

R₃ is an aromatic ring system selected from the group consisting of [2,2]bithiophenyl, 1-methyl-indole, 2,3-dihydro-benzo[1,4]dioxin, benzo[1,3]dioxole, benzothiophene, dibenzofuran, furane, naphthalene, phenyl, biphenyl, quinoline, thianthrene and thiophene, wherein said aromatic ring may be unsubstituted or substituted with one or more amino, cyano, formyl, halo, hydroxy, hydroxymethyl, lower-acyl, lower-acyl-amino, lower-alkoxy, lower-alkoxy-carbonyl, 2-(lower-alkoxy-carbonyl)-ethenyl, lower-alkyl, lower-alkyl-thio, nitro, trifluoromethoxy or trifluoromethyl, wherein said phenyl ring may additionally be substituted with phenoxy or benzyloxy,

or R₃ is:

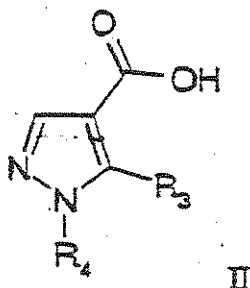


wherein Ar is a carbocyclic or heterocyclic aryl group which may be unsubstituted or substituted with one or more groups selected from the group consisting of halogen, lower alkyl, lower-alkoxy, trifluoromethyl, cyano and nitro; and

R₄ is unsubstituted lower alkyl;

and pharmaceutically acceptable salts thereof.

In a second aspect, there is provided a process for the preparation of a compound as defined above, which process comprises reacting a compound of formula II



5 with a compound HNR¹R², wherein R¹, R², R³ and R⁴ are as defined above.

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

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

20 In a fifth aspect, there is provided compounds as defined above for use as therapeutic active substances for the treatment and/or prophylaxis of diseases which are modulated by 11 β -hydroxysteroid dehydrogenase inhibitors.

It is to be understood that the terminology employed herein is for the purpose of describing particular embodiments, and is not intended to be limiting. Further, although any methods, devices and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods, devices and materials are now described.

In this specification the term "aryl" is used to mean a mono- or polycyclic aromatic ring system, in which the rings may be carbocyclic or may contain one or more atoms selected

from O, S, and N. Examples of aryl groups are phenyl, pyridyl, benzimidazolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, cinnolyl, furyl, imidazo[4,5-c]pyridinyl, imidazolyl, indolyl, isoquinolyl, isoxazolyl, naphthyl, [1,7]naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, purinyl, pyridazinyl, pyrazolyl, pyrido[2,3-d]pyrimidinyl, pyrimidinyl, pyrimido[3,2-c]pyrimidinyl, pyrrolo[2,3-d]pyrimidinyl, pyrrolyl, quinazolyl, quinolyl, quinoxalyl, tetrazolyl, thiadiazolyl, thiazolyl, thiophenyl, triazolyl, and the like.

As used herein, the term "alkyl" means, for example, a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical which may be substituted or unsubstituted. Where cyclic, the alkyl group is preferably C₃ to C₁₂, more preferably C₅ to C₁₀, more preferably C₅ to C₇. Where acyclic, the alkyl group is preferably C₁ to C₁₀, more preferably C₁ to C₆, more preferably methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, isobutyl or tertiary-butyl) or pentyl (including n-pentyl and isopentyl), more preferably methyl. It will be appreciated therefore that the term "alkyl" as used herein includes alkyl (branched or unbranched), substituted alkyl (branched or un-

branched), alkenyl (branched or unbranched), substituted alkenyl (branched or unbranched), alkynyl (branched or unbranched), substituted alkynyl (branched or unbranched), cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, cycloalkynyl and substituted cycloalkynyl. Saturated acyclic, branched or unbranched groups are preferred alkyl groups.

As used herein, the term "lower alkyl" means, for example, a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical wherein said cyclic lower alkyl group is C₅, C₆ or C₇, and wherein said acyclic lower alkyl group is C₁, C₂, C₃ or C₄, and is preferably selected from methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, sec-butyl, isobutyl or tertiary-butyl). It will be appreciated therefore that the term "lower alkyl" as used herein includes lower alkyl (branched or unbranched), lower alkenyl (branched or unbranched), lower alkynyl (branched or unbranched), cycloloweralkyl, cycloloweralkenyl and cycloloweralkynyl. Saturated acyclic, branched or unbranched groups are preferred lower alkyl groups.

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be, for example, 1 to 3 substituents present, preferably 1 substituent. Substituents may include, for example: carbon-containing groups such as alkyl, aryl, arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl); halogen atoms and halogen-containing groups such as haloalkyl (e.g. trifluoromethyl); oxygen-containing groups such as alcohols (e.g. hydroxyl, hydroxyalkyl, aryl(hydroxyl)alkyl), ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl), aldehydes (e.g. carboxaldehyde), ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl), acids (e.g. carboxy, carboxyalkyl), acid derivatives such as esters (e.g. alkoxy-carbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl), amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, arylaminocarbonyl), carbamates (e.g. alkoxycarbonylamino, arloxy-carbonylamino, aminocarbonyloxy, mono- or di-alkylaminocarbonyloxy, arylamino-carbonyloxy) and ureas (e.g. mono- or di-alkylaminocarbonylamino or arylaminocarbonylamino); nitrogen-containing groups such as amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl), azides, nitriles (e.g. cyano, cyanoalkyl), nitro; sulfur-containing groups such as thiols, thioethers, sulfoxides and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio,

arysulfinyl, arysulfonyl, arythioalkyl, arylsulfinylalkyl, arysulfonylalkyl); and heterocyclic groups containing one or more, preferably one, heteroatom, (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidiny, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazoliny, pyrazolidinyl, tetrahydro-
5 furanyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

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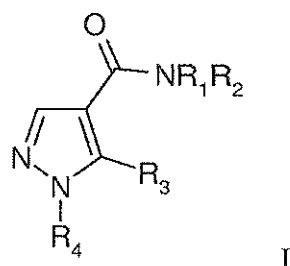
The lower alkyl groups may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be, for example, 1 to 3 substituents present, preferably 1 substituent.

15 As used herein, the term "alkoxy" means, for example, alkyl-O- and "alkoyl" means, for example, alkyl-CO-. Alkoxy substituent groups or alkoxy-containing substituent groups may be substituted by, for example, one or more alkyl groups. The term "lower alkoxy" means, for example, lower alkyl-O-.

20 As used herein, the term "halogen" means, for example, a fluorine, chlorine, bromine or iodine radical, preferably a fluorine, chlorine or bromine radical, and more preferably a fluorine or chlorine radical.

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically
25 acceptable salt of the compound of formula (I). Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric,
30 oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are fumaric, hydrochloric, hydrobromic, phosphoric, succinic, sulfuric and methanesulfonic acids. Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminum salts.

In detail, the present invention relates to a compound of the formula I:



5 wherein:

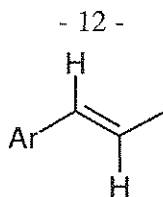
one of R_1 or R_2 is hydrogen or alkyl and the other is lower alkyl or $(CH_2)_pY$, wherein Y is a substituted or unsubstituted, saturated, partially unsaturated, or unsaturated mono-, bi- or tri-cyclic 5-10 membered cycloalkyl ring and p is 0 or 1, and wherein substituents on Y are
 10 lower alkyl, lower alkoxy, hydroxy, hydroxy-alkyl, alkyl-phenyl, phenyl-alkyl, pyridine or halogen,

or R_1 and R_2 , together with the N atom to which they are attached, form a substituted or unsubstituted ring Z, wherein Z is a 5- to 7-membered monocyclic or 7- to 10-membered
 15 bicyclic saturated, partially unsaturated or unsaturated substituted or unsubstituted heterocyclic ring which contains the N atom to which R_1 and R_2 are attached, and optionally another hetero atom which is selected from N, O and S, wherein the substituted heterocyclic ring is mono- or di- substituted with lower alkyl, hydroxy, hydroxy-alkyl, alkyl-phenyl, phenyl-alkyl, pyridine or halogen;

20

R_3 is an aromatic ring system selected from the group consisting of [2,2']bithiophenyl, 1-methyl-indole, 2,3-dihydro-benzo[1,4]dioxin, benzo[1,3]dioxole, benzothiophene, dibenzofuran, furane, naphthalene, phenyl, biphenyl, quinoline, thianthrene and thiophene, wherein said aromatic ring may be unsubstituted or substituted with one or more amino,
 25 cyano, formyl, halo, hydroxy, hydroxymethyl, lower-acyl, lower-acyl-amino, lower-alkoxy, lower-alkoxy-carbonyl, 2-(lower-alkoxy-carbonyl)-ethenyl, lower-alkyl, lower-alkyl-thio, nitro, trifluoromethoxy or trifluoromethyl, wherein said phenyl ring may additionally be substituted with phenoxy or benzyloxy,

30 or R_3 is:



wherein Ar is a carbocyclic or heterocyclic aryl group which may be unsubstituted or substituted with one or more groups selected from the group consisting of halogen, lower alkyl,
 5 lower alkoxy, trifluoromethyl, cyano and nitro; and

R₄ is lower alkyl;

and pharmaceutically acceptable salts thereof.

10

Preferred compounds of formula I as defined above are those, wherein R₁ is hydrogen and R₂ is a substituted 6-8 membered cycloalkyl ring. Saturated monocyclic cycloalkyl rings are preferred in this context. Other preferred compounds as defined above are those wherein R₂ is 1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl, 2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl, 3-noradamantyl, adamantan-1-yl, adamantan-1-yl-methyl, adamantan-2-yl, 1,2,3,4-
 15 tetrahydronaphthyl, cyclohexyl, cyclooctyl, or cycloheptyl.

Further preferred compounds as defined above are those, wherein Z is a 5-7 membered heterocyclic ring substituted with lower alkyl, hydroxy, hydroxy-alkyl, alkyl-phenyl, phenyl-alkyl, pyridine or halogen. Preferably, Z is selected from the group consisting of 2-ethyl-piperidine, 3-phenyl-pyrrolidine, 3-(pyridin-3-yl)-pyrrolidine, 4-chloro-decahydro-quinoline, 4a-bromo-decahydro-isoquinoline, 6-bromo-octahydro-isoquinoline, 3-cyclohexyl-piperidine, 3-benzyl-piperidine, decahydro-quinoline and decahydro-isoquinoline.

25

Preferably, R₃ is substituted or unsubstituted benzothiophene or phenyl. More preferably, R₃ is substituted with one or more halogen, lower-alkoxy or lower-alkyl.

Preferred compounds of formula I as defined above are those selected from the group
 30 consisting of

(3-Cyclohexyl-piperidin-1-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone,
 (1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(trans-octahydro-isoquinolin-2-yl)-methanone,

- (3-Benzyl-piperidin-1-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone,
(1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(3-phenyl-pyrrolidin-1-yl)-methanone,
(1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(3-pyridin-3-yl-pyrrolidin-1-yl)-methanone,
(1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
5 (1-Methyl-5-m-tolyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(1-Methyl-5-p-tolyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
3-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzonitrile,
4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzonitrile,
[5-(4-Isopropyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
10 [5-(3-Isopropyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[5-(4-tert-Butyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[1-Methyl-5-(1-methyl-1H-indol-5-yl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
(5-Biphenyl-4-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
15 (5-Biphenyl-3-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(1-Methyl-5-naphthalen-1-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(1-Methyl-5-quinolin-5-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(1-Methyl-5-quinolin-3-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzaldehyde,
20 3-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzaldehyde,
1-{4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-phenyl}-ethanone,
1-{3-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-phenyl}-ethanone,
[5-(3-Amino-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
N-{4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-phenyl}-acetamide,
25 (1-Methyl-5-thiophen-3-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(5-[2,2']Bithiophenyl-5-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-
methanone,
(5-Furan-3-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(5-Benzo[b]thiophen-2-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-
30 methanone,
(5-Benzo[b]thiophen-3-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-
methanone,
(1-Methyl-5-thianthren-1-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
[1-Methyl-5-(3-methylsulfanyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-

- methanone,
[1-Methyl-5-(4-methylsulfanyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[1-Methyl-5-(2-methylsulfanyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
5 methanone,
{5-[(E)-2-(4-Chloro-phenyl)-vinyl]-1-methyl-1H-pyrazol-4-yl}-(octahydro-quinolin-1-yl)-
methanone,
(4-Chloro-octahydro-quinolin-1-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone,
[5-(4-Chloro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
10 [5-(3-Chloro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[5-(3-Chloro-4-fluoro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[5-(5-Chloro-2,4-difluoro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
15 [5-(2-Fluoro-biphenyl-4-yl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[5-(3-Amino-4-chloro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[5-(2-Chloro-4-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
20 methanone,
[5-(5-Chloro-2-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[5-(3-Chloro-4-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
25 [5-(3-Chloro-2-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[5-(4-Chloro-3-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[5-(4-Chloro-2-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
30 methanone,
[1-Methyl-5-(3-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[1-Methyl-5-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,

- [5-(2-Fluoro-5-trifluoromethyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[5-(3-Chloro-4-trifluoromethyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 5 (4a-Bromo-octahydro-isoquinolin-2-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone,
[1-Methyl-5-(3-nitro-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[1-Methyl-5-(4-nitro-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
3-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzoic acid methyl ester,
- 10 4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzoic acid methyl ester,
(E)-3-{4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-phenyl}-acrylic acid methyl ester,
[5-(3-Hydroxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 15 [5-(3-Methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[5-(4-Methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
(5-Dibenzofuran-4-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
[1-Methyl-5-(4-phenoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[1-Methyl-5-(2-phenoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 20 [5-(3,4-Dimethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[1-Methyl-5-(2,3,4-trimethoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[5-(4-Hydroxymethyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 25 [5-(4-Benzyloxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[5-(3-Benzyloxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[5-(6-Ethoxy-naphthalen-2-yl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 30 [5-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
(5-Benzo[1,3]dioxol-5-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
[1-Methyl-5-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,

- [1-Methyl-5-(3-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [1-Methyl-5-(2-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 5 [5-(4-Chloro-2-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(3-Chloro-4-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(2-Chloro-4-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
- 10 methanone,
- [5-(5-Fluoro-2-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(2-Fluoro-3-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 15 [5-(4-Benzoyloxy-3-chloro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(2-Chloro-4-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(3-Chloro-4-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
- 20 methanone,
- [5-(4-Chloro-2-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(3-Chloro-4-propoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 25 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (adamantan-1-ylmethyl)-amide,
- 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid adamantan-1-ylamide,
- 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid hexahydro-2,5-methanopentalen-3a(1H)-amide,
- 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid cycloheptylamide,
- 30 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid ((1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amide,
- 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid ((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide,
- (1-Methyl-5-pyrrol-1-yl-1H-pyrazol-4-yl)-(3-phenyl-pyrrolidin-1-yl)-methanone,

- (1-Methyl-5-pyrrol-1-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(1-Methyl-5-pyrrol-1-yl-1H-pyrazol-4-yl)-(4aR,8aS)-octahydro-isoquinolin-2-yl-methanone,
(6-Bromo-octahydro-isoquinolin-2-yl)-(1-methyl-5-pyrrol-1-yl-1H-pyrazol-4-yl)-methanone,
5 1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid cyclooctylamide,
1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid adamantan-2-ylamide,
1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid (adamantan-1-ylmethyl)-amide,
1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid adamantan-1-ylamide,
10 1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid ((1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amide,
1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid ((1R,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide,
1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid ((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide,
15 1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid ((1R,2R,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide,
1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-1-yl)-amide,
20 1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid cyclohexylamide,
(3-Benzyl-piperidin-1-yl)-(1-methyl-5-pyrrol-1-yl-1H-pyrazol-4-yl)-methanone,
(2-Ethyl-piperidin-1-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone,
1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid methyl-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide, and
25 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid adamantan-2-yl-isopropyl-amide,
and pharmaceutically acceptable salts thereof.

The following compounds all constitute individual and separate preferred embodiments of the present invention:

- 30 (1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(trans-octahydro-isoquinolin-2-yl)-methanone,
[5-(4-Isopropyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
(5-Benzo[b]thiophen-2-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,

[5-(2-Chloro-4-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,

[5-(2-Chloro-4-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,

5 [5-(2-Chloro-4-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,

[5-(3-Chloro-4-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,

1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (adamantan-1-ylmethyl)-amide,

10 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid adamantan-1-ylamide,

1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid ((1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amide, and

1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid ((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide.

15 Compounds of formula (I) are individually preferred and pharmaceutically acceptable salts thereof are individually preferred, with the compounds of formula (I) being particularly preferred.

The compounds of formula (I) can have one or more asymmetric C atoms and can
20 therefore exist as an enantiomeric mixture, diastereomeric mixture or as optically pure compounds.

It will be appreciated that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion
25 back to the parent compound in vivo.

As described above, the novel compounds of the present invention have been found to inhibit 11 β -hydroxysteroid dehydrogenase. They can therefore be used in the treatment and prophylaxis of diseases which are modulated by 11 β -hydroxysteroid dehydrogenase inhibitors, preferably a metabolic disorder. Such diseases include type II diabetes, obesity and metabolic syndrome.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

The invention likewise embraces compounds as described above for use as therapeutically active substances, especially as therapeutically active substances for the treatment and/or prophylaxis of diseases which are modulated by 11 β -hydroxysteroid dehydrogenase inhibitors, particularly as therapeutically active substances for the treatment and/or prophylaxis of type II diabetes or metabolic syndrome.

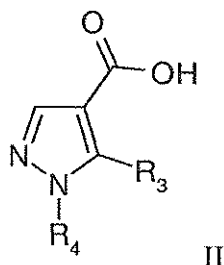
In another preferred embodiment, the invention relates to a method for the therapeutic and/or prophylactic treatment of diseases which are modulated by 11 β -hydroxysteroid dehydrogenase inhibitors, particularly for the therapeutic and/or prophylactic treatment of type II diabetes, obesity or metabolic syndrome, which method comprises administering a compound as defined above to a human being or animal. Preferably, said therapeutically effective amount is about 10 to about 1000 mg per day.

The invention also embraces the use of compounds as defined above for the therapeutic and/or prophylactic treatment of diseases which are modulated by 11 β -hydroxysteroid dehydrogenase inhibitors, particularly for the therapeutic and/or prophylactic treatment of type II diabetes, obesity or metabolic syndrome.

The invention also relates to the use of compounds as described above for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases which are modulated by 11 β -hydroxysteroid dehydrogenase inhibitors, particularly for the therapeutic and/or prophylactic treatment of type II diabetes, obesity or metabolic syndrome. Such medicaments comprise a compound as described above.

Prevention and/or treatment of type II diabetes or metabolic syndrome is the preferred indication. Type II diabetes is particularly preferred.

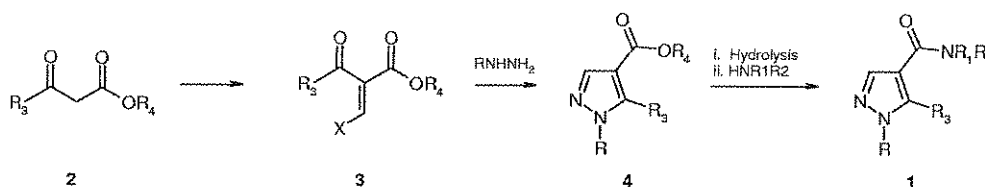
In another embodiment, the present invention refers to a process for the preparation of a compound as defined above, which process comprises reacting a compound of formula II



with a compound HNR^1R^2 , wherein R^1 , R^2 , R^3 and R^4 are as defined above.

Another embodiment of the present invention refers to compounds as defined above, when prepared by a process as defined above.

The compounds according to the present invention can be prepared according to the following general synthetic methods given below, by the methods given in the specific examples, or in analogy thereto.



Scheme 1

One general approach to the synthesis of compounds of the invention is shown in Scheme 1. 1. According to this process, a β -keto-ester of formula 2 is converted to a compound of formula 3 where X represents dialkylamino (such as dimethylamino) or lower-alkoxy (such as ethoxy) and then the compound of formula 3 is reacted with a hydrazine to give the compound of formula 4. The ester protective group in the compound of formula 2 is then cleaved and the resulting carboxylic acid is coupled with an amine of formula HNR_1R_2 to give the desired compound of formula 1. The reaction of a compound of formula 2 to give a compound of formula 3 can be carried out using conditions that are well known in the art. For example, in the case where X represents dimethylamino, the com-

compound of formula **3** can be prepared by treating a compound of formula **2** with N,N-dimethylformamide dimethyl acetal in an inert solvent such as an aromatic hydrocarbon (for example, toluene) at a temperature between about 50 °C and about 100 °C. Examples of conditions for this reaction can be found in the literature, for example, in H. H. Wassermann et al. *Tetrahedron Lett.* **1984**, 25, 3743-3746, in S. Gelin et al. *Synthesis* **1983**, 566-568, and in J. Svete et al. *Synthesis* **1990**, 70-72. In the case where X represents ethoxy, the compound of formula **3** can be prepared by treating a compound of formula **2** with triethylorthoformate in the presence of acetic anhydride at the reflux temperature. Examples of conditions for this reaction can be found in the literature, for example, in L. Claisen *Liebigs Ann. Chem.* **1897**, 297, 1-18; in L. Crombie et al. *J. Chem. Soc. Perkin Trans. I* **1979**, 464-471; in M. S. S. Palanki et al. *J. Med. Chem.* **2000**, 43, 3995-4004; and in M. T. Herrero et al. *Tetrahedron* **2002**, 58, 8581-8589.

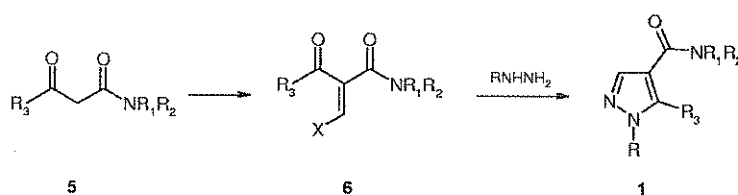
The reaction of the compound of formula **3** with a hydrazine can be carried out under a variety of conditions. For example, the compound of formula **3** can be reacted with a hydrazine or the acid addition salt of a hydrazine in an inert solvent such as an alcohol (for example, ethanol). In the case where an acid addition salt of the hydrazine is used, then the reaction is carried out in the additional presence of a base such as a tertiary alkylamine (for example, triethylamine or diisopropylethylamine). The reaction is conveniently carried out at a temperature between about -20 °C and about 80 °C. Examples of conditions for this reaction can be found in the literature, for example, in J. R. Beck et al. *J. Heterocycl. Chem.* **1987**, 24, 739-740; in G. Menozzi et al. *J. Heterocycl. Chem.* **1987**, 24, 1669-1676; in F. R. Busch et al. PCT Int. Appl. WO 2003051845; in J. F. Lambert et al. PCT Int. Appl. WO 2002044133; in H. Shimotori et al. US 4,792,565; and in H. Ohki et al. *Bioorg. Med. Chem. Lett.* **2002**, 12, 3191-3193.

The cleavage of a compound of formula **4** to the corresponding carboxylic acid is carried out using reaction conditions that are well known in the field of organic synthesis, many of which are outlined in "Protective Groups in Organic Synthesis" [T. W. Greene and P. G. M. Wuts, 2nd Edition, John Wiley & Sons, N.Y. 1991]. For example, in the case where R₄ represents methyl or ethyl, the reaction can be conveniently effected by treating the compound with one equivalent of an alkali metal hydroxide, such as potassium hydroxide, sodium hydroxide, or lithium hydroxide, preferably lithium hydroxide, in a suitable solvent, such as a mixture of tetrahydrofuran, methanol, and water. The reaction can be carried out

at a temperature between about 0 °C and about room temperature, preferably at about room temperature. As another example, in the case where R₄ represents a group that can be cleaved under acidic conditions, such as a tert-butyl group, the ester may be treated with a strong inorganic acid, for example a hydrohalic acid such as hydrogen chloride or hydrogen bromide, or a strong organic acid, for example a halogenated alkane carboxylic acid such as trifluoroacetic acid and the like. The reaction is conveniently carried out in the presence of an inert organic solvent (such as dichloromethane) and at a temperature between about 0 °C and about room temperature, preferably at about room temperature. As a final (but not limiting) example, in the case where R₄ represents a group that can be cleaved by catalytic hydrogenation, and with the further condition that the rest of the molecule is stable to such conditions, the reaction may be carried out by hydrogenation in the presence of a noble metal catalyst such as palladium-on-carbon in the presence of an inert solvent (for example, an alcohol such as ethanol) at about room temperature and under atmospheric pressure.

The coupling of a carboxylic acid of structure 4 where R₄ represents hydrogen with an amine of structure HNR₁R₂, according to Scheme 1, can be achieved using methods well known to one of ordinary skill in the art. For example, the transformation can be carried out by reaction of a carboxylic acid of structure 4 where R₄ represents hydrogen or of an appropriate derivative thereof such as an activated ester, with an amine of structure HNR₁R₂ or a corresponding acid addition salt (e.g., the hydrochloride salt) in the presence, if necessary, of a coupling agent, many examples of which are well known *per se* in peptide chemistry. The reaction is conveniently carried out by treating the carboxylic acid of structure 4 where R₄ represents hydrogen with the hydrochloride of the amine of structure HNR₁R₂ in the presence of an appropriate base, such as diisopropylethylamine, a coupling agent such as O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, and in the optional additional presence of a substance that increases the rate of the reaction, such as 1-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole, in an inert solvent, such as a chlorinated hydrocarbon (e.g., dichloromethane) or N,N-dimethylformamide or N-methylpyrrolidinone, at a temperature between about 0 °C and about room temperature, preferably at about room temperature. Alternatively, the reaction can be carried out by converting the carboxylic acid of formula 4 where R₄ represents hydrogen to an activated ester derivative, such as the N-hydroxysuccinimide ester, and subsequently reacting this with the amine of structure HNR₁R₂ or a corresponding acid addition salt. This reaction

- sequence can be carried out by reacting the carboxylic acid of formula 4 where R_4 represents hydrogen with N-hydroxysuccinimide in the presence of a coupling agent such as N,N'-dicyclohexylcarbodiimide in an inert solvent such as tetrahydrofuran at a temperature between about 0 °C and about room temperature. The resulting N-hydroxysuccinimide ester is then treated with the amine of structure HNR_1R_2 or a corresponding acid addition salt, in the presence of a base, such as an organic base (e.g., triethylamine or diisopropylethylamine or the like) in a suitable inert solvent such as N,N-dimethylformamide at around room temperature.
- The reaction sequence shown in Scheme 1 can also be carried out using solid-phase synthesis, in the case where X represents a polymer-bound amino group. Following this approach, the compound of formula 2 is treated with N-formylimidazole dimethyl acetal and a polymer-bound amine such as an aniline-functionalized cellulose derivative (for example, 4-amino-phenyl-sulfonyl-ethoxy-cellulose, which is available from Iontosorb, Usti nad Labem, Czech Republic) in the presence of an acid catalyst such as camphor-sulfonic acid in an inert solvent, such as N,N-dimethylformamide at a temperature around 80 °C, to give a compound of formula 3 where X represents a polymer-bound aniline. The compound of formula 3 is then converted into the compound of formula 4 by treatment with a hydrazine in an inert solvent such as an alcohol (for example, isopropanol) at a temperature around the boiling point of the solvent. Examples of conditions for this reaction can be found in the literature, for example, in L. De Luca et al. *J. Comb. Chem.* **2003**, 5, 465-471.



Scheme 2

- A pyrazole-4-carboxamide of formula 1 can be prepared according to Scheme 2, where a β -keto-amide of formula 5 is converted to a compound of formula 6 where X represents dialkylamino (such as dimethylamino) or lower-alkoxy (such as ethoxy) and then the compound of formula 6 reacts with a hydrazine to give the compound of formula 1. The reaction of a compound of formula 5 to give a compound of formula 6 can be carried out using

conditions that are well known in the art. For example, in the case where X represents dimethylamino, the compound of formula **6** can be prepared by treating a compound of formula **5** with N,N-dimethylformamide dimethyl acetal in an inert solvent such as an aromatic hydrocarbon (for example, toluene) at a temperature between about 50 °C and about 100 °C. Examples of conditions for this reaction can be found in the literature, for example, in R. Zupet et al. *J. Heterocycl. Chem.* **1991**, 28, 1731-1740; in D. E. Seitz et al. *Tetrahedron Lett.* **1995**, 36, 1413-1416; in A. V. Rama Rao et al. *Tetrahedron Lett.* **1990**, 31, 1439-42; and in P. Kocienski et al. *Tetrahedron Lett.* **1988**, 29, 4481-4. In the case where X represents ethoxy, the compound of formula **6** can be prepared by treating a compound of formula **5** with triethylorthoformate in the presence of acetic anhydride at the reflux temperature. Examples of conditions for this reaction can be found in the literature, for example, in J. H. Dewar et al. *J. Chem. Soc.* **1961**, 3254-3260.

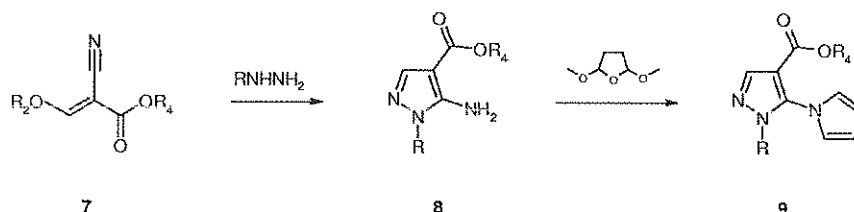
The reaction of the compound of formula **6** with a hydrazine can be carried out under a variety of conditions. For example, the compound of formula **6** can be reacted with a hydrazine or the acid addition salt of a hydrazine in an inert solvent such as an alcohol (for example, ethanol). In the case where an acid addition salt of the hydrazine is used, then the reaction is carried out in the additional presence of a base such as a tertiary alkylamine (for example, triethylamine or diisopropylethylamine). The reaction is conveniently carried out at a temperature between about -20 °C and about 80 °C. Examples of conditions for this reaction can be found in the literature, for example, in A. X. Wang et al. *Bioorg. Med. Chem. Lett.* **1998**, 8, 2787-2792; in T. A. Elmaati et al. *Pol. J. Chem.* **2002**, 76, 945-952 Chemical Abstracts AN 2002:501464; and in G. Giacomelli et al. *Eur. J. Org. Chem.* **2003**, 537-541

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The reaction sequence shown in Scheme 2 can also be carried out in the case where X represents an aniline. Thus, a compound of formula **6** can be prepared from a compound of formula **5** by treatment with an N-(alkoxymethylene)-aniline, in the optional presence of an inert solvent such as kerosene, at elevated temperature such as between about 125 °C and about 140 °C. Examples of conditions for this reaction can be found in the literature, for example, in F. B. Dains *Chem. Ber.* **1902**, 35, 2496-2500; in F. B. Dains et al. *J. Am. Chem. Soc.* **1909**, 31, 1148-1157; in F. B. Dains et al. *J. Am. Chem. Soc.* **1918**, 40, 562-569; and in O. S. Wolfbeis *Chem. Ber.* **1981**, 114, 3471-3484. The compound of formula **6** can then be converted to the compound of formula **1** by treatment with a hydrazine in an inert

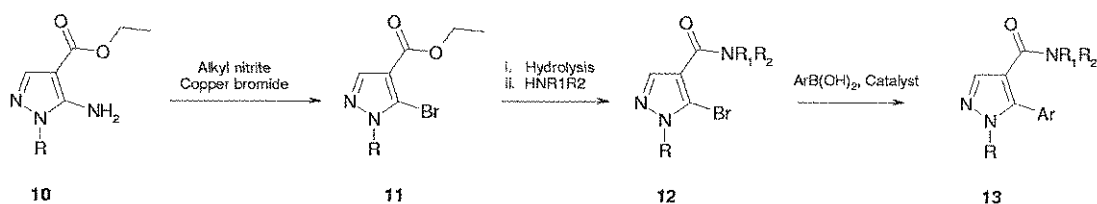
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solvent such as ethanol at a temperature around the reflux temperature of the solvent. Examples of conditions for this reaction can be found in the literature, for example, in F. B. Dains et al. *J. Am. Chem. Soc.* **1909**, *31*, 1148-1157; in F. B. Dains et al. *J. Am. Chem. Soc.* **1916**, *38*, 1515; in F. B. Dains et al. *J. Am. Chem. Soc.* **1918**, *40*, 562-569; and in A. N. Borisevich et al. *Ukrainskii Khimicheskii Zhurnal* **1986**, *52*, 641-7 Chemical Abstracts AN 1987:458919.



Scheme 3

As shown in Scheme 3, a 1-alkyl-5-pyrrolyl-pyrazole-4-carboxylic acid derivative of formula **9** can be prepared starting from a 3-alkoxy-2-cyano-acrylic acid derivative of formula **7** by reaction with a hydrazine of formula $RNHNH_2$ to give an intermediate 5-amino-pyrazole of formula **8**, which can then be reacted with 2,5-dimethoxy-tetrahydrofuran to give the 5-pyrrolyl-pyrazole of formula **9**. This can be converted to a carboxamide of the invention by reactions analogous to those discussed above with reference to Scheme 1. The pyrazole-forming annulation reaction can be conveniently carried out by treating a 3-alkoxy-2-cyano-acrylic acid ester of formula **7** (such as 3-ethoxy-2-cyano-acrylic acid ethyl ester) with a hydrazine of formula $RNHNH_2$ in an inert solvent such as ethanol at the reflux temperature. The subsequent annulation to form the pyrrole ring is conveniently carried out by heating the intermediate 5-amino-pyrazole with 2,5-dimethoxy-tetrahydrofuran in an organic acid such as acetic acid at a temperature of around 100 °C. An example of conditions suitable for this process can be found in the literature, for example, in M. Kopp et al. *J. Heterocycl. Chem.* **2001**, *38*, 1045-1050. Further examples of procedures for the preparation of 5-amino-1-aryl-pyrazole-4-carboxylate esters can be found in J. Svetlik *Heterocycles* **1984**, *22*, 2513-2516; in J. R. Beck et al. *J. Heterocycl. Chem.* **1987**, *24*, 267-270; and in T. Luebbbers et al. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 821-826. The carboxylate ester of formula **9** can then be hydrolyzed to the corresponding carboxylic acid and coupled with an amine of formula HNR_1R_2 using procedures analogous to those described above for the conversion of a carboxylate ester of formula **4** to a compound of the invention of formula **1**.



Scheme 4

- 5 As shown in Scheme 4, a 1-alkyl-5-pyrrolyl-pyrazole-4-carboxylic acid derivative of formula **13** can be prepared starting from a 5-amino-pyrazole-4-carboxylate ester of formula **10** by diazotization of the amino group in the presence of a brominating agent such as copper(II) bromide. The reaction is conveniently carried out by treating the compound of formula **10** with an alkyl nitrite such as tert-butyl nitrite or isoamyl nitrite in an inert solvent
- 10 such as a halogenated hydrocarbon (for example, carbon tetrachloride) at a temperature around 50 °C, in the presence of a bromine source such as bromine, copper(II) bromide, dibromomethane, or bromoform. Conditions appropriate for this reaction can be found in the literature, for example in J. R. Beck and M. P. Lynch US 4,620,865 and in H. Mizukawa JP 2002003410. The conversion of the ester of formula **11** to an amide of formula **12**
- 15 is analogous to the conversion of a compound of formula **4** to a compound of formula **1** as discussed above, and can be carried out using similar reactions. The conversion of a compound of formula **12** to a compound of the invention of formula **13** can be carried out using a Suzuki reaction with an organoboron intermediate such as an aryl-boronic acid or an ester thereof, a reaction that is well known to one of average skill in the art. For example, the
- 20 reaction can be conveniently carried out by reacting a compound of formula **12** with an aryl-boronic acid in a convenient inert solvent such as a polar aprotic solvent (e.g., N,N-dimethylformamide) or an ether (e.g., dioxane) or water, in the presence of a catalytic amount of a palladium(0) complex (e.g., tetrakis(triphenylphosphine)palladium(0)) or a compound which can be reduced in situ to give palladium(0) (for example, palladium(II) acetate or bis(triphenylphosphine)-palladium(II) chloride), in the optional additional presence of a catalytic amount of a phosphine ligand, for example tri-o-tolylphosphine or tri-tert-butylphosphine, or alternatively in the presence of a preformed complex of palladium(0) with a phosphine ligand such as bis(tri-cyclohexyl-phosphine)palladium, and also
- 25 in the presence of an inorganic base, for example, an alkali metal carbonate, bicarbonate, hydroxide or phosphate (e.g., potassium phosphate or sodium carbonate or sodium hydroxide) at a temperature between about room temperature and about 100 °C, and preferably at
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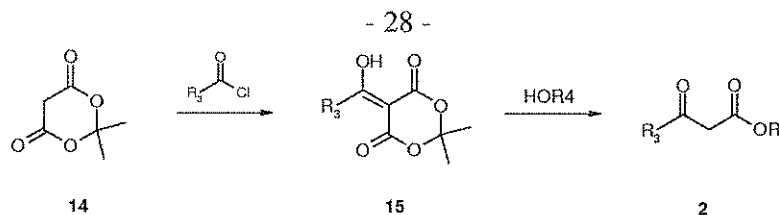
between about room temperature and about 50 °C. Conditions appropriate for this reaction can be seen in the literature, for example in X.-J. Wang and K. Grozinger *Tetrahedron Lett.* **2000**, *41*, 4713-4716. The starting material of formula **10** can be made from a 3-alkoxy-2-cyano-acrylic acid ester of formula **7** by reaction with an alkyl-hydrazine by reactions analogous to those described above for the preparation of a compound of formula **8**. Conditions appropriate for this reaction can be found in the literature, for example in F. Bondavalli et al. *J. Med. Chem.* **2002**, *45*, 4875-4887; in S. Schenone et al. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2529-2531; in M. Kopp et al. *J. Heterocycl. Chem.* **2001**, *38*, 1045-1050; and in P. Seneci et al. *Synth. Commun.* **1999**, *29*, 311-341.



Scheme 5

As shown in Scheme 5, a compound of formula **1** in which R₁ represents lower alkyl can be prepared from a compound of formula **1** in which R₁ represents hydrogen, by reaction with a strong base (such as sodium hydride) in an inert solvent (such as dimethylformamide) at room temperature to give the corresponding anion. This is then reacted without isolation with a lower-alkyl halide of formula R₁X, again at room temperature, to give the desired compound of formula **1** in which R₁ represents lower alkyl.

Methods suitable for the preparation of many β -keto-esters of formula **2** are known in the literature using a variety of synthetic methods. A listing of many of these methods can be found in "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" [R. C. Larock, VCH Publishers, Inc. New York, 1989], for example on pages 685, 694-695, and 768. Additional examples of synthetic methods appropriate for the preparation of many β -keto-esters of formula **2** can be found in "Advanced Organic Chemistry" [J. March, 3rd Edition, John Wiley & Sons, Inc. New York, 1985], on pages 437-439, and 823-824. In addition, more than 100 β -keto-esters of formula **2** are listed as commercially available in the Available Chemicals Directory which is well known to one of average skill in the art of organic synthesis.



Scheme 6

One example of a method to prepare a β -keto-ester of formula **2** is outlined in Scheme 6.

Meldrum's acid (**14**) is treated with an acyl chloride of formula R_3COCl in an anhydrous inert solvent such as a halogenated hydrocarbon (e.g. methylene chloride or ethylene chloride). The reaction is carried out in the presence of an anhydrous organic base, such as pyridine, triethylamine, or diisopropylethylamine, at around room temperature. Conditions suitable for this reaction can be found in the literature, for example in H. Emtenäs et al. *J. Org. Chem.* **2001**, 26, 6756 -6761. The resulting intermediate of formula **15** is then heated with an alcohol of formula HOR_4 , either using the alcohol as solvent (for example in the case where the alcohol is methanol or ethanol), or in an inert solvent such as benzene (for example in the case where the alcohol is benzyl alcohol or tert-butyl alcohol). The reaction is conveniently carried out at a temperature between about 60 °C and about 80 °C. Conditions suitable for this reaction can be found in the literature, for example in Y. Oikawa et al. *J. Org. Chem.* **1978**, 43, 2087-2088.



Scheme 7

β -Keto-amides of formula **5** can be prepared from the intermediate of formula **15** by treatment with a stoichiometric amount of an amine of formula HNR_1R_2 in a suitable inert solvent such as toluene at the refluxing temperature. Conditions suitable for this reaction can be found in the literature, for example in C. S Pak et al. *Synthesis* **1992**, 1213-1214.

A variety of methods are known for the preparation of hydrazines and are reviewed in "The Chemistry of the Hydrazo, Azo, and Azoxy Groups. Part 1" [J. Timberlake and J. Stowell; S. Patai Ed.; John Wiley & Sons, Ltd. London 1975, 69-107]. Examples of processes useful for the preparation of alkyl-hydrazines include the reaction of an aldehyde or ketone

- with a hydrazide followed by reduction and hydrolysis (CH 307629, Chem. Abs. 51:25623; N. I. Ghali et al. *J. Org. Chem.* **1981**, *46*, 5413-5414); Hofmann reaction of a urea (J. Viret et al. *Tetrahedron* **1987**, *43*, 891-894); electrophilic amination of an alkyl-amine: (L. F. Audrieth and L. H. Diamond *J. Am. Chem. Soc.* **1954**, *76*, 4869-4871; A. Koziara et al. *Synth. Commun.* **1995**, *25*, 3805-3812); Mitsunobu reaction of an alcohol with N-tert-butoxycarbonylaminophthalimide followed by hydrolysis (N. Brosse et al. *Tetrahedron Lett.* **2000**, *41*, 205-207); conversion of an alkyl-amine to the corresponding N-alkylsydnone followed by hydrolysis (J. Fugger et al. *J. Am. Chem. Soc.* **1955**, *77*, 1843-1848); reaction of an alkyl bromide with N'-isopropylidene-phosphorohydrazidic acid diethyl ester or diphenylphosphinic hydrazide followed by deprotection (S. Zawadzki et al. *Synthesis* **1987**, 485-487; B. Mlotkowska and Z. Zwierzak *Tetrahedron Lett.* **1978**, *19*, 4731-4734). In addition, more than a dozen substituted or unsubstituted alkyl-hydrazines are listed as commercially available in the Available Chemicals Directory.
- Many amines of formula HNR_1R_2 are commercially available and known to one skilled in the art. In addition, there are a variety of methods known to one of average skill in the art for the synthesis of amines of formula HNR_1R_2 . Many of these methods are enumerated in "The Chemistry of the Amino Group" [M. S. Gibson; S. Patai Ed.; John Wiley & Sons, Ltd. London 1968, 37-77], in "Advanced Organic Chemistry" [J. March, 3rd Edition, John Wiley & Sons, Inc. New York, 1985], on pages 1153-1154, and in "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" [R. C. Larock, VCH Publishers, Inc. New York, 1989] on pages 1061-1063. As one example of the preparation of an amine of formula HNR_1R_2 , a solution of the oxime derived from (1R)-(+)-camphor in an alcohol such as amyl alcohol is treated with sodium added in small pieces over an extended period such as about four hours. The reaction is carried out at the reflux temperature of the solvent, and the product is (-)-endobornylamine hydrochloride, a compound of formula HR_1R_2 where R_1 represents hydrogen and R_2 represents the bornyl moiety. Exact conditions for carrying out this reaction can be found in the literature, for example in L. A. Paquette and R. F. Doehner, Jr. *J. Org. Chem.* **1980**, *45*, 5105-5113. As another example of the preparation of an amine of formula HNR_1R_2 , *trans*-decahydroquinoline can be prepared by the dissolving metal reduction of $\Delta^{1,9}$ -octahydroquinoline which is in turn prepared in a multistep sequence from N-1-cyclohexenylpyrrolidine and acrylonitrile. Conditions for these reactions can be found in F. W. Vierhapper and E. L. Eliel *J. Org. Chem.* **1975**, *40*, 2734-2742 and in L. A. Cohen and B. Witkop *J. Am. Chem. Soc.* **1955**, *77*, 6595-6600. As

a further example of the synthesis of an amine of formula HNR_1R_2 , 1-hydroxyadamantan-4-one reacts with hydroxylamine hydrochloride in refluxing ethanol in the presence of aqueous sodium hydroxide to give 1-hydroxyadamantan-4-one oxime. This is then reduced with lithium aluminum hydride in an inert solvent such as tetrahydrofuran at the reflux temperature to give 4-aminoadamantan-1-ol, which is conveniently isolated and characterized as the hydrochloride salt. Conditions for these reactions can be found in the literature, for example in H. W. Geluk and J. L. M. A. Schlattmann *Tetrahedron* **1968**, 24, 5369-5377. As a final but not limiting example of the synthesis of an amine of formula HNR_1R_2 , a secondary amine can be prepared by making use of a process called reductive amination, which is well known to one of average skill in the art of organic synthesis, whereby an amine is treated with a ketone to give an imine which is reduced by one of a number of reducing agents. Many examples of conditions that can be used for this reaction are enumerated in "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" [R. C. Larock, VCH Publishers, Inc. New York, 1989] on pages 421-423. For example, the amine and ketone can be treated with a reducing agent such as tetrabutylammonium cyanoborohydride in an inert solvent such as a halogenated hydrocarbon (e.g., dichloromethane) in the presence of methanolic HCl at about room temperature.

Starting materials of formula **7** are conveniently prepared by treating a cyanoacetate ester with a trialkyl orthoformate, in the presence of an acid anhydride catalyst such as acetic anhydride, at 80-160 °C. Conditions for such a reaction can be found in the literature, for example in R. G. Jones *J. Am. Chem. Soc.* **1952**, 74, 4889-4891; in N. J. Cusack et al. *J. Chem. Soc. C* **1971**, 1501-1507; and in O. Ackermann et al. US 4,277,418.

In the practice of the method of the present invention, an effective amount of any one of the compounds of this invention or a combination of any of the compounds of this invention or a pharmaceutically acceptable salt thereof, is administered via any of the usual and acceptable methods known in the art, either singly or in combination. The compounds or compositions can thus be administered orally (e.g., buccal cavity), sublingually, parenterally (e.g., intramuscularly, intravenously, or subcutaneously), rectally (e.g., by suppositories or washings), transdermally (e.g., skin electroporation) or by inhalation (e.g., by aerosol), and in the form of solid, liquid or gaseous dosages, including tablets and suspensions. The administration can be conducted in a single unit dosage form with continuous therapy or in a single dose therapy ad libitum. The therapeutic composition can also be in the form of an oil emulsion or dispersion in conjunction with a lipophilic salt such as pamoic acid, or in the form of a biodegradable sustained-release composition for subcutaneous or intramuscular administration.

Useful pharmaceutical carriers for the preparation of the compositions hereof, can be solids, liquids or gases; thus, the compositions can take the form of tablets, pills, capsules, suppositories, powders, enterically coated or other protected formulations (e.g. binding on ion-exchange resins or packaging in lipid-protein vesicles), sustained release formulations, solutions, suspensions, elixirs, aerosols, and the like. The carrier can be selected from the various oils including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly (when isotonic with the blood) for injectable solutions. For example, formulations for intravenous administration comprise sterile aqueous solutions of the active ingredient(s) which are prepared by dissolving solid active ingredient(s) in water to produce an aqueous solution, and rendering the solution sterile. Suitable pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, gelatin, malt, rice, flour, chalk, silica, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The compositions may be subjected to conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting or emulsifying agents, salts for adjusting osmotic pressure, buffers and the like. Suitable pharmaceutical carriers and their formulation are described in Remington's Pharmaceutical Sciences by E. W. Martin. Such compositions will, in any event, contain an effective amount of the active compound together

with a suitable carrier so as to prepare the proper dosage form for proper administration to the recipient.

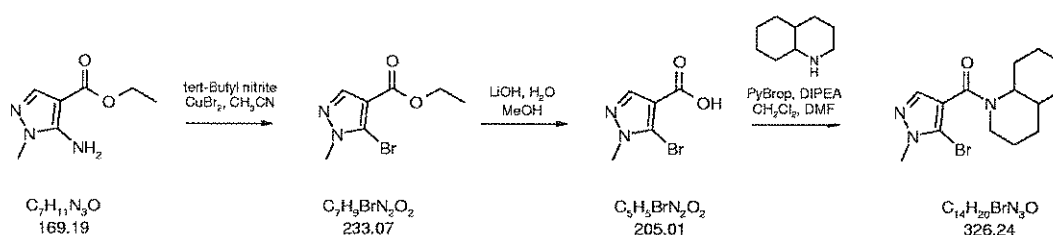
The dose of a compound of the present invention depends on a number of factors, such as, for example, the manner of administration, the age and the body weight of the subject, and the condition of the subject to be treated, and ultimately will be decided by the attending physician or veterinarian. Such an amount of the active compound as determined by the attending physician or veterinarian is referred to herein, and in the claims, as an "effective amount". For example, the dose of a compound of the present invention is typically in the range of about 10 to about 1000 mg per day.

The invention will now be further described in the Examples below, which are intended as an illustration only and do not limit the scope of the invention.

EXAMPLES**PART I: PREFERRED INTERMEDIATES**

- 5 Reagents were purchased from Aldrich, Sigma, Maybridge, Advanced ChemTech, and Lancaster or other suppliers as indicated below and used without further purification. LC/MS (liquid chromatography/mass spectroscopy) spectra were recorded using the following system. For measurement of mass spectra, the system consists of a Micromass Platform II spectrometer: ES Ionization in positive mode (mass range: 150 -1200 amu). The simultaneous chromatographic separation was achieved with the following HPLC system:
- 10 ES Industries Chromegabond WR C-18 3u 120Å (3.2 x 30mm) column cartridge; Mobile Phase A: Water (0.02% TFA) and Phase B: Acetonitrile (0.02% TFA); gradient 10% B to 90% B in 3 minutes; equilibration time of 1 minute; flow rate of 2 mL/minute.

- 15 **Intermediate 1: (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone**

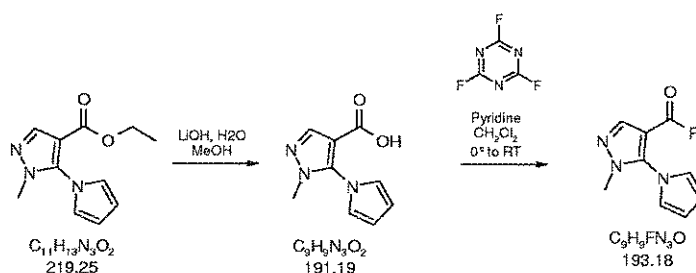


- 20 **Step 1. 5-Bromo-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester**
 To a mixture of t-butyl nitrite (29.5 mL, 221.5 mmol), cupric bromide (39.7 g, 177.5 mmol), and acetonitrile was added 5-amino-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (25 g, 148 mmol) in portions over 30 minutes. The reaction mixture was stirred at ambient temperature for 2 h, then at 65 °C for 1 h. The mixture was then poured into 6N HCl (400 mL) and extracted with dichloromethane. After concentration *in vacuo*, the crude residue was purified by flash chromatography with a gradient of 0-20% ethyl acetate/hexanes to give 5-bromo-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (28 g, 81%).
- 25
- 30 **Step 2. (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone**

To a solution of 5-bromo-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (6.9 g, 29.6 mmol) in CH₃OH (25 mL) and water (25 mL) was added LiOH (0.78 g, 32.6 mmol). The reaction mixture was stirred at reflux for 4 h, and then the solution was concentrated under reduced pressure to remove the methanol. The residue was diluted with water and the solution was acidified to pH 2 with concentrated HCl (~3 mL). The resulting mixture was then extracted with ethyl acetate. The combined organic extracts were concentrated *in vacuo* to give 5-bromo-1-methyl-1H-pyrazole-4-carboxylic acid, which was used without further purification.

5-Bromo-1-methyl-1H-pyrazole-4-carboxylic acid (29.6 mmol), decahydroquinoline (Aldrich Chemical Company, Inc., Milwaukee, WI; 4.9 g, 35.5 mmol), diisopropylethylamine (11 mL, 59.2 mmol), and PyBrop (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate) (Chem-Impex International, Inc., Wood Dale, IL; 16.6 g, 35.5 mmol) were mixed together in dry dichloromethane (70 mL) and dry dimethylformamide (20 mL). The mixture was stirred overnight at room temperature. At this time, the mixture was diluted with dichloromethane and extracted three times with water. The combined dichloromethane extracts were evaporated, and the residue was purified by flash chromatography, eluting with 0-10% ethyl acetate/hexanes to give 5-bromo-1-methyl-1H-pyrazol-4-yl)-(octahydroquinolin-1-yl)-methanone (7.9 g, 82% yield).

Intermediate 2: 1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride

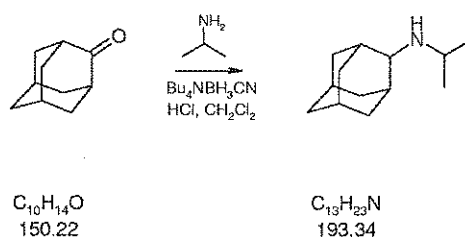


To a solution of 1-methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid ethyl ester (Maybridge plc, Cornwall, UK; 20 g, 91.2 mmol) in methanol (100 mL) and water (100 mL) was added LiOH (2.4 g, 100.3 mmol). The reaction mixture was stirred at reflux for 4 hours and then concentrated under reduced pressure to remove the methanol. The residue was diluted with water, acidified to pH 2 with concentrated HCl (9 mL), and extracted with

ethyl acetate. The combined extracts were evaporated *in vacuo* to give 1-methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid which was used without further purification.

To a stirred solution of 1-methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid (7.65 g, 40 mmol) in dry dichloromethane (150 mL) and pyridine (3.2 mL, 40 mmol) under a nitrogen atmosphere was added cyanuric fluoride (5.4 g, 40 mmol) at 0 °C. The reaction mixture was stirred for two hours during which time the reaction temperature was allowed to rise to room temperature. Crushed ice was then added along with additional dichloromethane. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. Concentration of the combined organic layers under reduced pressure gave 1-methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride which was used in the next step without further purification.

Intermediate 3: Adamantan-2-yl-isopropyl-amine



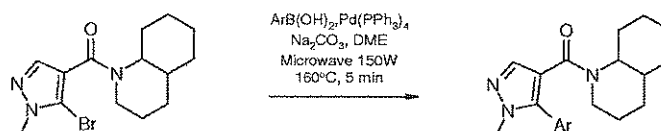
Methanolic HCl (2.5 M; 13.3 mmol) is added to a solution of 2-adamantanone (1.00 g, 6.7 mmol) in dichloromethane (25 mL) and then isopropylamine (2.5 mL, 29.4 mmol) is added, followed by tetrabutylammonium cyanoborohydride (1.41 g, 5 mmol) and approximately 1 g of 4A molecular sieves. The reaction mixture is stirred at room temperature until the reaction is complete, as judged by TLC. Then the mixture is filtered and the filtrate is acidified to pH 1 with 1 M HCl, and the solvent is evaporated. The residue is taken up in water and extracted with ether. The aqueous layer is made basic to pH 10 with NaOH solution and the resulting mixture is extracted several times with ether. The combined ether layers are washed with water and brine, dried (magnesium sulfate), filtered, and evaporated to give adamantan-2-yl-isopropyl-amine.

PART II: PREPARATION OF PREFERRED COMPOUNDS

Method A

Preparation of compounds of the invention according to Method A

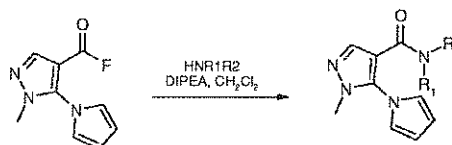
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In a Personal Chemistry microwave process tube (Biotage AB, Sweden), tetrakis(triphenylphosphine)palladium (5 mg) was added to a nitrogen degassed mixture of the boronic acid (0.15 mmol), 2M aqueous sodium carbonate solution (2 mL), and (5-bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (of Intermediate 1; 49 mg, 0.15 mmol) in dry DME (1.5mL). The tube was sealed with a septum and was submitted to 150 W microwave irradiation using a Personal Chemistry Microwave Synthesis system (Biotage AB, Sweden) at 160 °C for 5 minutes. The reaction mixture was cooled to room temperature and then filtered through celite and a silica plug. The eluant was then partitioned between ethyl acetate and water and the water layer was extracted three times with ethyl acetate. The organic layers were combined, concentrated *in vacuo* and the desired product was obtained after purification by C-18 reversed phase HPLC with a gradient of 10-100% Acetonitrile/Water.

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Method B

Preparation of compounds of the invention according to Method B

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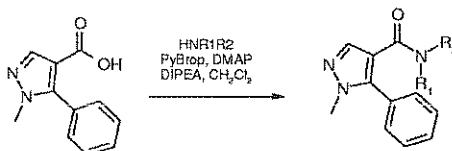
Commercially available amines (0.2 mmol) were distributed to 10 mL screw top Pyrex tubes. To each tube was added 1-methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (of Intermediate 2; 39 mg, 0.2 mmol) in dry dichloromethane (2 mL) and diisopropylethylamine (1 mL). The reaction mixture was stirred by agitation at room temperature overnight. At this time, the reaction mixture was diluted with dichloromethane (3

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mL) and washed with water (2 x 2 mL). The organic layers were combined, and concentrated *in vacuo*. The residue was purified by C-18 reversed phase HPLC with a gradient of 10-100% acetonitrile/water to obtain the desired product.

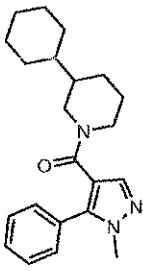
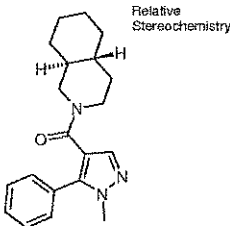
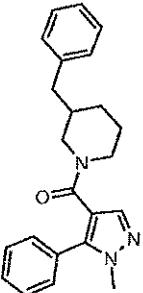
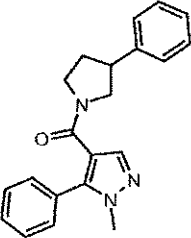
5 Method C

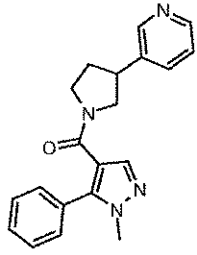
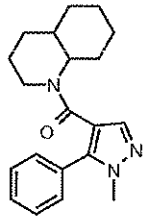
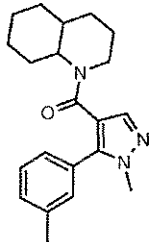
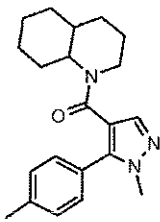
Preparation of compounds of the invention according to Method C

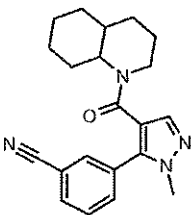
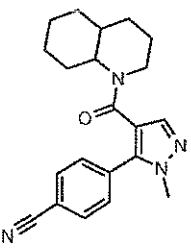
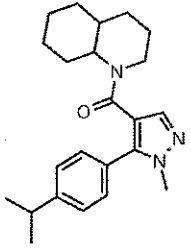
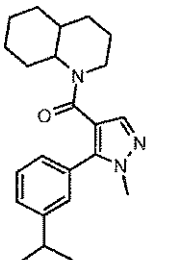


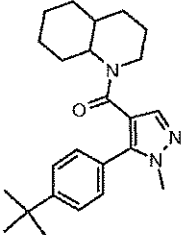
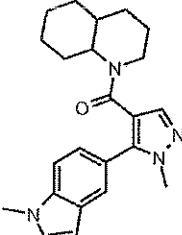
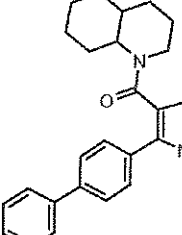
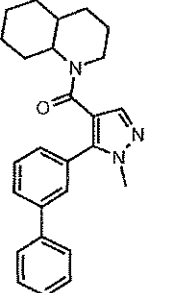
- 10 A mixture of the amine (0.2 mmol), 1-methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (40 mg, 0.2 mmol, Maybridge plc, Cornwall, UK), DIPEA (0.14 mL, 0.8 mmol, Aldrich), Py-Brop (Chem-Impex International, Inc., Wood Dale, IL; 102 mg, 0.8 mmol) and DMAP (0.5 mg, 0.004 mmol, Aldrich) in dry dichloromethane (2 mL) was stirred overnight at room temperature. Water was added and the mixture was extracted three times with di-
- 15 chloromethane. The combined organic extracts were concentrated under reduced pressure purified by C-18 reversed phase HPLC with a gradient of 10-100% acetonitrile/water containing 0.1% TFA as a modifier to give the product.

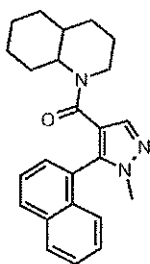
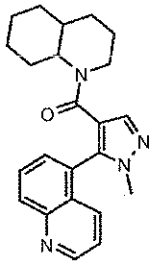
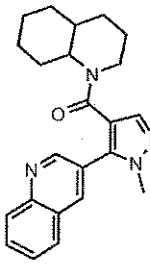
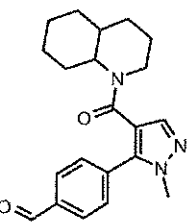
The compounds of the invention in Example numbers 1-107 below were prepared by one of the three methods described above.

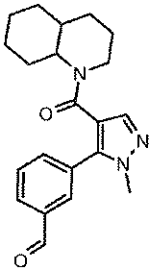
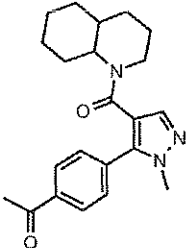
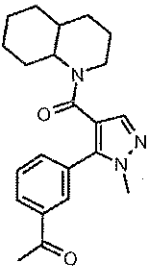
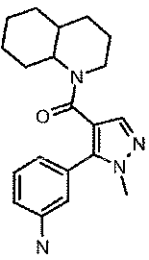
No.	Structure	Name	Synthetic Method	Starting Materials	Measured Mass (M+H)
1		(3-Cyclohexyl-piperidin-1-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) 3-Cyclohexyl-piperidine hydrochloride (Array Biopharma Inc., Boulder, CO)	352
2		(1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(trans-octahydro-isoquinolin-2-yl)-methanone	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) Trans-Decahydro-isoquinoline (TCI America, Portland, OR)	324
3		(3-Benzyl-piperidin-1-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) 3-Benzyl-piperidine (Tyger Scientific Inc., Ewing, NJ)	360
4		(1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(3-phenyl-pyrrolidin-1-yl)-methanone	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) 3-Phenyl-pyrrolidine (Array Biopharma Inc., Boulder, CO)	332

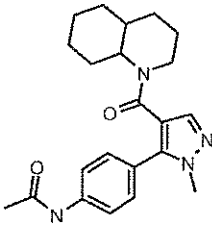
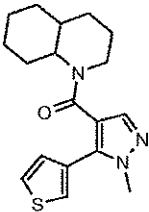
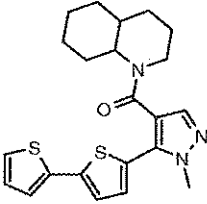
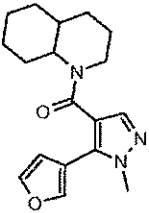
5		(1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(3-pyridin-3-yl-pyrrolidin-1-yl)-methanone	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) 3-Pyrrolidin-3-yl-pyridine (Array Bio-pharma Inc., Boulder, CO)	333
6		(1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) Decahydro-quinoline (Aldrich Chemical Company, Inc., Milwaukee, WI)	324
7		(1-Methyl-5-m-tolyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	A	Methyl-phenyl-boronic acid quino-line (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	338
8		(1-Methyl-5-p-tolyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	A	Methylphenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	338

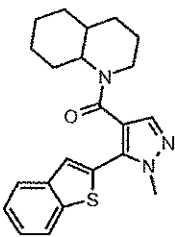
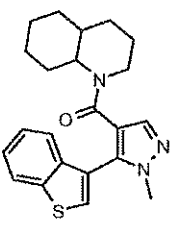
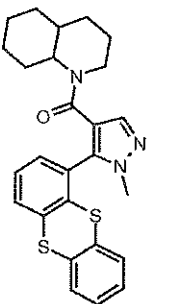
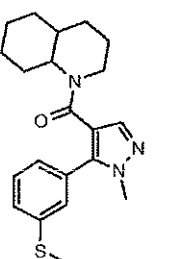
9		3-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzonitrile	A	Cyano-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	349
10		4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzonitrile	A	Cyano-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	349
11		[5-(4-Isopropyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	4-Isopropyl-phenyl-boronic acid (Lancaster Synthesis Ltd., Lancashire, UK) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	366
12		[5-(3-Isopropyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Isopropyl-phenyl-boronic acid (Lancaster Synthesis Ltd., Lancashire, UK) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	366

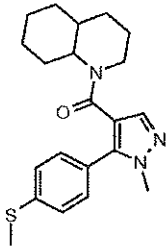
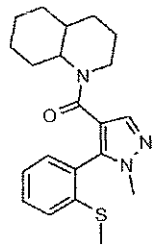
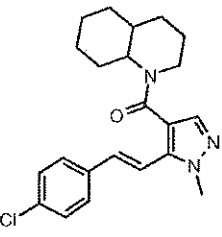
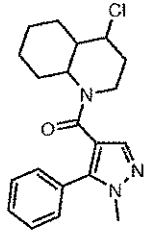
13		[5-(4-tert-Butyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	tert-Butyl-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	380
14		[1-Methyl-5-(1-methyl-1H-indol-5-yl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	5-(1-Methyl-1H-indole-5-boronic acid (Frontier Scientific, Inc., Logan, UT) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	377
15		(5-Biphenyl-4-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	A	Biphenyl-4-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	400
16		(5-Biphenyl-3-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	A	Biphenyl-3-boronic acid (Lancaster Synthesis Ltd., Lancashire, UK) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	400

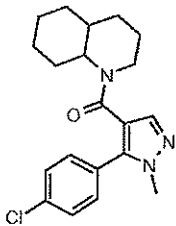
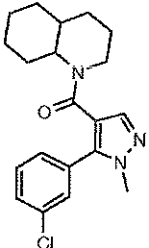
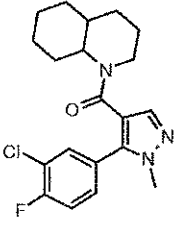
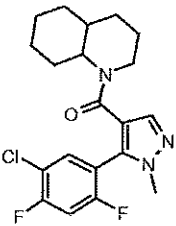
17		(1-Methyl-5-naphthalen-1-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	A	Naphthalene-1-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	374
18		(1-Methyl-5-quinolin-5-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	A	Quinoline-5-boronic acid (Matrix Scientific, Columbia, SC) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	375
19		(1-Methyl-5-quinolin-3-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	A	Quinoline-3-boronic acid (Frontier Scientific, Inc., Logan, UT) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	375
20		4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzaldehyde	A	Formyl phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	352

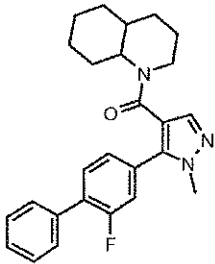
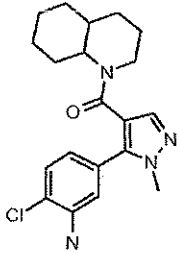
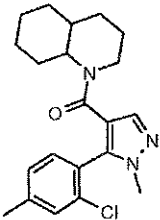
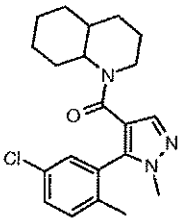
21		3-[2-Methyl-4-(octahydroquinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzaldehyde	A	Formyl phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	352
22		1-{4-[2-Methyl-4-(octahydroquinoline-1-carbonyl)-2H-pyrazol-3-yl]-phenyl}-ethanone	A	Acetyl-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	366
23		1-{3-[2-Methyl-4-(octahydroquinoline-1-carbonyl)-2H-pyrazol-3-yl]-phenyl}-ethanone	A	Acetyl-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	366
24		[5-(3-Amino-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Amino-phenyl-boronic acid (Alfa Aesar, Ward Hill, MA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	339

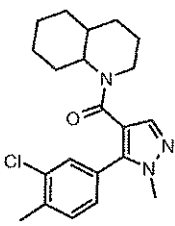
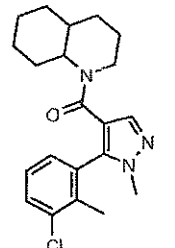
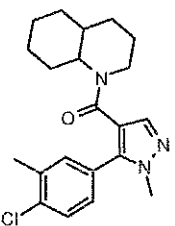
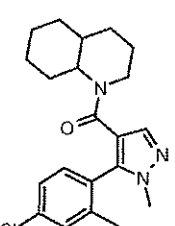
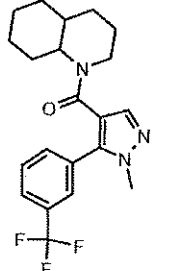
25		N-{4-[2-Methyl-4-(octahydroquinoline-1-carbonyl)-2H-pyrazol-3-yl]-phenyl}-acetamide	A	Acetamido-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydroquinolin-1-yl)-methanone (Intermediate 1)	381
26		(1-Methyl-5-thiophen-3-yl-1H-pyrazol-4-yl)-(octahydroquinolin-1-yl)-methanone	A	Thiophene-3-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydroquinolin-1-yl)-methanone (Intermediate 1)	330
27		(5-[2,2']Bithiophenyl-5-yl-1-methyl-1H-pyrazol-4-yl)-(octahydroquinolin-1-yl)-methanone	A	[2,2']Bithiophenyl-boronic acid (Maybridge plc, Cornwall, UK) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydroquinolin-1-yl)-methanone (Intermediate 1)	412
28		(5-Furan-3-yl-1-methyl-1H-pyrazol-4-yl)-(octahydroquinolin-1-yl)-methanone	A	Furan-3-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydroquinolin-1-yl)-methanone (Intermediate 1)	314

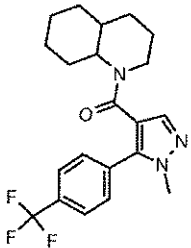
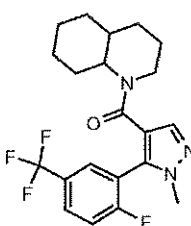
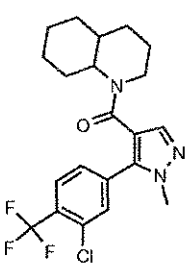
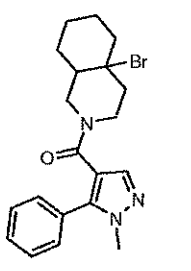
29		(5-Benzo[b]thiophen-2-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	A	Benzothiophen-2-yl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	380
30		(5-Benzo[b]thiophen-3-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	A	Benzothiophen-3-yl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	380
31		(1-Methyl-5-thianthren-1-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	A	Thianthren-1-yl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	462
32		[1-Methyl-5-(3-methylsulfanylphenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Methylsulfanylphenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	370

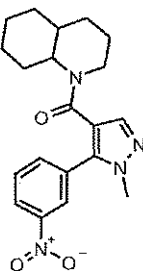
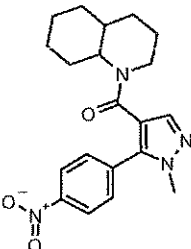
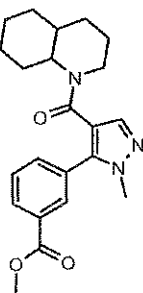
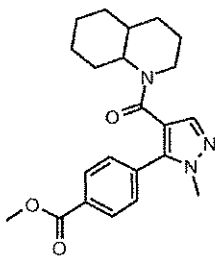
33		[1-Methyl-5-(4-methylsulfanyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Methylsulfanyl-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI)	370
34		[1-Methyl-5-(2-methylsulfanyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Methylsulfanyl-phenyl-boronic acid (Lancaster Synthesis Ltd., Lancashire, UK)	370
35		{5-[(E)-2-(4-Chloro-phenyl)-vinyl]-1-methyl-1H-pyrazol-4-yl}-(octahydro-quinolin-1-yl)-methanone	A	2-(4-Chloro-phenyl)-vinyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI)	384
36		(4-Chloro-octahydro-quinolin-1-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) 4-Chloro-Decahydro-quinoline (Matrix Scientific, Columbia, SC)	358

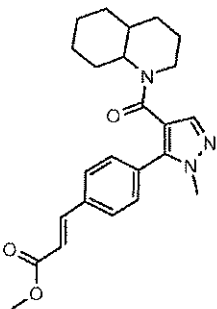
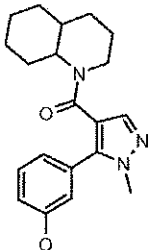
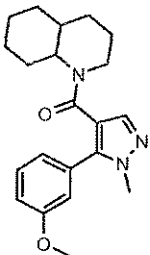
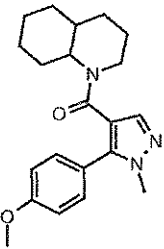
37		[5-(4-Chloro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Chloro-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	358
38		[5-(3-Chloro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Chloro-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	358
39		[5-(3-Chloro-4-fluoro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Chloro-4-fluoro-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	376
40		[5-(5-Chloro-2,4-difluoro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Chloro-2,4-difluoro-phenyl-boronic acid (Frontier Scientific, Inc., Logan, UT) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	394

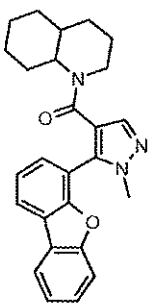
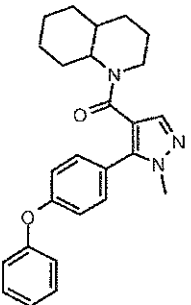
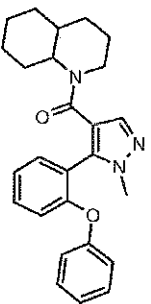
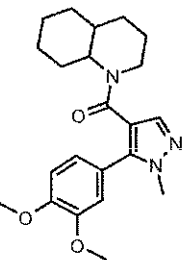
41		[5-(2-Fluoro-biphenyl-4-yl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Fluoro-biphenyl-4-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	418
42		[5-(3-Amino-4-chloro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Amino-4-chloro-phenyl-boronic acid hydrochloride (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	373
43		[5-(2-Chloro-4-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Chloro-4-methyl-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	372
44		[5-(5-Chloro-2-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Chloro-2-methyl-phenyl-boronic acid (Matrix Scientific, Columbia, SC) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	372

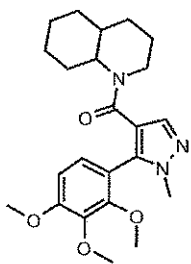
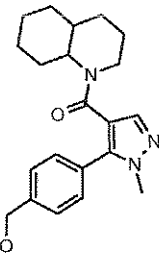
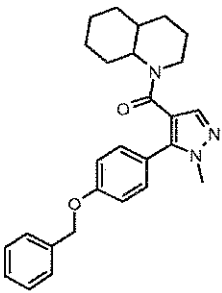
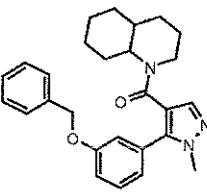
45		[5-(3-Chloro-4-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Chloro-4-methyl-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	372
46		[5-(3-Chloro-2-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Chloro-2-methyl-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	372
47		[5-(4-Chloro-3-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Chloro-3-methyl-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	372
48		[5-(4-Chloro-2-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Chloro-2-methyl-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	372
49		[1-Methyl-5-(3-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	3-Trifluoromethyl-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	392

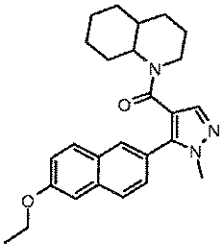
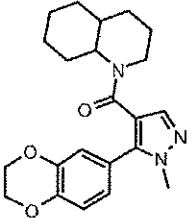
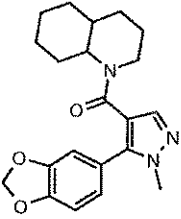
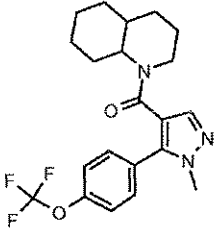
50		[1-Methyl-5-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Trifluoromethyl-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	392
51		[5-(2-Fluoro-5-trifluoromethyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	2-Fluoro-5-trifluoromethyl-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	410
52		[5-(3-Chloro-4-trifluoromethyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	3-Chloro-4-trifluoromethyl-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	426
53		(4a-Bromo-octahydro-isoquinolin-2-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) 4a-Bromoperhydroisoquinoline hydrobromide (Maybridge plc, Cornwall, UK)	402

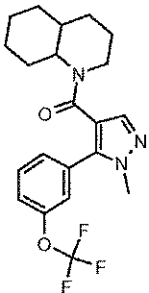
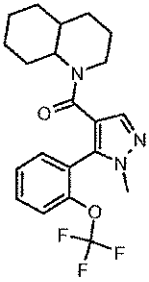
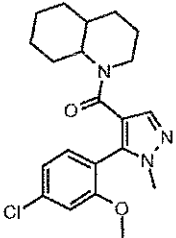
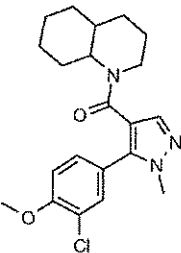
54		[1-Methyl-5-(3-nitro-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Nitrophenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI)	369
55		[1-Methyl-5-(4-nitro-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Nitrophenyl-boronic acid (Combi-Blocks Inc., San Diego, CA)	369
56		3-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzoic acid methyl ester	A	Phenyl-boronic acid methyl ester (Combi-Blocks Inc., San Diego, CA)	382
57		4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzoic acid methyl ester	A	Benzoic acid methyl ester boronic ester (Combi-Blocks Inc., San Diego, CA)	382

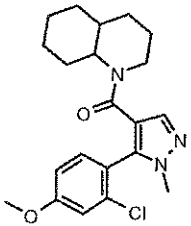
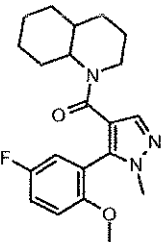
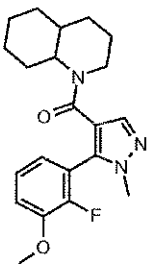
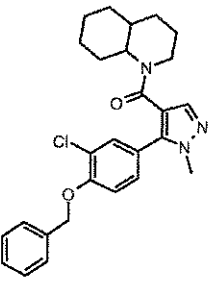
58		(E)-3-{4-[2-Methyl-4-(octahydroquinoline-1-carbonyl)-2H-pyrazol-3-yl]-phenyl}-acrylic acid methyl ester	A	4-(2-Methoxycarbonylvinyl)-phenylboronic acid (Combi-Blocks Inc., San Diego, CA)	408
59		[5-(3-Hydroxyphenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydroquinolin-1-yl)-methanone	A	3-Hydroxyphenylboronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI)	340
60		[5-(3-Methoxyphenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydroquinolin-1-yl)-methanone	A	3-Methoxyphenylboronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI)	354
61		[5-(4-Methoxyphenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydroquinolin-1-yl)-methanone	A	4-Methoxyphenylboronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI)	354

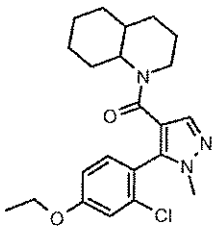
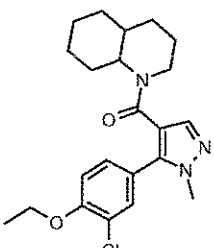
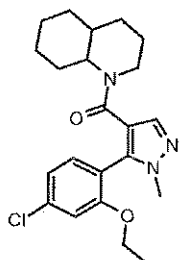
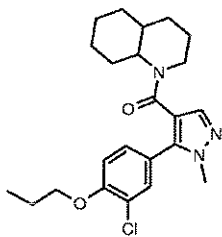
62		(5-Dibenzofuran-4-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	A	Dibenzofuran-4-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	414
63		[1-Methyl-5-(4-phenoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	4-Phenoxy-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	416
64		[1-Methyl-5-(2-phenoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	2-Phenoxy-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	416
65		[5-(3,4-Dimethoxyphenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	3,4-Dimethoxyphenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	384

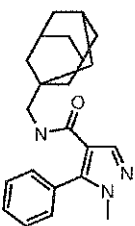
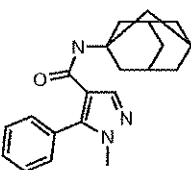
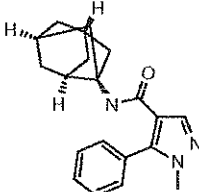
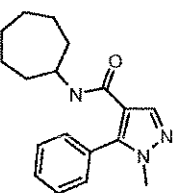
66		[1-Methyl-5-(2,3,4-trimethoxyphenyl)-1H-pyrazol-4-yl]-(octahydroquinolin-1-yl)-methanone	A	2,3,4-Trimethoxyphenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydroquinolin-1-yl)-methanone (Intermediate 1)	414
67		[5-(4-Hydroxymethylphenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydroquinolin-1-yl)-methanone	A	4-Hydroxymethylphenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydroquinolin-1-yl)-methanone (Intermediate 1)	354
68		[5-(4-Benzoyloxyphenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydroquinolin-1-yl)-methanone	A	4-Benzoyloxyphenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydroquinolin-1-yl)-methanone (Intermediate 1)	430
69		[5-(3-Benzoyloxyphenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydroquinolin-1-yl)-methanone	A	3-Benzoyloxyphenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydroquinolin-1-yl)-methanone (Intermediate 1)	431

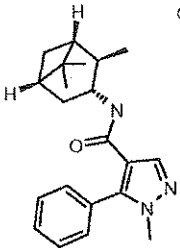
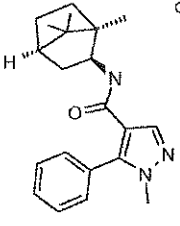
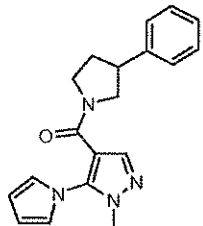
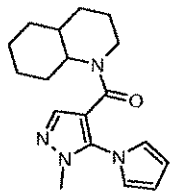
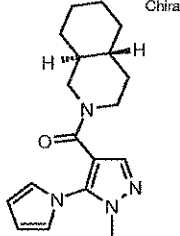
70		[5-(6-Ethoxy-naphthalen-2-yl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Ethoxy-naphthalene-2-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	418
71		[5-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	2,3-Dihydro-benzo[1,4]dioxine-6-boronic acid (Frontier Scientific, Inc., Logan, UT) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	382
72		(5-Benzo[1,3]dioxol-5-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	A	Benzo[1,3]dioxole-5-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	368
73		[1-Methyl-5-(4-trifluoromethoxyphenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	4-Trifluoromethoxyphenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	408

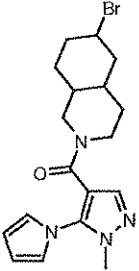
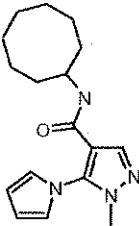
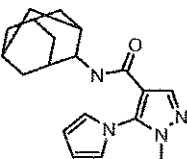
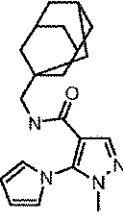
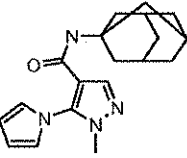
74		[1-Methyl-5-(3-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	3-Trifluoromethoxy-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	408
75		[1-Methyl-5-(2-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	2-Trifluoromethoxy-phenyl-boronic acid (Frontier Scientific, Inc., Logan, UT) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	408
76		[5-(4-Chloro-2-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	4-Chloro-2-methoxy-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	388
77		[5-(3-Chloro-4-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	3-Chloro-4-methoxy-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	388

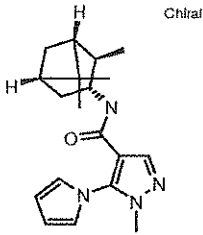
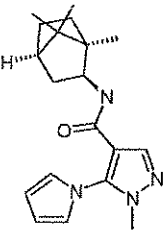
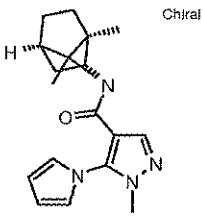
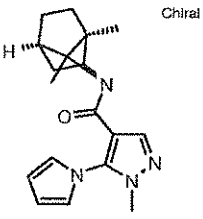
78		[5-(2-Chloro-4-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	2-Chloro-4-methoxy-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	388
79		[5-(5-Fluoro-2-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	Fluoro-2-methoxy-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	372
80		[5-(2-Fluoro-3-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	2-Fluoro-3-methoxy-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	372
81		[5-(4-Benzoyloxy-3-chloro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	4-Benzoyloxy-3-chloro-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	464

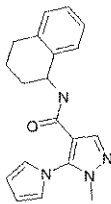
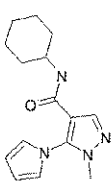
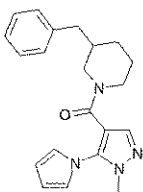
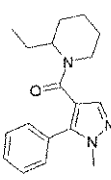
82		[5-(2-Chloro-4-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	2-Chloro-4-ethoxy-phenyl-boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	402
83		[5-(3-Chloro-4-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	3-Chloro-4-ethoxy-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	402
84		[5-(4-Chloro-2-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	4-Chloro-2-ethoxy-phenyl boronic acid (Combi-Blocks Inc., San Diego, CA) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	402
85		[5-(3-Chloro-4-propoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	A	3-Chloro-4-propoxy-phenyl-boronic acid (Aldrich Chemical Company, Inc., Milwaukee, WI) (5-Bromo-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone (Intermediate 1)	416

86		1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (adamantan-1-ylmethyl)-amide	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) 1-Adamantane-methylamine (Aldrich Chemical Company, Inc., Milwaukee, WI)	350
87		1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid adamantan-1-ylamide	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) 1-Adamantanamine (Aldrich Chemical Company, Inc., Milwaukee, WI)	336
88		1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid hexahydro-2,5-methanopentalen-3a(1H)-amide	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) 3-Aminonoradamantane hydrochloride (Aldrich Chemical Company, Inc., Milwaukee, WI)	322
89		1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid cycloheptylamide	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) Cycloheptylamine (Aldrich Chemical Company, Inc., Milwaukee, WI)	298

90		1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid ((1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amide	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) (-)-Isopinocampheylamine (Aldrich Chemical Company, Inc., Milwaukee, WI)	338
91		1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid ((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) (R)-(+)-Bornylamine (Aldrich Chemical Company, Inc., Milwaukee, WI)	338
92		(1-Methyl-5-pyrrol-1-yl-1H-pyrazol-4-yl)-(3-phenyl-pyrrolidin-1-yl)-methanone	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) 3-Phenyl-pyrrolidine (Array Biopharma Inc., Boulder, CO)	321
93		(1-Methyl-5-pyrrol-1-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) Decahydro-quinoline (Aldrich Chemical Company, Inc., Milwaukee, WI)	313
94		(1-Methyl-5-pyrrol-1-yl-1H-pyrazol-4-yl)-(4aR,8aS)-octahydro-isoquinolin-2-yl-methanone	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) Trans-Decahydro-isoquinoline (TCI America, Portland, OR)	313

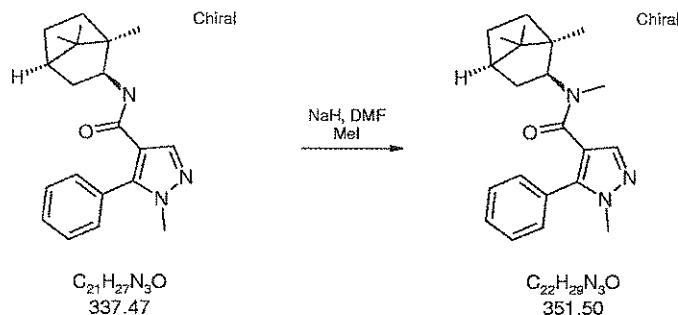
95		(6-Bromo-octahydro-isoquinolin-2-yl)-(1-methyl-5-pyrrol-1-yl-1H-pyrazol-4-yl)-methanone	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) 6-Bromoperhydroisoquinoline hydrobromide (available from Apollo Scientific Ltd., Cheshire, UK)	391
96		1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid cyclooctylamide	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) Cyclooctylamine (Aldrich Chemical Company, Inc., Milwaukee, WI)	301
97		1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid adamantan-2-ylamide	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) 2-Adamantanamine hydrochloride (Aldrich Chemical Company, Inc., Milwaukee, WI)	325
98		1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid (adamantan-1-ylmethyl)-amide	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) 1-Adamantanemethylamine (Aldrich Chemical Company, Inc., Milwaukee, WI)	339
99		1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid adamantan-1-ylamide	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) 1-Adamantanamine (Aldrich Chemical Company, Inc., Milwaukee, WI)	325

100		1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid ((1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amide	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) (-)-Isopinocampheylamine (Aldrich Chemical Company, Inc., Milwaukee, WI)	327
101		1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid ((1R,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-amine hydrochloride (Maybridge plc, Cornwall, UK)	327
102		1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid ((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) (R)-(+)-Bornylamine (Aldrich Chemical Company, Inc., Milwaukee, WI)	327
103		1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid ((1R,2R,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) (R)-(-)-Isobornylamine hydrochloride (Fluka Chemie GmbH, Buchs, Switzerland)	327

104		1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid (1,2,3,4-tetrahydronaphthalen-1-yl)-amide	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) 1,2,3,4-Tetrahydro-1-naphthylamine (Aldrich Chemical Company, Inc., Milwaukee, WI)	321
105		1-Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid cyclohexylamide	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) Cyclohexylamine (Alfa Aesar, Ward Hill, MA)	273
106		(3-Benzyl-piperidin-1-yl)-(1-methyl-5-pyrrol-1-yl-1H-pyrazol-4-yl)-methanone	B	Methyl-5-pyrrol-1-yl-1H-pyrazole-4-carbonyl fluoride (Intermediate 2) 3-Benzyl-piperidine (Tyger Scientific Inc., Ewing, NJ)	349
107		(2-Ethyl-piperidin-1-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone	C	Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) Ethyl-piperidine (Aldrich Chemical Company, Inc., Milwaukee, WI)	298

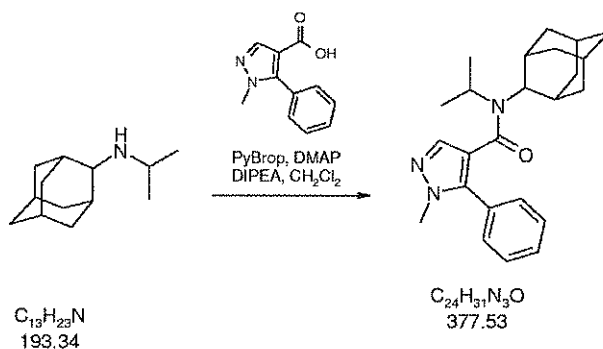
Example 108: 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid methyl-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide

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Sodium hydride (60% dispersion in mineral oil; 15 mg, 0.375 mmol) is added to a cooled (~0 °C) solution of 1-methyl-5-phenyl-1H-pyrazole-4-carboxylic acid ((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide (of Example 91; 100 mg, 0.3 mmol) in dry dimethylformamide (10 mL) and the mixture is allowed to stir for 30 min. Methyl iodide (30 µL, 0.49 mmol) is added and the solution is stirred at room temperature until the reaction is complete, as judged by TLC. Water is added and the solution is extracted twice with ethyl acetate. The combined organic layers are washed with water and brine, dried (magnesium sulfate), filtered, evaporated, and purified by C-18 reversed phase HPLC with a gradient of 10-100% acetonitrile/water containing 0.1% TFA as a modifier to give 1-methyl-5-phenyl-1H-pyrazole-4-carboxylic acid methyl-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide.

Example 109: 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid adamantan-2-yl-isopropyl-amide



Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid adamantan-2-yl-isopropyl-amide is prepared from adamantan-2-yl-isopropyl-amine (of intermediate 3) and 1-methyl-5-phenyl-

1H-pyrazole-4-carboxylic acid (Maybridge plc, Cornwall, UK) according to general procedure C.

Example 110: Testing of Compounds of the Invention in vitro

5

The in vitro inhibition of 11 β -HSD1 by compounds of the present invention were demonstrated by means of the following test:

Purified human HSD1 was diluted in 50 mM Tris-HCl, 100 mM NaCl, 0.1 mg/ml BSA, 0.02% Lubrol, 20 mM MgCl₂, 10 mM glucose 6-phosphate, 0.4 mM NADPH, 60 U/ml glucose 6-phosphate dehydrogenase to a concentration of 1.5 ug/ml (Enzyme Solution). Cortisone (100 uM) in DMSO was diluted to 1 uM with 50 mM Tris-HCl, 100 mM NaCl (Substrate Solution). Testing compounds (40 uM) in DMSO were diluted 3 fold in series in DMSO and further diluted 20 fold in Substrate Solution. Enzyme Solution (10 ul/ well) was added into 384 well microtiter plates followed by diluted compound solutions (10 ul/well) and mixed well. Samples were then incubated at 37 °C for 30 min. EDTA/biotin-cortisol solution (10 ul/well) in 28 mM EDTA, 100 nM biotin-cortisol, 50 mM Tris-HCl, 100 mM NaCl was then added followed by 5 ul/well of anti-cortisol antibody (3.2 ug/ml) in 50 mM Tris-HCl, 100 mM NaCl, 0.1 mg/ml BSA and the solution was incubated at 37 °C for 30 min. Five ul per well of Eu-conjugated anti-mouse IgG (16 nM) and APC-conjugated streptavidin (160 nM) in 50 mM Tris-HCl, 100 mM NaCl, 0.1 mg/ml BSA were added and the solution was incubated at room temperature for 2 hours. Signals were quantitated by reading time-resolved fluorescence on a Victor 5 reader (Wallac).

Percent inhibition of HSD1 activity by an agent at various concentrations was calculated by the formula % Inhibition = 100* [1-(Fs-Fb)/(Ft-Fb)], where:

Fs is the fluorescence signal of the sample which included the agent,

Fb is the fluorescence signal in the absence of HSD1 and agent,

Ft is the fluorescence signal in the presence of HSD1, but no agent.

30

The inhibitory activities of test compounds were determined by the IC₅₀s, or the concentration of compound that gave 50% inhibition. The compounds of the present invention preferably exhibit IC₅₀ values below 10 μ M, preferably in the range between 10 μ M and 1 nM, more preferably between 2 μ M and 5 nM.

The results of the in vitro inhibition of 11 β -HSD1 by representative compounds of the present invention are shown in the following Table:

5

Compound	Name	IC ₅₀ (μ M)
Example 12	[5-(3-Isopropyl-phenyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	0.059
Example 19	(1-Methyl-5-quinolin-3-yl-1 <i>H</i> -pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone	0.189
Example 21	3-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2 <i>H</i> -pyrazol-3-yl]-benzaldehyde	1.0
Example 33	[1-Methyl-5-(4-methylsulfanyl-phenyl)-1 <i>H</i> -pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	0.078
Example 36	(4-Chloro-octahydro-quinolin-1-yl)-(1-methyl-5-phenyl-1 <i>H</i> -pyrazol-4-yl)-methanone	0.6
Example 39	[5-(3-Chloro-4-fluoro-phenyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	0.208
Example 46	[5-(3-Chloro-2-methyl-phenyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	0.038
Example 49	[1-Methyl-5-(3-trifluoromethyl-phenyl)-1 <i>H</i> -pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	0.16
Example 52	[5-(3-Chloro-4-trifluoromethyl-phenyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	0.195
Example 55	[1-Methyl-5-(4-nitro-phenyl)-1 <i>H</i> -pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	0.552
Example 59	[5-(3-Hydroxy-phenyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	0.7
Example 67	[5-(4-Hydroxymethyl-phenyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	0.121
Example 82	[5-(2-Chloro-4-ethoxy-phenyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone	0.021
Example 96	1-Methyl-5-pyrrol-1-yl-1 <i>H</i> -pyrazole-4-carboxylic acid cyclooctylamide	0.058
Example 106	(3-Benzyl-piperidin-1-yl)-(1-methyl-5-pyrrol-1-yl-1 <i>H</i> -pyrazol-4-yl)-methanone	1.48
Example 107	(2-Ethyl-piperidin-1-yl)-(1-methyl-5-phenyl-1 <i>H</i> -pyrazol-4-yl)-methanone	0.26

Example 111: Testing of Compounds of the Invention in vivo

The in vivo inhibition of 11 β -HSD1 by compounds of the present invention can be demonstrated by means of the following test:

The compound of the invention is formulated in 7.5% Modified Gelatin in water and is administered IP at 100 mg/kg to mice (male C57Bl/6J, age ~97 Days). After 30 minutes, cortisone formulated in gelatin is administered by s.c. injection at 1 mg/kg. After a further 40 minutes, blood samples are taken from the mice and are analyzed using LC-MS for the concentrations of cortisone, cortisol, and drug.

Percent inhibition of HSD1 activity by the inhibitor is calculated by the following formula:

$$\% \text{ Inhibition} = 100 * [1 - (C_{\text{inh}}/C_{\text{veh}})]$$

where:

C_{veh} is the conversion of cortisone to cortisol when the animal is dosed with vehicle, and

C_{inh} is the conversion of cortisone to cortisol when the animal is dosed with inhibitor, where the conversion C is given by the formula $C = [\text{Cortisol}] / ([\text{Cortisol}] + [\text{Cortisone}])$.

* * *

It is to be understood that the invention is not limited to the particular embodiments of the invention described above, as variations of the particular embodiments may be made and still fall within the scope of the appended claims.

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients

Per tablet

Kernel:

Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg

Film Coat:

Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxyde (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

- 5 The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is mixed with sodium starch glycolate and magnesium stearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aqueous solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	<u>Per capsule</u>
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

- 5 The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Polyethylene Glycol 400	150.0 mg
Acetic Acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

- 10 The active ingredient is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by Acetic Acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example D

Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Capsule contents

Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg

Gelatin capsule

Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titan dioxide	0.4 mg
Iron oxide yellow	1.1 mg

- 5 The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example E

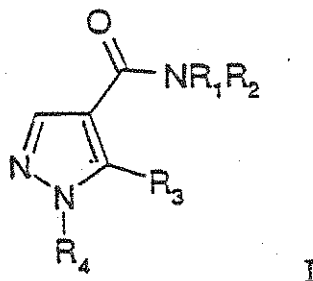
Sachets containing the following ingredients can be manufactured in a conventional manner:

Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg
Microcrystalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidon K 30	10.0 mg
Magnesiumstearate	10.0 mg
Flavoring additives	1.0 mg

- 5 The active ingredient is mixed with lactose, microcrystalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidon in water. The granulate is mixed with magnesiumstearate and the flavouring additives and filled into sachets.

Claims:

1. A compound of the formula I:



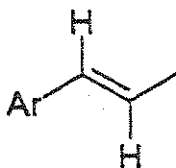
wherein:

one of R_1 or R_2 is hydrogen or unsubstituted alkyl and the other is unsubstituted lower alkyl or $(CH_2)_p Y$, wherein Y is a substituted or unsubstituted, saturated, partially unsaturated, or unsaturated mono-, bi- or tri-cyclic 5-10 membered cycloalkyl ring and p is 0 or 1, and wherein substituents on Y are lower alkyl, lower alkoxy, hydroxy, hydroxy-alkyl, alkyl-phenyl, phenyl-alkyl, pyridine or halogen,

or R_1 and R_2 , together with the N atom to which they are attached, form a substitute or unsubstituted ring Z, wherein Z is selected from the group consisting of 2-ethyl-piperidine, 3-phenyl-pyrrolidine, 3-(pyridin-3-yl)-pyrrolidine, 4-chloro-decahydro-quinoline, 4a-bromo-decahydro-isoquinoline, 6-bromo-octahydro-isoquinoline, 3-cyclohexyl-piperidine, 3-benzyl-piperidine, decahydro-quinoline and decahydro-isoquinoline;

R_3 is an aromatic ring system selected from the group consisting of [2,2']bithiophenyl, 1-methyl-indole, 2,3-dihydro-benzo[1,4]dioxin, benzo[1,3]dioxole, benzothiophene, dibenzofuran, furane, naphthalene, phenyl, biphenyl, quinoline, thianthrene and thiophene, wherein said aromatic ring may be unsubstituted or substituted with one or more amino, cyano, formyl, halo, hydroxy, hydroxymethyl, lower-acyl, lower-acyl-amino, lower-alkoxy, lower-alkoxy-carbonyl, 2-(lower-alkoxy-carbonyl)-ethenyl, lower-alkyl, lower-alkyl-thio, nitro, trifluoromethoxy or trifluoromethyl, wherein said phenyl ring may additionally be substituted with phenoxy or benzyloxy,

or R₃ is:



- 5 wherein Ar is a carbocyclic or heterocyclic aryl group which may be unsubstituted or substituted with one or more groups selected from the group consisting of halogen, lower alkyl, lower alkoxy, trifluoromethyl, cyano and nitro; and

R₄ is unsubstituted lower alkyl;

10

and pharmaceutically acceptable salts thereof.

2. The compound according to claim 1, wherein R₁ is hydrogen and R₂ is a substituted 6-8 membered cycloalkyl ring.

15

3. The compound according to claim 1, wherein R₂ is 1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl, 2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl, 3-noradamantyl, adamantan-1-yl, adamantan-1-yl-methyl, adamantan-2-yl, 1,2,3,4-tetrahydronaphthyl, cyclohexyl, cyclooctyl, or cycloheptyl.

4. The compound according to claim 1, wherein R₃ is substituted or unsubstituted benzothiophene or phenyl.

5. The compound according to claim 4, wherein R₃ is substituted with one or more halogen, lower-alkoxy or lower-alkyl.

- 5 6. A compound according to claim 1, selected from the group consisting of
(3-Cyclohexyl-piperidin-1-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone,
(1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(trans-octahydro-isoquinolin-2-yl)-methanone,
(3-Benzyl-piperidin-1-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone,
(1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(3-phenyl-pyrrolidin-1-yl)-methanone,
10 (1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(3-pyridin-3-yl-pyrrolidin-1-yl)-methanone,
(1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(1-Methyl-5-m-tolyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(1-Methyl-5-p-tolyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
3-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzonitrile,
15 4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzonitrile,
[5-(4-Isopropyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[5-(3-Isopropyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[5-(4-tert-Butyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[1-Methyl-5-(1-methyl-1H-indol-5-yl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
20 methanone,
(5-Biphenyl-4-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(5-Biphenyl-3-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(1-Methyl-5-naphthalen-1-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(1-Methyl-5-quinolin-5-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
25 (1-Methyl-5-quinolin-3-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzaldehyde,
3-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzaldehyde,
1-{4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-phenyl}-ethanone,
1-{3-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-phenyl}-ethanone,
30 [5-(3-Amino-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
N-{4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-phenyl}-acetamide,
(1-Methyl-5-thiophen-3-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(5-[2,2']Bithiophenyl-5-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-
methanone,

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- (5-Furan-3-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
(5-Benzo[b]thiophen-2-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-
methanone,
(5-Benzo[b]thiophen-3-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-
5 methanone,
(1-Methyl-5-thianthren-1-yl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
[1-Methyl-5-(3-methylsulfanyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[1-Methyl-5-(4-methylsulfanyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
10 methanone,
[1-Methyl-5-(2-methylsulfanyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
{5-[(E)-2-(4-Chloro-phenyl)-vinyl]-1-methyl-1H-pyrazol-4-yl}-(octahydro-quinolin-1-yl)-
methanone,
15 (4-Chloro-octahydro-quinolin-1-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone,
[5-(4-Chloro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[5-(3-Chloro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
[5-(3-Chloro-4-fluoro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
20 [5-(5-Chloro-2,4-difluoro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[5-(2-Fluoro-biphenyl-4-yl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[5-(3-Amino-4-chloro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
25 methanone,
[5-(2-Chloro-4-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[5-(5-Chloro-2-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
30 [5-(3-Chloro-4-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[5-(3-Chloro-2-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
methanone,
[5-(4-Chloro-3-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-

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- methanone,
 [5-(4-Chloro-2-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
 methanone,
 [1-Methyl-5-(3-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
 5 methanone,
 [1-Methyl-5-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
 methanone,
 [5-(2-Fluoro-5-trifluoromethyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-
 yl)-methanone,
 10 [5-(3-Chloro-4-trifluoromethyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-
 yl)-methanone,
 (4a-Bromo-octahydro-isoquinolin-2-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone,
 [1-Methyl-5-(3-nitro-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
 [1-Methyl-5-(4-nitro-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
 15 3-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzoic acid methyl
 ester,
 4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-benzoic acid methyl
 ester,
 (E)-3-{4-[2-Methyl-4-(octahydro-quinoline-1-carbonyl)-2H-pyrazol-3-yl]-phenyl}-acrylic
 20 acid methyl ester,
 [5-(3-Hydroxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
 [5-(3-Methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
 [5-(4-Methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
 (5-Dibenzofuran-4-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone,
 25 [1-Methyl-5-(4-phenoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
 [1-Methyl-5-(2-phenoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
 [5-(3,4-Dimethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
 methanone,
 [1-Methyl-5-(2,3,4-trimethoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
 30 methanone,
 [5-(4-Hydroxymethyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-
 methanone,
 [5-(4-Benzoyloxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
 [5-(3-Benzoyloxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,

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- [5-(6-Ethoxy-naphthalen-2-yl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 5 [5-Benzo[1,3]dioxol-5-yl-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [1-Methyl-5-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [1-Methyl-5-(3-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 10 [1-Methyl-5-(2-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(4-Chloro-2-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(3-Chloro-4-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 15 [5-(2-Chloro-4-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(5-Fluoro-2-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 20 [5-(2-Fluoro-3-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(4-Benzoyloxy-3-chloro-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(2-Chloro-4-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 25 [5-(3-Chloro-4-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- [5-(4-Chloro-2-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 30 [5-(3-Chloro-4-propoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone,
- 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (adamantan-1-ylmethyl)-amide,
- 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid adamantan-1-ylamide,
- 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid hexahydro-2,5-methanopentalen-

3a(1H)-amide,

1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid cycloheptylamide,

1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid ((1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amide,

1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid ((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide,

(2-Ethyl-piperidin-1-yl)-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-methanone,

1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid methyl-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide, and

1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid adamantan-2-yl-isopropyl-amide, and pharmaceutically acceptable salts thereof.

7. The compound according to claim 1, wherein said compound is (1-Methyl-5-phenyl-1H-pyrazol-4-yl)-(trans-octahydro-isoquinolin-2-yl)-methanone.

8. The compound according to claim 1, wherein said compound is [5-(4-Isopropyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone.

9. The compound according to claim 1, wherein said compound is (5-Benzo[b]thiophen-2-yl-1-methyl-1H-pyrazol-4-yl)-(octahydro-quinolin-1-yl)-methanone.

10. The compound according to claim 1, wherein said compound is [5-(2-Chloro-4-methyl-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone.

11. The compound according to claim 1, wherein said compound is [5-(2-Chloro-4-methoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone.

12. The compound according to claim 1, wherein said compound is [5-(2-Chloro-4-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone.

13. The compound according to claim 1, wherein said compound is [5-(3-Chloro-4-ethoxy-phenyl)-1-methyl-1H-pyrazol-4-yl]-(octahydro-quinolin-1-yl)-methanone.

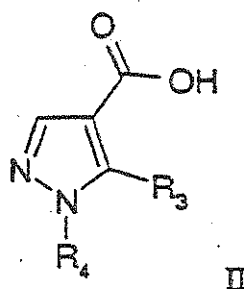
14. The compound according to claim 1, wherein said compound is 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid (adamantan-1-ylmethyl)-amide.

15. The compound according to claim 1, wherein said compound is 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid adamantan-1-ylamide.

16. The compound according to claim 1, wherein said compound is 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid ((1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amide.

17. The compound according to claim 1, wherein said compound is 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid ((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide.

18. A process for the preparation of a compound according to any of claims 1 to 17, which process comprises reacting a compound of formula II



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with a compound HNR^1R^2 , wherein R^1 , R^2 , R^3 and R^4 are as defined in any of claims 1 to 17.

10 19. Compounds according to any of claims 1 to 17, when prepared by a process according to claim 18.

20. Pharmaceutical compositions comprising a compound according to any of claims 1 to 17 and a pharmaceutically acceptable carrier and/or adjuvant.

15 21. Compounds as defined in any of claims 1 to 17 for use as therapeutic active substances.

22. Compounds as defined in any of claims 1 to 17 for use as therapeutic active substances for the treatment and/or prophylaxis of diseases which are modulated by 11β -hydroxysteroid dehydrogenase inhibitors.

23. The use of compounds as defined in any of claims 1 to 17 for the preparation of
medicaments for the therapeutic and/or prophylactic treatment of diseases which are modu-
5 lated by 11β -hydroxysteroid dehydrogenase inhibitors.

24. The use of compounds as defined in any of claims 1 to 17 for the preparation of
medicaments for the therapeutic and/or prophylactic treatment of type II diabetes, obesity
or metabolic syndrome.