

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
18 December 2008 (18.12.2008)

PCT

(10) International Publication Number  
**WO 2008/152093 A2**

(51) International Patent Classification:

*C07D 401/14* (2006.01)    *C07D 417/14* (2006.01)  
*C07D 403/12* (2006.01)    *A61K 31/506* (2006.01)  
*C07D 403/14* (2006.01)    *A61K 31/519* (2006.01)  
*C07D 405/14* (2006.01)    *A61P 15/18* (2006.01)

Berlin (DE). **LINDENTHAL, Bernhard** [DE/DE]; Wilkestr. 19, 13507 Berlin (DE). **LANGER, Gernot** [DE/DE]; Mainstr. 32, 14612 Falkensee (DE). **WINTERMANTEL, Tim** [DE/DE]; Monbijouplatz 9, 10178 Berlin (DE).

(21) International Application Number:

PCT/EP2008/057387

(22) International Filing Date: 12 June 2008 (12.06.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

07075499.9                      13 June 2007 (13.06.2007)    EP

(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(71) Applicant (for all designated States except US): **BAYER SCHERING PHARMA AKTIENGESELLSCHAFT** [DE/DE]; Müllerstr. 178, 13353 Berlin (DE).

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BUCHMANN, Bernd** [DE/DE]; Erdmannstr. 44, 16540 Hohen Neuendorf (DE). **BRÄUER, Nico** [DE/DE]; Reuterallee 7a, 14612 Falkensee (DE). **KOPPITZ, Marcus** [DE/DE]; Scharnhorststr. 28, 10115 Berlin (DE). **PETERS, Olaf** [DE/DE]; Langenhainer Strasse 8, 99891 Tabarz (DE). **TER LAAK, Antonius** [NL/DE]; Hedwigstr. 11, 12159

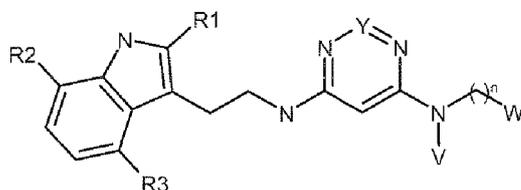
Published:

— without international search report and to be republished upon receipt of that report



WO 2008/152093 A2

(54) Title: DIAMINOPYRIMIDINES AS MODULATORS OF THE EP2 RECEPTOR



(I)

(57) Abstract: The present invention relates to diam inopyrimidines of the general formula I, process for their preparation, and the use thereof for the manufacture of pharmaceutical compositions for the treatment of disorders and indications connected with the EP<sub>2</sub> receptor.

**Diaminopyrimidines as modulators of the EP<sub>2</sub> receptor**

The present invention relates to diaminopyrimidines as EP<sub>2</sub> receptor modulators, processes for their preparation, and their use as medicaments.

5 It has long been known that prostaglandins are key molecules in the processes of female reproductive biology such as, for example, control of ovulation, of fertilization, of nidation, of decidualization (e.g. placenta formation) and of menstruation. Prostaglandins likewise play an important part in the pathological changes in the reproductive tract, including menorrhagia, dysmenorrhea, 10 endometriosis and cancer. The mechanism by which prostaglandins bring about these changes has not yet been completely elucidated. Recent results indicate that prostaglandins, their receptors and signal transduction pathways thereof are involved in processes such as angiogenesis, apoptosis, proliferation, and in inflammatory/antiinflammatory and immunological processes.

15

The effects of prostaglandins are mediated by their G protein-coupled receptors which are located on the cell surface. Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) is of particular interest, having a wide variety of cellular effects through binding to functionally different receptor subtypes, namely the EP<sub>1</sub>, EP<sub>2</sub>, EP<sub>3</sub> and EP<sub>4</sub> receptors. The 20 receptor subtypes to which prostaglandin E<sub>2</sub> binds appear to be of particular interest for the receptor-mediated effects which are involved in the control of fertility. It has thus been possible to show that the reproductive functions in EP<sub>2</sub> knockout mice (EP<sub>2</sub><sup>-/-</sup>), i.e. in mice no longer having a functional PGE<sub>2</sub> receptor of the EP<sub>2</sub> subtype, are impaired, and that these animals have a smaller "litter size" (Matsumoto *et al.*, 2001, *Biology of Reproduction* 64, 1557-1565). It was 25 likewise possible to show that these EP<sub>2</sub> knockout mice (Hizaki *et al.* *Proc Natl Acad Sci U. S. A.* 1999 Aug 31; 96(18):10501-10506) show distinctly reduced cumulus expansion and severe subfertility, which is to be regarded as causally connected with diminished reproductive processes such as ovulation and 30 fertilization.

The EP<sub>2</sub> receptor accordingly represents an important target for developing medicaments for controlling female fertility. The existence of the 4 subclasses of the PGE<sub>2</sub> receptor opens up the possibility of targeted development of 35 selectively active compounds. However, to date, scarcely any selective EP<sub>2</sub> receptor ligands which bind to the EP<sub>2</sub> subtypes of the PGE<sub>2</sub> receptor are known, since most known compounds also bind to the other PGE<sub>2</sub> receptor subtypes such as, for example, to the EP<sub>4</sub> receptor.

EP<sub>2</sub> receptor antagonists are described, for example in the application US2005059742 (Jabbour, Medical Research Council). A method in which an EP<sub>2</sub> and/or an EP<sub>4</sub> antagonist can be employed for the treatment of menorrhagia and dysmenorrhea is claimed. AH6809 is disclosed as antagonist of the EP<sub>2</sub> or EP<sub>4</sub> receptor, but no other specific antagonists and no new compounds are disclosed.

In an earlier application of the same group (EP1467738), EP<sub>2</sub> or EP<sub>4</sub> antagonists are described for the treatment of pathological conditions such as, for example, allergic disorders, Alzheimer's disease, pain, abortion, painful menstruation, menorrhagia and dysmenorrhea, endometriosis, bone disorders, ischemia etc. The described compounds are, however, distinguished by a particularly high affinity for the EP<sub>3</sub> receptor. A further application (WO04/032964) describes novel compounds which are likewise distinguished by a particularly high affinity for the EP<sub>3</sub> receptor, but also have EP<sub>2</sub>-antagonistic effects and which are used for the treatment and prophylaxis of allergic disorders.

Ono Pharmaceutical claims in the application WO03/016254 the preparation of benzene or saturated carboxylic acid derivatives which are substituted by aryl or heterocycles, inter alia as PGE<sub>2</sub> receptor antagonists. The disclosed compounds are claimed for the treatment of a large number of disorders, including allergic disorders, Alzheimer's disease, pain, abortion, painful menstruation, menorrhagia and dysmenorrhea, endometriosis, bone disorders, ischemia etc. The described compounds are, however, distinguished by a particularly high affinity for the EP<sub>3</sub> receptor. A further application (WO04/032964) describes novel compounds which are likewise distinguished by a particularly high affinity for the EP<sub>3</sub> receptor, but also have EP<sub>2</sub>-antagonistic effects and which are used for the treatment and prophylaxis of allergic disorders.

The application WO04/39807 of Merck Frosst, Canada, discloses the preparation of pyridopyrrolizines and pyridoindolizines. However, these compounds are distinguished by good binding to the PGD<sub>2</sub> receptor, and this receptor represents a different subtype of the prostaglandin receptor.

Naphthalene derivatives as EP<sub>4</sub> receptor ligands are disclosed in application US2004102508 of SmithKline Beecham Corporation. The claimed compounds

are used for the treatment or prophylaxis of pain, allergic reactions and neurodegenerative disorders.

5 EP<sub>4</sub> antagonists ( $\gamma$ -lactams) are claimed in the application WO03/103604 (Applied Research Systems). The compounds bind approximately 60-fold better to the EP<sub>4</sub> than to the EP<sub>2</sub> receptor and are claimed inter alia for the treatment of premature labor, dysmenorrhea, asthma, infertility or fertility impairments. The same company claims in the applications WO03/053923 (substituted pyrrolidines) or WO03/035064 (substituted pyrazolidinones) compounds for the  
10 treatment of disorders associated with prostaglandins, such as, for example, infertility, hypertension and osteoporosis. The compounds bind to the EP<sub>4</sub>- and to the EP<sub>2</sub> receptor subtypes. The application WO03/037433 claims  $\omega$ -cycloalkyl, 17 heteroaryl prostaglandin derivatives as EP<sub>2</sub> receptor antagonists, in particular for the treatment of elevated intraocular pressure.

15

The application WO03/064391 (Pfizer Products) describes metabolites of [3-[[N-(4-tert-butylbenzyl)(pyridin-3-ylsulfonyl)amino]methyl]acetic acid which inhibit the binding of [<sup>3</sup>H] prostaglandin E<sub>2</sub> to the EP<sub>2</sub> receptor. The use of these metabolites for the treatment of osteoporosis is disclosed.

20 Tani *et al.* claim in the application US2005124577 8-azaprostaglandin derivatives for the treatment of immunological disorders, allergic disorders, premature labor, abortion, etc. The compounds bind to the EP<sub>2</sub> and to the EP<sub>4</sub> receptor.

25 European patent application EP 1306087 describes EP<sub>2</sub> receptor agonists which are used for the treatment of erectile dysfunction (Ono Pharmaceuticals). The same class of structures is described in European patent EP 860430 (Ono Pharmaceuticals), and their use for the manufacture of a medicament for the treatment of immunological disorders, asthma and abortion is claimed.  
30 WO04/009117 describes EP<sub>2</sub> and EP<sub>4</sub> receptor agonists for the treatment of disorders caused by uterine contraction, for example painful menstruation (Ono Pharmaceuticals).

35 The applications WO03/74483 and WO03/09872 describe agonists which bind equally to the EP<sub>2</sub> and to the EP<sub>4</sub> receptor (Ono Pharmaceuticals).

Agonists of the EP<sub>2</sub> and of the EP<sub>4</sub> receptors are frequently described in connection with the treatment of osteoporosis (WO99/19300 (Pfizer),

US2003/0166631 (Dumont Francis), WO03/77910 (Pfizer), WO03/45371 (Pfizer), WO03/74483 and WO03/09872 (Ono Pharmaceuticals)) and for glaucoma treatment (WO04/37813, WO04/37786, WO04/19938, WO03/103772, WO03/103664, WO03/40123, WO03/47513, WO03/47417 (Merck Frosst Canada)) and US6410591 and US6747037 (Allergan).

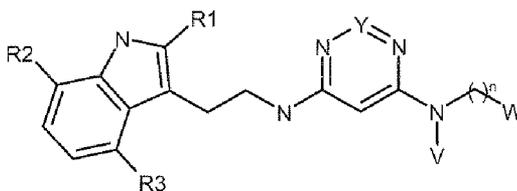
The patent application WO04/12656 (Applied Research Systems) claims EP<sub>2</sub> receptor agonists in connection with inflammation.

The patent application WO03/77919 (Merck & Co. Inc.) claims EP<sub>4</sub> receptor agonists for the treatment of fertility.

However, to date, no selective EP<sub>2</sub> receptor agonists and antagonists which control the processes which are ultimately responsible for ovulation, fertilization, nidation and decidualization and thus contribute to promoting or inhibiting fertility are known.

It is therefore an object of the present invention to provide stable EP<sub>2</sub> receptor antagonists.

This object is achieved by the provision of compounds of the general formula I



where

25

Y is a CH group or a C(C<sub>1</sub>-C<sub>4</sub>-alkyl) group,

V is a hydrogen, a C<sub>1</sub>-C<sub>4</sub>-alkyl group,

30

n is 0, 1 or 2,

W is a 6-10-membered, mono- or bicyclic aryl ring which is in each case unsubstituted or optionally substituted once to three times,

- a 5-10-membered, mono- or bicyclic heteroaryl ring which is in each case unsubstituted or optionally substituted once to three times,
- 5 an 8-12-membered aryl- or heteroaryl-cycloalkyl or -cycloalkenyl group which is in each case unsubstituted or optionally substituted once to three times,
- an 8-12-membered aryl- or heteroaryl-heterocyclyl or -heterocyclenyl group which is in each case unsubstituted or optionally substituted once to three times,
- 10 a 3-12-membered, mono-, bi- or tricyclic cycloalkyl radical which is in each case unsubstituted or optionally substituted once,
- where the substituents are linked either directly or via a spacer U to W and may be selected from the group of halogen, cyano,  $R^4$ ,  $OR^4$ ,  $OC(O)R^4$ ,  $S(O)_nR^4$ , where n is 0,
- 15  $1, 2, SO_2NR^4R^5, SO_2NR^5C(O)R^4, NR^4R^5, NR^5C(O)R^4, NR^5SO_2R^4, C(O)NR^5SO_2R^4, C(OH)R^4R^5, C(O)R^4, C(NOHR^4, CO_2R^4, C(O)NR^4R^5,$
- or
- in the case where n = 0 together with V is a pyrrolidine, piperidine,
- 20 morpholine or thiomorpholine residue which is in each case unsubstituted or optionally substituted once,
- or else
- in the case where n = 0 together with V is a piperazine residue, which is unsubstituted or optionally N-substituted,
- 25 where the substituents are linked either directly or via a spacer U to W and may be selected from the group of halogen, cyano,  $R^4$ ,  $OR^4$ ,  $OC(O)R^4$ ,  $S(O)_nR^4$ , where n is 0,
- $1, 2, SO_2NR^4R^5, SO_2NR^5C(O)R^4, NR^4R^5, NR^5C(O)R^4, NR^5SO_2R^4, C(O)NR^5SO_2R^4, C(OH)R^4R^5, C(O)R^4,$
- 30  $C(NOHR^4, CO_2R^4, C(O)NR^4R^5,$
- U is a  $C_1$ - $C_4$ -alkylene,  $C_2$ - $C_4$ -alkenylidene,  $C_2$ - $C_4$ -alkynylidene,  $O$ - $C_1$ - $C_4$ -alkylene,  $C(O)$ - $C_1$ - $C_4$ -alkylene,  $S(O)_n$ - $C_1$ - $C_4$ -alkylene,

where n is 0, 1, 2, N(R<sup>5</sup>)-C<sub>1</sub>-C<sub>4</sub>-alkylene, C(O)-N(R<sup>5</sup>)-C<sub>1</sub>-C<sub>4</sub>-alkylene, N(R<sup>5</sup>)-C(O)-C<sub>1</sub>-C<sub>4</sub>-alkylene spacer,

- 5 R<sup>1</sup> is a C<sub>1</sub>-C<sub>4</sub>-alkyl group or cyano,
- R<sup>2</sup> is a hydrogen, halogen, cyano, a C<sub>1</sub>-C<sub>4</sub>-alkyl group,
- R<sup>3</sup> is a hydrogen, halogen, cyano, a C<sub>1</sub>-C<sub>4</sub>-alkyl group,
- 10 R<sup>4</sup> is a hydrogen, a C<sub>1</sub>-C<sub>4</sub>-alkyl group, a C<sub>2</sub>-C<sub>4</sub>-alkenyl group, a C<sub>2</sub>-C<sub>4</sub>-alkynyl group, a C<sub>3</sub>-C<sub>6</sub>-cycloalkyl group, a CH<sub>2</sub>-C<sub>3</sub>-C<sub>6</sub>-cycloalkyl group, a 6-membered aryl ring, a 5-6-membered heteroaryl ring or a CH<sub>2</sub>-aryl or heteroaryl group, where the aryl radical is 6-membered and the heteroaryl radical is 5 or 6-membered,
- 15 R<sup>5</sup> is a hydrogen, a C<sub>1</sub>-C<sub>4</sub>-alkyl group and
- R<sup>4</sup>, R<sup>5</sup> together form a 3-6-membered cycloalkyl or a heteroatom-containing ring,
- 20 and the isomers, diastereomers, enantiomers and salts thereof, and cyclodextrin clathrates, which overcome the known disadvantages and have improved properties, i.e. a good activity, good solubility and stability.
- 25 Examples of the C<sub>1</sub>-C<sub>4</sub>-alkyl substituents indicated under V, Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are a methyl, ethyl, *n*-propyl, *n*-butyl group, and of the branched C<sub>3</sub>-C<sub>4</sub>-alkyl groups are an *isopropyl*, *isobutyl*, *sec-butyl*, *tert-butyl* group. The alkyl groups may optionally be substituted once or more than once by halogen atoms (e.g. fluorine, chlorine or bromine).
- 30 The C<sub>2</sub>-C<sub>4</sub>-alkenyl substituents in R<sup>4</sup> are in each case straight-chain or branched, meaning for example the following radicals: vinyl-, allyl-, homoallyl-, (*E*)-but-2-enyl-, (*Z*)-but-2-enyl-, 2-methylvinyl-.

The alkenyl groups may optionally be substituted once or more than once by halogen atoms (e.g. fluorine, chlorine or bromine).

5 The C<sub>2</sub>-C<sub>4</sub>-alkynyl substituents R<sup>4</sup> are in each case straight-chain or branched, meaning for example the following radicals: ethynyl, prop-1-ynyl, but-1-ynyl, but-2-ynyl.

The alkynyl groups may optionally be substituted once by halogen atoms (e.g. fluorine, chlorine or bromine).

10 The C<sub>1</sub>-C<sub>4</sub>-alkylene spacers indicated under U are straight-chain or branched spacers, for example methylene, ethylene, propylene, butylene spacers. The C<sub>1</sub>-C<sub>4</sub>-alkylene spacers may optionally be substituted once or more than once by halogen atoms, (e.g. fluorine, chlorine or bromine).

15 The C<sub>2</sub>-C<sub>4</sub>-alkenylidene spacers in U are in each case straight-chain or branched, meaning for example the following radicals: ethenylidene, propenylidene, butenylidene.

The C<sub>2</sub>-C<sub>4</sub>-alkenylidene groups may be substituted once or more than once by halogen atoms (e.g. fluorine, chlorine or bromine).

20

The C<sub>2</sub>-C<sub>4</sub>-alkynylidene spacers in U are in each case straight-chain or branched, meaning for example the following radicals: ethynylidene, propynylidene, butynylidene.

25 The C<sub>2</sub>-C<sub>4</sub>-alkynylidene groups may optionally be substituted once by halogen atoms (e.g. fluorine, chlorine or bromine).

Halogen means the following: fluorine, chlorine, bromine, iodine.

30 The C<sub>3</sub>-C<sub>12</sub>-cycloalkyl indicated under W takes the form of monocyclic alkyl rings such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, or cyclooctyl, but also bicyclic rings such as, for example, decahydronaphthalene, tricyclic rings or bridged rings such as, for example, adamantanyl, and heteroatom-containing heterocycles such as, for example, aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepanyl, [1,4]-diazepanyl,  
35 tetrahydrofuranyl, thiomorpholinyl.

The C<sub>3</sub>-C<sub>12</sub>-cycloalkyl groups are linked via one of the substitutable positions and may optionally be substituted once to twice by halogen atoms, (e.g. fluorine,

chlorine or bromine) or an oxo group. The N and S atoms may optionally be oxidized to an N-oxide, S-oxide, S,S-dioxide.

5 The C<sub>3</sub>-C<sub>6</sub>-cycloalkyl indicated under R<sup>4</sup> takes the form of alkyl rings such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and of heteroatom-containing heterocycles such as, for example, aziridinyl, azetidiny, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl.

10 The C<sub>3</sub>-C<sub>6</sub>-cycloalkyl groups are linked via one of the substitutable positions and may optionally be substituted once to twice by halogen atoms (e.g. fluorine, chlorine or bromine) or an oxo group. The N and S atoms may optionally be oxidized to an N-oxide, S-oxide, S,S-dioxide.

15 The 6-10-membered, mono- or bicyclic aryl radical which may optionally be substituted once to three times and which is indicated in W is connected to the framework via one of the possible linkage positions. The 6-10-membered, mono- or bicyclic aryl or heteroaryl radical may optionally be substituted once to three times by halogen atoms (e.g. fluorine, chlorine or bromine), C<sub>1</sub>-C<sub>4</sub>-alkyl groups or a hydroxy group.

20 Examples which may be mentioned for a 6-10-membered, mono- or bicyclic aryl radical are the following: phenyl, naphthyl.

25 The 5-10-membered, mono- or bicyclic heteroaryl radical which may optionally be substituted once to three times and which is indicated in W means 5-10-membered ring systems which may, instead of the carbon, comprise one or more, identical or different heteroatoms such as oxygen, nitrogen or sulfur in the ring, may be mono- or bicyclic and are connected to the framework via one of the possible linkage positions. The 5-10-membered, mono- or bicyclic heteroaryl radicals may optionally be substituted once to three times by halogen atoms (e.g. 30 fluorine, chlorine or bromine), C<sub>1</sub>-C<sub>4</sub>-alkyl groups or a hydroxy group. If the heteroaryl radical is substituted by a hydroxy group, the corresponding tautomers are included if the hydroxy group on the heteroaryl radical is capable thereof. The N atoms may optionally be oxidized to an N-oxide.

35 The 5-10-membered, mono- or bicyclic heteroaryl radicals may take the form of a pyridyl, pyrimidyl, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, cinnolinyl, benzofuranyl, benzothienyl, indolyl, benzimidazolyl, 2,1,3-benzothiadiazolyl, 1H-benzotriazolyl, benzothiazolyl, benzoxazolyl,

benzoxazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, isothiazolyl, thiazolyl, isothiazolyl, pyrrolyl, pyrazolyl, pyrazinyl, pyridazinyl, triazinyl, carbazolyl, 1H-pyrazolo[3,4-d]pyrimidyl, 1H-indazolyl, triazolyl, oxadiazolyl, tetrazolyl or an imidazolyl group which is linked via one of the substitutable positions.

5

The 6-membered aryl radical indicated in R<sup>4</sup> is a phenyl radical which may optionally be substituted once to twice by halogen atoms (e.g. fluorine, chlorine or bromine), C<sub>1</sub>-C<sub>4</sub>-alkyl groups or a hydroxy group.

10 The 5-6-membered heteroaryl radical indicated in R<sup>4</sup> means 5-6-membered ring systems which, instead of the carbon, may comprise one or more, identical or different heteroatoms such as oxygen, nitrogen or sulfur in the ring, and are connected to the framework via one of the possible linkage positions. The 5-6-membered heteroaryl radicals may optionally be substituted once to twice by  
15 halogen atoms (e.g. fluorine, chlorine or bromine), C<sub>1</sub>-C<sub>4</sub>-alkyl groups or a hydroxy group. If the heteroaryl radical is substituted by a hydroxy group, the corresponding tautomers are included if the hydroxy group on the heteroaryl radical is capable thereof. The N atoms may optionally be oxidized to an  
20 N-oxide.

20

The 5-6-membered heteroaryl groups may take the form of a pyridyl, pyrimidyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, pyrazolyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, oxadiazolyl, tetrazolyl or an imidazolyl group which is linked via one of the substitutable positions.

25

The 8-12-membered aryl- or heteroaryl-cycloalkyl or -cycloalkenyl groups mentioned under W are unsubstituted or optionally substituted once to three times and comprise optionally instead of the carbon one or more, identical or different heteroatoms such as oxygen, nitrogen or sulfur in the heteroaryl

30 moiety. The nitrogen atoms are optionally oxidized to an N-oxide. The 8-12-membered aryl- or heteroaryl-cycloalkyl or -cycloalkenyl groups are linked via one of the substitutable positions and additionally substituted optionally in the cycloalkyl or cycloalkenyl moiety once to twice by an oxo group. The 8-12-membered aryl- or heteroaryl-cycloalkyl or -cycloalkenyl groups may optionally  
35 be substituted once to three times by halogen atoms (e.g. fluorine, chlorine or bromine) or C<sub>1</sub>-C<sub>4</sub>-alkyl groups.

An aryl-cycloalkyl group is for example 1,2,3,4-tetrahydronaphthalenyl, indanyl, 3,4-dihydro-2H-naphthalen-1-onyl, indan-1-onyl.

A heteroaryl-cycloalkyl group is for example 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-

5 tetrahydroquinoxalinyl, 4,5,6,7-tetrahydro-1H-benzimidazolyl, 4,5,6,7-tetrahydro-benzoxazolyl, 4,5,6,7-tetrahydrobenzthiazolyl, 2,4,5,6-tetrahydrocyclopenta-pyrazolyl.

An aryl-cycloalkenyl group is for example 1,2-dihydronaphthalenyl, 1H-indenyl.

A hetaryl-cycloalkenyl group is for example 5,6-dihydroquinolinyl, 5,6-  
10 dihydroisoquinolinyl, 5,6-dihydroquinazolinyl, 5,6-dihydroquinoxalinyl, 4,5-dihydro-1H-benzimidazolyl, 4,5-dihydrobenzoxazolyl, 4,5-dihydro-benzthiazolyl.

The 8-12-membered aryl- or heteroaryl-heterocyclyl or -heterocyclenyl groups  
15 mentioned under W are unsubstituted or optionally substituted once to three times and comprise one or more, identical or different heteroatoms such as oxygen, nitrogen or sulfur in the heteroaryl and heterocyclyl or heterocyclenyl moiety. The nitrogen atoms in the heteroaryl moiety are optionally oxidized to an N-oxide. The oxygen, nitrogen or sulfur atoms in the heterocyclyl or heterocyclenyl moiety are optionally oxidized to an N-oxide, S-oxide, S,S-  
20 dioxide. The 8-12-membered aryl- or heteroaryl-heterocyclyl or -heterocyclenyl groups are linked via one of the substitutable positions and additionally are optionally substituted in the heterocyclyl or heterocyclenyl moiety once to twice by an oxo group. The 8-12-membered aryl- or heteroaryl-heterocyclyl or -heterocyclenyl groups may optionally be substituted once to three times by  
25 halogen atoms (e.g. fluorine, chlorine or bromine) or C<sub>1</sub>-C<sub>4</sub>-alkyl groups.

An aryl-heterocyclyl group is for example 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinazolinyl, 1,2,3,4-tetrahydroquinoxalinyl, 1,2,3,4-tetrahydrophthalazinyl, 2,3-dihydro-1H-indolyl, 2,3-dihydro-benzofuranyl, 2,3-dihydro-1H-isoindolyl, benzo[1,3]dioxolyl, 2,3-dihydro-  
30 benzoxazolyl, chromanyl, 2,3-dihydrobenzo[1,4]dioxinyl, 2,3-dihydrophthalazine-1,4-dionyl, isoindole-1,3-dionyl, 2-methylisoindole-1,3-dionyl, 2,3-dihydro-isoindol-1-onyl.

A heteroaryl-heterocyclyl group is for example 2,3-dihydro-1H-pyrrol-  
[3,4-b]quinolin-2-yl, 1,2,3,4-tetrahydrobenz[b][1,7]naphthyridin-2-yl, 1,2,3,4-  
35 tetrahydrobenz[b][1,6]naphthyridin-2-yl, 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-2-yl, 1,2,3,4-tetrahydro-9H-pyrido[4,3-b]indol-2-yl, 2,3-dihydro-1H-pyrrolo[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[4,3-b]indol-3-yl, 1H-2,3,4,5-tetrahydro-

azepino[4,5-b]indol-2-yl, 5,6,7,8-tetrahydro[1,7]naphthyridyl, 1,2,3,4-tetrahydro[2,7]naphthyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 3,4-dihydro-2H-1-oxa[4,6]diazanaphthalenyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridyl, 6,7-dihydro[5,8]diazanaphthalenyl, 1,2,3,4-tetrahydro[1,5]-naphthyridinyl, 1,2,3,4-tetrahydro[1,6]naphthyridinyl, 1,2,3,4-tetrahydro[1,7]naphthyridinyl, 1,2,3,4-tetrahydro[1,8]naphthyridinyl, 1,2,3,4-tetrahydro[2,6]naphthyridinyl.

An aryl-heterocyclenyl group is for example 3H-indolinyl, 1H-2-oxoquinolyl, 2H-1-oxoisoquinolyl, 1,2-dihydroquinolinyl, 3,4-dihydroquinolinyl, 10 1,2-dihydroisoquinolinyl, 3,4-dihydroisoquinolinyl, 4H-chromenyl, 4-methylchromen-2-onyl.

A heteroaryl-heterocyclenyl group is for example 7,8-dihydro[1,7]naphthyridinyl, 1,2-dihydro[2,7]-naphthyridinyl, 6,7-dihydro-3H-imidazo[4,5-c]pyridyl, 1,2-dihydro-1,5-naphthyridinyl, 1,2-dihydro-1,6-naphthyridinyl, 1,2-dihydro-1,7-naphthyridinyl, 1,2-dihydro-1,8-naphthyridinyl, 1,2-dihydro-2,6-naphthyridinyl. 15

The 3-6-membered cycloalkyl ring formed by ring closure of R<sup>4</sup> and R<sup>5</sup> may be for example a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

20 Examples of a 3-6-membered, heteroatom-containing ring formed by ring closure of R<sup>4</sup> and R<sup>5</sup> which may be mentioned are the following: aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl. The N and S atoms may optionally be oxidized to an N-oxide, S-oxide, S,S-dioxide.

25 Preference is given to the compounds of the general formula I, where

Y is a CH group or a C(C<sub>1</sub>-C<sub>4</sub>-alkyl) group,

V is a hydrogen, a CH<sub>3</sub> group,

30

n is 0, 1 or 2,

W is a 6-10-membered, mono- or bicyclic aryl ring which is in each case unsubstituted or optionally substituted once to three times, 35 a 5-10-membered, mono- or bicyclic heteroaryl ring which is in each case unsubstituted or optionally substituted once to three times,

an 8-12-membered aryl- or heteroaryl-cycloalkyl or -cycloalkenyl group which is in each case unsubstituted or optionally substituted once to three times,

5 an 8-12-membered aryl- or heteroaryl-heterocyclyl or -heterocyclenyl group which is in each case unsubstituted or optionally substituted once to three times,

a 3-6 membered cycloalkyl radical which is in each case unsubstituted or optionally substituted once,

10 where the substituents are linked either directly or via a spacer U to W and may be selected from the group of halogen, cyano,  $R^4$ ,  $OR^4$ ,  $OC(O)R^4$ ,  $S(O)_nR^4$ , where n is 0, 1, 2,  $SO_2NR^4R^5$ ,  $SO_2NR^5C(O)R^4$ ,  $NR^4R^5$ ,  $NR^5C(O)R^4$ ,  $NR^5SO_2R^4$ ,  $C(O)NR^5SO_2R^4$ ,  $C(OH)R^4R^5$ ,  $C(O)R^4$ ,  $C(NOHR^4)$ ,  $CO_2R^4$ ,  $C(O)NR^4R^5$ ,

15 or

in the case where n = 0 together with V is a pyrrolidine, piperidine, morpholine or thiomorpholine residue which is in each case unsubstituted or optionally substituted once,

or else

20 in the case where n = 0 together with V is a piperazine radical, which is unsubstituted or optionally N-substituted,

25 where the substituents are linked either directly or via a spacer U to W and may be selected from the group of halogen, cyano,  $R^4$ ,  $OR^4$ ,  $OC(O)R^4$ ,  $S(O)_nR^4$ , where n is 0, 1, 2,  $SO_2NR^4R^5$ ,  $SO_2NR^5C(O)R^4$ ,  $NR^4R^5$ ,  $NR^5C(O)R^4$ ,  $NR^5SO_2R^4$ ,  $C(O)NR^5SO_2R^4$ ,  $C(OH)R^4R^5$ ,  $C(O)R^4$ ,  $C(NOHR^4)$ ,  $CO_2R^4$ ,  $C(O)NR^4R^5$ ,

30 U is a  $C_1$ - $C_4$ -alkylene,  $C_2$ - $C_4$ -alkenylidene,  $C_2$ - $C_4$ -alkynylidene,  $O$ - $C_1$ - $C_4$ -alkylene,  $C(O)$ - $C_1$ - $C_4$ -alkylene,  $S(O)_n$ - $C_1$ - $C_4$ -alkylene, where n is 0, 1, 2,  $N(R^5)$ - $C_1$ - $C_4$ -alkylene,  $C(O)$ - $N(R^5)$ - $C_1$ - $C_4$ -alkylene,  $N(R^5)$ - $C(O)$ - $C_1$ - $C_4$ -alkylene spacer,

$R^1$  is a  $C_1$ - $C_4$ -alkyl group or cyano,

- R<sup>2</sup> is a hydrogen, halogen, cyano, a C<sub>1</sub>-C<sub>4</sub>-alkyl group,
- R<sup>3</sup> is a hydrogen, halogen, cyano, a C<sub>1</sub>-C<sub>4</sub>-alkyl group,
- 5 R<sup>4</sup> is a hydrogen, a C<sub>1</sub>-C<sub>4</sub>-alkyl group, a C<sub>2</sub>-C<sub>4</sub>-alkenyl group, a C<sub>2</sub>-C<sub>4</sub>-alkynyl group, a C<sub>3</sub>-C<sub>6</sub>-cycloalkyl group, a CH<sub>2</sub>-C<sub>3</sub>-C<sub>6</sub>-cycloalkyl group, a 6-membered aryl ring, a 5-6-membered heteroaryl ring or a CH<sub>2</sub>-aryl or heteroaryl group, where the aryl radical is 6-
- 10 membered and the heteroaryl radical is 5 or 6-membered,
- R<sup>5</sup> is a hydrogen, a C<sub>1</sub>-C<sub>4</sub>-alkyl group,
- R<sup>4</sup>, R<sup>5</sup> together form a 3-6-membered cycloalkyl or a heteroatom-containing ring.
- 15 Preference is given to the compounds of the general formula I, where
- Y is a CH group or a C(C<sub>1</sub>-alkyl) group,
- 20 V is a hydrogen, a CH<sub>3</sub> group,
- n is 0, 1 or 2,
- 25 W is a 6-10-membered, mono- or bicyclic aryl ring which is in each case unsubstituted or optionally substituted once to three times, a 5-10-membered, mono- or bicyclic heteroaryl ring which is in each case unsubstituted or optionally substituted once to three times,
- 30 an 8-12-membered aryl- or heteroaryl-cycloalkyl or -cycloalkenyl group which is in each case unsubstituted or optionally substituted once to three times,
- 35 an 8-12-membered aryl- or heteroaryl-heterocyclyl or -heterocyclenyl group which is in each case unsubstituted or optionally substituted once to three times,
- a 3-6-membered cycloalkyl radical which is in each case unsubstituted or optionally substituted once,
- where the substituents are linked either directly or via a spacer U to W and may be selected from the group of

halogen, cyano,  $R^4$ ,  $OR^4$ ,  $OC(O)R^4$ ,  $S(O)_nR^4$ , where n is 0, 1, 2,  $SO_2NR^4R^5$ ,  $SO_2NR^5C(O)R^4$ ,  $NR^4R^5$ ,  $NR^5C(O)R^4$ ,  $NR^5SO_2R^4$ ,  $C(O)NR^5SO_2R^4$ ,  $C(OH)R^4R^5$ ,  $C(O)R^4$ ,  $C(NOHR^4)$ ,  $CO_2R^4$ ,  $C(O)NR^4R^5$ ,

5

or

in the case where n = 0 together with V is a pyrrolidine, piperidine, morpholine or thiomorpholine residue which is in each case unsubstituted or optionally substituted once,

10

or else

in the case where n = 0 together with V is a piperazine residue which is unsubstituted or optionally N-substituted,

where the substituents are linked either directly or via a spacer U to W and may be selected from the group of

15

halogen, cyano,  $R^4$ ,  $OR^4$ ,  $OC(O)R^4$ ,  $S(O)_nR^4$ , where n is 0, 1, 2,  $SO_2NR^4R^5$ ,  $SO_2NR^5C(O)R^4$ ,  $NR^4R^5$ ,  $NR^5C(O)R^4$ ,  $NR^5SO_2R^4$ ,  $C(O)NR^5SO_2R^4$ ,  $C(OH)R^4R^5$ ,  $C(O)R^4$ ,  $C(NOHR^4)$ ,  $CO_2R^4$ ,  $C(O)NR^4R^5$ ,

20 U

is a  $C_1$ - $C_4$ -alkylene,  $C_2$ - $C_4$ -alkenylidene,  $C_2$ - $C_4$ -alkynylidene,  $O$ - $C_1$ - $C_4$ -alkylene,  $C(O)$ - $C_1$ - $C_4$ -alkylene,  $S(O)_n$ - $C_1$ - $C_4$ -alkylene, where n is 0, 1, 2,  $N(R^5)$ - $C_1$ - $C_4$ -alkylene,  $C(O)$ - $N(R^5)$ - $C_1$ - $C_4$ -alkylene,  $N(R^5)$ - $C(O)$ - $C_1$ - $C_4$ -alkylene spacer,

25  $R^1$ 

is a  $C_1$ -alkyl group or cyano,

 $R^2$ 

is a hydrogen, halogen, cyano, a  $C_1$ -alkyl group,

 $R^3$ 

is a hydrogen, halogen, cyano, a  $C_1$ -alkyl group,

30

 $R^4$ 

is a hydrogen, a  $C_1$ - $C_4$ -alkyl group, a  $C_2$ - $C_4$ -alkenyl group, a  $C_2$ - $C_4$ -alkynyl group, a  $C_3$ - $C_6$ -cycloalkyl group, a  $CH_2$ - $C_3$ - $C_6$ -cycloalkyl group, a 6-membered aryl ring, a 5-6-membered heteroaryl ring or a  $CH_2$ -aryl or heteroaryl group, where the aryl radical is 6-membered and the heteroaryl radical is 5 or 6-membered,

35

 $R^5$ 

is a hydrogen, a  $C_1$ - $C_4$ -alkyl group and

R<sup>4</sup>, R<sup>5</sup> together form a 3-6-membered cycloalkyl or a heteroatom-containing ring.

- 5 The following compounds corresponding to the present invention are very particularly preferred:
1. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-pyridin-2-ylpyrimidine-4,6-diamine
  - 10 2. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-pyridin-3-ylpyrimidine-4,6-diamine
  3. N-(3-Chlorophenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
  4. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(3-trifluoromethylphenyl)-  
15 pyrimidine-4,6-diamine
  5. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-fluorophenyl)-pyrimidine-4,6-diamine
  6. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-pyridin-3-ylmethylpyrimidine-4,6-diamine
  - 20 7. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-phenylpyrimidine-4,6-diamine
  8. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(2-methoxyphenyl)-pyrimidine-4,6-diamine
  9. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(3-methoxyphenyl)-  
25 pyrimidine-4,6-diamine
  10. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-methoxyphenyl)-pyrimidine-4,6-diamine
  11. N-(4-Chlorophenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
  - 30 12. N-Cyclohexyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]pyrimidine-4,6-diamine
  13. N-(4-Dimethylaminophenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine

14. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-pyrazin-2-ylpyrimidine-4,6-diamine
15. N-Benzyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]pyrimidine-4,6-diamine
- 5 16. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-methoxybenzyl)-pyrimidine-4,6-diamine
17. N-Biphenyl-2-ylmethyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
18. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-[1,2,4]triazol-1-yl-10 phenyl)pyrimidine-4,6-diamine
19. [2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-[6-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)pyrimidin-4-yl]amine
20. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-methylbenzyl)-pyrimidine-4,6-diamine
- 15 21. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-trifluoromethylphenyl)-pyrimidine-4,6-diamine
22. N-Biphenyl-3-ylmethyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
23. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-20 N-thiazol-2-ylbenzenesulfonamide
24. N-(4,6-Dimethylpyrimidin-2-yl)-4-{6-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}benzenesulfonamide
25. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(6-methylpyridin-2-yl)-pyrimidine-4,6-diamine
- 25 26. 5-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-indan-1-one
27. 6-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-3,4-dihydro-2H-naphthalen-1-one
28. 5-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-30 isoindole-1,3-dione
29. 6-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-nicotinamide

30. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-naphthalen-1-yl-pyrimidine-4,6-diamine
31. N-Benzo[1,3]dioxol-5-yl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
- 5 32. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-indol-5-yl)-pyrimidine-4,6-diamine
33. N-(1H-Benzotriazol-5-yl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
34. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-indan-5-ylpyrimidine-4,6-  
10 diamine
35. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-isoindole-1,3-dione
36. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-benzamide
- 15 37. 6-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-2,3-dihydrophthalazine-1,4-dione
38. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(5-methyl-2H-pyrazol-3-yl)pyrimidine-4,6-diamine
39. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-quinolin-3-ylpyrimidine-  
20 4,6-diamine
40. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-quinolin-5-ylpyrimidine-4,6-diamine
41. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-quinolin-8-ylpyrimidine-4,6-diamine
- 25 42. 5-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-2-methylisoindole-1,3-dione
43. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)pyrimidine-4,6-diamine
44. N-(2,5-Dimethyl-2H-pyrazol-3-yl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]pyrimidine-4,6-diamine
- 30 45. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(2-trifluoromethyl-1H-benzoimidazol-5-yl)pyrimidine-4,6-diamine

46. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-[3-(1H-tetrazol-5-yl)-phenyl]pyrimidine-4,6-diamine
47. 3-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-benzenesulfonamide
- 5 48. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-indazol-5-yl)-pyrimidine-4,6-diamine
49. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-indazol-6-yl)-pyrimidine-4,6-diamine
50. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-isoquinolin-1-yl-  
10 pyrimidine-4,6-diamine
51. N-Benzothiazol-6-yl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
52. N-(4-tert-Butylphenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
- 15 53. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(5-trifluoromethylpyridin-2-yl)pyrimidine-4,6-diamine
54. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-isoquinolin-3-yl-pyrimidine-4,6-diamine
55. (4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-  
20 ylamino}phenyl)acetonitrile
56. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(2,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)pyrimidine-4,6-diamine
57. N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]pyrimidine-4,6-diamine
- 25 58. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-phenoxyphenyl)-pyrimidine-4,6-diamine
59. 7-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-4-methylchromen-2-one
60. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(2-methylbenzothiazol-5-  
30 yl)pyrimidine-4,6-diamine
61. [2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl](2-methyl-6-piperidin-1-yl-pyrimidin-4-yl)amine

62. N-Biphenyl-4-yl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
63. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyridin-2-yl-pyrimidine-4,6-diamine
- 5 64. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyridin-3-yl-pyrimidine-4,6-diamine
65. N-(3-Chlorophenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
66. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(3-trifluoromethylphenyl)pyrimidine-4,6-diamine
- 10 67. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-fluorophenyl)-2-methylpyrimidine-4,6-diamine
68. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(2-fluorophenyl)-2-methylpyrimidine-4,6-diamine
- 15 69. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(2-trifluoromethylphenyl)pyrimidine-4,6-diamine
70. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyridin-4-yl-pyrimidine-4,6-diamine
71. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-phenethyl-pyrimidine-4,6-diamine
- 20 72. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyridin-2-ylmethylpyrimidine-4,6-diamine
73. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyridin-3-ylmethylpyrimidine-4,6-diamine
- 25 74. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyridin-4-ylmethylpyrimidine-4,6-diamine
75. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-phenyl-pyrimidine-4,6-diamine
76. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(2-methoxyphenyl)-2-methylpyrimidine-4,6-diamine
- 30 77. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(3-methoxyphenyl)-2-methylpyrimidine-4,6-diamine

78. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-methoxyphenyl)-2-methylpyrimidine-4,6-diamine
79. N-(4-Chlorophenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
- 5 80. N-Cyclohexyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
81. N-(4-Dimethylaminophenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
82. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyrazin-2-yl-pyrimidine-4,6-diamine
- 10 83. N-Benzyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
84. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-methoxybenzyl)-2-methylpyrimidine-4,6-diamine
- 15 85. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(3-methylisothiazol-5-yl)pyrimidine-4,6-diamine
86. [2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-[2-methyl-6-(4-pyridin-2-yl)piperazin-1-yl]pyrimidin-4-yl]amine
87. N-Biphenyl-2-ylmethyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
- 20 88. [2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-[2-methyl-6-(4-pyrimidin-2-yl)piperazin-1-yl]pyrimidin-4-yl]amine
89. [6-(4-Benzylpiperazin-1-yl)-2-methylpyrimidin-4-yl][2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]amine
- 25 90. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(4-[1,2,4]triazol-1-ylphenyl)pyrimidine-4,6-diamine
91. N-(4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}phenyl)acetamide
92. N-(2-Fluorobenzyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
- 30 93. N-Cyclohexylmethyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine

94. N-(4-Fluorobenzyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
95. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(3-trifluoromethylbenzyl)pyrimidine-4,6-diamine
- 5 96. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(4-methylbenzyl)pyrimidine-4,6-diamine
97. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(4-trifluoromethylbenzyl)pyrimidine-4,6-diamine
98. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(4-trifluoromethylphenyl)pyrimidine-4,6-diamine
- 10 99. N-Biphenyl-4-ylmethyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
100. N-Biphenyl-3-ylmethyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
- 15 101. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-N-methylbenzamide
102. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-N-thiazol-2-ylbenzenesulfonamide
103. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-N-pyrimidin-2-ylbenzenesulfonamide
- 20 104. N-(4,6-Dimethylpyrimidin-2-yl)-4-{6-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}benzenesulfonamide
105. N-Acetyl-4-{6-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}benzenesulfonamide
- 25 106. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(6-methylpyridin-2-yl)pyrimidine-4,6-diamine
107. 5-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}indan-1-one
108. 6-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-3,4-dihydro-2H-naphthalen-1-one
- 30 109. 5-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}isoindole-1,3-dione

110. 6-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}nicotinamide
111. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-naphthalen-1-ylpyrimidine-4,6-diamine
- 5 112. N-Benzo[1,3]dioxol-5-yl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
113. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-indol-5-yl)-2-methylpyrimidine-4,6-diamine
114. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-indan-5-yl-2-  
10 methylpyrimidine-4,6-diamine
115. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}isoindole-1,3-dione
116. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}benzamide
- 15 117. 6-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-2,3-dihydrophthalazine-1,4-dione
118. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(5-methyl-2H-pyrazol-3-yl)pyrimidine-4,6-diamine
119. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-quinolin-3-yl-  
20 pyrimidine-4,6-diamine
120. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-quinolin-5-ylpyrimidine-4,6-diamine
121. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-quinolin-6-ylpyrimidine-4,6-diamine
- 25 122. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-quinolin-8-ylpyrimidine-4,6-diamine
123. 5-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-2-methylisoindole-1,3-dione
124. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(1H-  
30 pyrazolo[3,4-d]pyrimidin-4-yl)pyrimidine-4,6-diamine
125. N-(2,5-Dimethyl-2H-pyrazol-3-yl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine

126. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(2-trifluoromethyl-1H-benzimidazol-5-yl)pyrimidine-4,6-diamine
127. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-[3-(1H-tetrazol-5-yl)phenyl]pyrimidine-4,6-diamine
- 5 128. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(6-methoxypyridin-3-yl)-2-methylpyrimidine-4,6-diamine
129. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-[1,3,5]triazin-2-ylpyrimidine-4,6-diamine
130. 3-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methyl-  
10 pyrimidin-4-ylamino}benzenesulfonamide
131. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-indazol-5-yl)-2-methylpyrimidine-4,6-diamine
132. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-indazol-6-yl)-2-methylpyrimidine-4,6-diamine
- 15 133. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-isoquinolin-1-yl-2-methylpyrimidine-4,6-diamine
134. N-Benzothiazol-6-yl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
135. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-[1,2,4]triazin-  
20 3-ylpyrimidine-4,6-diamine
136. N-(4-tert-Butylphenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
137. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(5-trifluoromethylpyridin-2-yl)pyrimidine-4,6-diamine
- 25 138. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-isoquinolin-3-yl-2-methylpyrimidine-4,6-diamine
139. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(2,4,5,6-tetrahydrocyclopentapyrazol-3-yl)pyrimidine-4,6-diamine
140. N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-  
30 indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
141. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(4-phenoxyphenyl)pyrimidine-4,6-diamine

142. 7-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-4-methylchromen-2-one

143. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(2-methyl-benzothiazol-5-yl)pyrimidine-4,6-diamine

5

The present invention relates to the use of the compounds of the invention for manufacturing medicaments which comprise at least one of the compounds of formula I.

10 The present invention likewise relates to medicaments which comprise the compounds of the invention with suitable formulating substances and carriers.

Compared with known prostaglandin E<sub>2</sub> ligands, the novel EP<sub>2</sub> agonists and antagonists are distinguished by greater selectivity and stability.

15

The present invention relates to medicaments for the treatment and prophylaxis of disorders which include fertility impairments, infectious disorders, cancer, viral infections, cardiovascular disorders, elevated intraocular pressure, glaucoma, skeletal system disorders, angiogenetic disorders, uterine contraction impairments, pain, neuroinflammatory disorders, immunomodulatory infections and nephrological disorders.

20

Fertility impairments mean the disorders which lead to no ovulation taking place, no fertilization taking place, that the blastocyte development is impaired, that no nidation of a fertilized oocyte occurs and no decidualization takes place, infectious disorders mean disorders caused by unicellular parasites, cancer means solid tumors and leukemia, viral infections mean for example cytomegalievirus infections, hepatitis, hepatitis B and C and HIV disorders, immunomodulatory infections mean for example avian influenza, cardiovascular disorders mean ischemic reperfusion disorder, stenoses, arterioscleroses and restenoses, angiogenetic disorders mean for example endometriosis and fibrosis, elevated intraocular pressure means glaucoma, uterine contraction impairments mean for example painful menstruation, skeletal system disorders mean osteoporosis, neuroinflammatory disorders mean multiple sclerosis, Alzheimer's disease, pain and nephrological disorders mean glomerulonephritis.

30

35

The present invention likewise relates to medicaments for the treatment and prophylaxis of the disorders detailed above, which comprise at least one compound of the general formula I, and medicaments with suitable formulating substances and carriers.

5

For the compounds of the invention to be used as medicaments they are brought into the form of a pharmaceutical product which, besides the active ingredient, comprises inert organic or inorganic pharmaceutical carrier materials which are suitable for enteral or parenteral administration, such as, for example, 10 water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols etc. The pharmaceutical products may be in solid form, for example as tablets, coated tablets, suppositories, capsules, in semisolid form, for example as ointments, creams, gels, suppositories, emulsions or in liquid form, for example as solutions, suspensions or emulsions.

15

They comprise where appropriate excipients which are intended to act for example as fillers, binders, disintegrants, lubricants, solvents, solubilizers, masking flavors, colorant, emulsifiers. Examples of types of excipients for the purpose of the invention are saccharides (mono-, di-, tri-, oligo-, and/or 20 polysaccharides), fats, waxes, oils, hydrocarbons, anionic, nonionic, cationic natural, synthetic or semisynthetic surfactants. They additionally comprise where appropriate excipients such as preservatives, stabilizers, wetting agents or emulsifiers; salts to modify the osmotic pressure or buffers.

The present invention likewise relates to these pharmaceutical products.

25

It is expedient to produce aerosol solutions for inhalation.

Suitable for oral use are in particular tablets, coated tablets or capsules with talc and/or hydrocarbon carriers or binders, such as, for example, lactose, corn 30 starch or potato starch. Use can also take place in liquid form, such as, for example, as solution to which, where appropriate, a sweetener is added. Clathrates are likewise also suitable for oral use of such compounds, examples of clathrates which may be mentioned being those with alpha-, beta-, gamma-cyclodextrin or else beta-hydroxypropylcyclodextrin.

35

Sterile, injectable, aqueous or oily solutions are used for parenteral administration. Particularly suitable are injection solutions or suspensions, especially aqueous solutions of active compounds in polyethoxylated castor oil.

Examples suitable and customary for vaginal administration are pessaries, tampons or intrauterine device.

- 5 Appropriately prepared crystal suspensions can be used for intraarticular injection.

It is possible to use for intramuscular injection aqueous and oily injection solutions or suspensions and appropriate depot preparations.

10

For rectal administration, the novel compounds can be used in the form of suppositories, capsules, solutions (e.g. in the form of enemas) and ointments both for systemic and for local therapy.

- 15 The novel compounds can be used in the form of aerosols and inhalations for pulmonary administration.

For local use on the eyes, external auditory canal, middle ear, nasal cavity and paranasal sinuses, the novel compounds can be used as drops, ointments and

20

tinctures in appropriate pharmaceutical preparations.

Formulations possible for topical application are gels, ointments, fatty ointments, creams, pastes, dusting powders, milk and tinctures. The dosage of the compounds of the general formula I should in these preparations be 0.01% -

25

20% in order to achieve an adequate pharmacological effect.

The dosage of the active ingredients may vary depending on the route of administration, age and weight of the patient, nature and severity of the disorder to be treated and similar factors. Treatment can take place by single dosages or

30 by a large number of dosages over a prolonged period. The daily dose is 0.5 – 1000 mg, preferably 50 - 200 mg, it being possible to give the dose as a single dose to be administered once or divided into 2 or more daily doses.

- 35 Carrier systems which can be used are also surface-active excipients such as salts of bile acids or animal or vegetable phospholipids, but also mixtures thereof, and liposomes or constituents thereof.

The present invention likewise relates to the formulations and dosage forms described above.

5 Administration of the compounds of the invention can take place by any conventional method, including oral and parenteral, e.g. by subcutaneous or intramuscular injections. The present invention likewise relates to enteral, parenteral, vaginal and oral administrations.

10 The compounds of the invention of the general formula I bind to the EP<sub>2</sub> receptor and have agonistic or antagonistic effect. It is possible to determine whether an agonistic or an antagonistic effect is present by an agonism test (see Example 1.2.1. of the Biological Examples) or by an antagonism test (see Example 1.2.2. of the Biological Examples).

15 Antagonists mean molecules which bind to their corresponding receptors and which inhibit the initiation of the signal transduction pathway(s) coupled to the receptor by the naturally occurring ligand(s). The antagonists normally compete with the naturally occurring ligand of the receptor for binding to the receptor. However, other modifications of the receptor are also possible by molecules  
20 which prevent the signal transduction pathways coupled to the receptor being activated by the naturally occurring ligand(s) (e.g. non-competitive, steric modifications of the receptor).

Receptor antagonists typically bind selectively to their particular receptor and not  
25 to other receptors. They normally have a higher binding affinity than the natural ligand. Although antagonists which have a higher affinity for the receptor than the natural ligand are preferred, it is likewise possible to employ antagonists having a lower affinity. However, other modifications of the receptor are also possible by molecules which prevent the signal transduction pathways coupled  
30 to the receptor being activated by the naturally occurring ligand(s) (e.g. non-competitive, steric modifications of the receptor).

The antagonists preferably bind reversibly to their corresponding receptors.

35 The EP<sub>2</sub> receptor antagonist has a preferred affinity for the EP<sub>2</sub> receptor compared with any other EP receptor. The antagonism is measured in the presence of the natural agonist (PGE<sub>2</sub>).

Agonists mean molecules which bind to their corresponding receptors and normally compete with the naturally occurring ligand of the receptor for binding to the receptor, and which stimulate the initiation of the signal transduction pathway coupled to the receptor. Agonists may also assist the binding of the natural ligand.

Receptor agonists typically bind selectively to their particular receptor and not to other receptors. They normally have a higher binding affinity than the natural ligand. Although agonists which have a higher affinity for the receptor than the natural ligand are preferred, it is likewise possible to employ agonists having a lower affinity.

The agonists preferably bind reversibly to their corresponding receptors.

The EP<sub>2</sub> receptor agonist has a preferred affinity for the EP<sub>2</sub> receptor compared with any other EP receptor.

Agonists are tested via the initiation of the signal transduction and/or physiological effect mediated by the corresponding receptor.

The compounds or low molecular weight substances which bind to a receptor are referred to as ligands. Their binding is normally reversible. Binding of a ligand to the corresponding receptor activates or inactivates the signal transduction pathway coupled to the receptor. The ligand mediates its intracellular effect in this manner. Ligands mean agonists and antagonists of a receptor.

The substance of Example 6 shows no inhibition in the cellular agonism test but a good activity ( $IC_{50} = 1.6 \times 10^{-6} \text{ M}$ ) in the antagonism test.

The present invention likewise relates to the use of the substances of the invention as EP<sub>2</sub> receptor antagonists for the treatment of disorders which are caused by disturbances in the signal transduction chain in which the EP<sub>2</sub> receptor is involved, such as, for example, pain and fertility impairments, and which are likewise suitable for controlling fertility.

The oocyte is surrounded in the preovulatory antral follicle by cumulus cells which form a dense ring of cells around the oocyte. After the lutenizing hormone

peak (LH peak), a series of processes is activated and leads to a large morphological change in this ring of cells composed of cumulus cells. In this case, the cumulus cells form an extracellular matrix which leads to so-called cumulus expansion (Vanderhyden *et al.* Dev Biol. 1990 Aug;140(2):307-317).

- 5 This cumulus expansion is an important constituent of the ovulatory process and of the subsequent possibility of fertilization.

Prostaglandins, and here prostaglandin E<sub>2</sub>, whose synthesis is induced by the LH peak, are of crucial importance in cumulus expansion. Prostanoid EP<sub>2</sub> knockout mice (Hizaki *et al.*. Proc Natl Acad Sci U S A. 1999 Aug 31;96(18):10501-6.) show a distinctly reduced cumulus expansion and severe subfertility, demonstrating the importance of the prostanoid EP<sub>2</sub> receptor for this process.

- 15 The substances of the invention have inhibitory effects in cumulus expansion tests.

The present invention relates to the use of the substances of the invention for controlling fertility.

- 20 The present invention relates to the use of the substances of the invention for inhibiting cumulus expansion and thus ovulation and fertilization for contraception.

Prostaglandins play an important part in angiogenesis (Sales, Jabbour, 2003, 25 Reproduction 126, 559 – 567; Kuwano et al., 2004, FASEB J. 18, 300–310; Kamiyama et al., 2006, Oncogene 25, 7019–7028; Chang et al. 2005, Prostaglandins & other Lipid Mediators 76, 48–58).

Endometriosis is a chronic disorder caused by impairments of blood vessels.

- 30 About 10% of women regularly suffer from heavy bleeding during menstruation, caused by changes in the blood vessels of the endometrium. In addition, structural differences in the blood vessels have been observed, such as, for example, incomplete formation of the smooth muscle cell layer (Abberton *et al.*, 1999, Hum. Reprod. 14, 1072-1079). Since the blood loss during menstruation is partly controlled by constriction of the blood vessels, it is obvious that the 35 defects in the smooth muscles make a substantial contribution to the bleeding.

The present invention relates to the use of the substances of the general formula I for treating endometriosis.

5 Prostaglandins play an important part in uterine contraction, and excessively strong contractions are responsible for painful menstruation (Sales, Jabbour, 2003, *Reproduction* 126, 559 – 567).

The present invention relates to the use of the substances of the general formula I for the treatment of painful menstruation.

10

Increasing research results also demonstrate the importance of EP receptors, and especially of the EP<sub>2</sub> receptor, in a large number of types of cancer (e.g. breast cancer, colon carcinoma, lung cancer, prostate cancer, leukemia, skin cancer), suggesting future possibilities of employing modulators (antagonists or agonists) of the EP<sub>2</sub> receptor for the therapy and prevention (prophylactic and/or adjuvant) of cancer (Fulton et al. *Cancer Res* 2006; 66(20): 9794-7; Castellone et al. *Science* VOL 310 2005, 1504-1510; Chang et al. *Cancer Res* 2005; 65(11): 4496-9); Hull et al. *Mol Cancer Ther* 2004;3(8):1031–9; Richards et al. *J Clin Endocrinol Metab* 88: 2810–2816, 2003; Sinha et al. 2007, *Cancer Res*; 20 67(9):4507–13; Wang et al. 2004, *Seminars in Oncology*, Vol 31, No 1, Suppl 3: pp 64-73), Jain et al. *Cancer Res* 2006; 66(13): 6638-48)).

The present invention relates to the use of the substances of the general formula I for the treatment and prevention of cancers.

25

Prostaglandins also play an important part in processes counteracting osteoporosis. The present invention therefore relates to the use of the substances of the invention for the treatment of osteoporosis.

30 Reinold *et al.* (*J. Clin. Invest.* 115, 673-679 (2005)) describes PGE<sub>2</sub> receptors of the EP<sub>2</sub> subtype as the key signaling elements in inflammatory hyperalgesia. Mice no longer having this receptor (EP<sub>2</sub><sup>-/-</sup>) do not experience spinal inflammatory pain. There is evidence that an inflammatory, increased pain sensitivity can be treated by targeted modulation of EP<sub>2</sub> receptors.

35

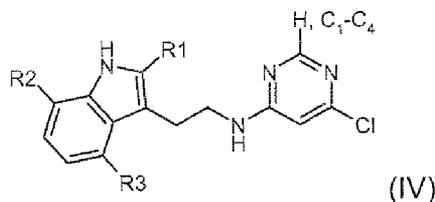
The present invention relates to the use of the substances of the invention for the treatment of inflammatory hyperalgesia.

Prostaglandins are important mediators of inflammatory processes. Recent research results show the involvement of the EP<sub>2</sub> receptor in inflammatory bowel diseases (e.g. Crohn's disease): Sheibanie et al. The Journal of Immunology, 2007, 178: 8138-8147.

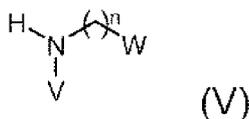
5

The present invention relates to the use of the substances of the invention for the treatment of inflammatory disorders, for example inflammatory bowel diseases, such as Crohn's disease.

10 The invention additionally relates to a process for preparing the compounds of the invention of the general formula I, which comprises reacting a compound of the general formula IV



15 in which R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> have the meanings indicated above, with an amine of the general formula V



20 in which V and W have the meanings indicated above by methods known to the skilled worker.

The reaction of the chloropyrimidine of the general formula IV with an amine of the general formula V can take place in an inert solvent or solvent mixture such as, for example, N,N-dimethylformamide, N,N-dimethylacetamide, toluene, n-butanol, tetrahydrofuran, where appropriate with the addition of an auxiliary base such as, for example, N,N-dimethylaminopyridine, diisopropylethylamine, triethylamine, at temperatures between +20°C and +165°C, preferably at 60°C to 120°C.

30 A further possibility consists of carrying out the reaction of the chloropyrimidine of the general formula IV with an amine of the general formula V in an inert

solvent or solvent mixture such as, for example, N-methylpyrrolidinone, toluene with palladium catalysis (with, for example, Pd(OAc)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd<sub>2</sub>(dba)<sub>3</sub>, PdCl<sub>2</sub>(dppf)) and addition of a base such as, for example, sodium tert-butoxide and of a suitable ligand such as, for example, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl at temperatures between +40°C and +150°C.

In the case where n = 0, W = aryl or heteroaryl in the meanings indicated above, and V = H, a further possibility consists of carrying out the reaction of the chloropyrimidine of the general formula IV with the appropriate amine in an inert solvent or solvent mixture such as, for example, n-butanol, acetonitrile with addition of an acid such as, for example, hydrochloric acid, trifluoroacetic acid, at temperatures between +40°C and +120°C.

The salts are prepared in a conventional way by mixing a solution of the compound of the formula I with the equivalent amount or an excess of a base or acid, which is in solution where appropriate, and separating off the precipitate or working up the solution in a conventional way.

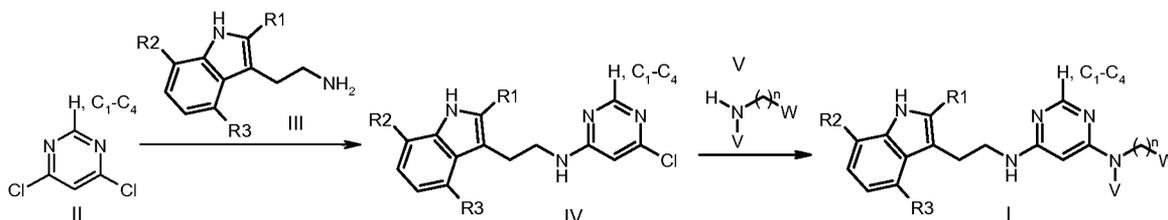
The invention thus also relates to medicaments based on compounds of the general formula I and usual excipients or carriers.

Where the preparation of the starting compounds is not described, they are known or can be prepared in analogy to known compounds or processes described herein. It is likewise possible to carry out all the reactions described herein in parallel reactors or using combinatorial techniques.

The compounds of the invention of the general formula I can be prepared as described in the examples.

Starting from 4,6-dichloropyrimidines of the general formula II, the compounds of the general formula IV can be prepared by reacting with tryptamines of the general formula III by methods known to the skilled worker (scheme 1).

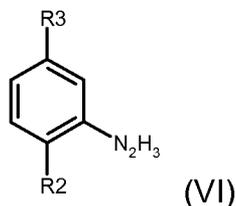
## Scheme 1



5

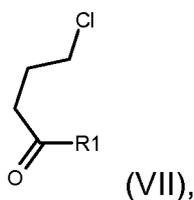
The tryptamines of the general formula III are either known or can be prepared for example by reacting in a manner known per se the known hydrazines VI, where appropriate prepared from the corresponding known anilines by nitrosation followed by a reduction,

10



in which R<sup>2</sup> and R<sup>3</sup> have the meaning indicated above,

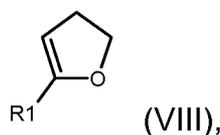
15 a) with a ketone of the general formula VII in which R<sup>1</sup> has the meaning indicated above, in a Fischer indole cyclization



or

20

b) with an enol ether of the general formula VIII in which R<sup>1</sup> has the meaning indicated above, in a Fischer indole cyclization (Org. Lett. 2004, 79ff),



25

and converting the subsequently obtained alcohol by methods known to the skilled worker by conversion into a leaving group such as tosylate, mesylate, trifluoromesylate, chloride, bromide or iodide and subsequent reaction with, for example, sodium azide followed by a hydrolysis with  $\text{PPh}_3/\text{H}_2\text{O}$  in tetrahydrofuran into the amino function.

The compounds of the invention of the general formula I can be prepared by reacting compounds of the general formula IV with amines of the general formula V by processes known to the skilled worker (scheme 1). The further compounds of the general formula I can be obtained by an analogous procedure using homologous reagents to the reagents described in the examples.

The substituents on the radical W of the compounds of the general formula I obtained in this way can be converted by methods known to the skilled worker further into diverse functional groups and thus further compounds of the general formula I.

For example, a bromide or chloride can be replaced by means of palladium(0)-catalyzed reactions by an aryl or heteroaryl ring, a substituted alkene or alkyne, amine or a cyano group.

A carboxy function, cyano group or an amine can be converted into esters and amides of the general formula I for example by methods known to the skilled worker.

It is likewise possible for example to convert ester functions or a cyano group in compounds of the general formula I after reduction to the aldehyde by methods known to the skilled worker into further olefins or secondary alcohols substituted by alkyl or aryl radicals. It is likewise possible for a cyano group in compounds of the general formula I to be converted by methods known to the skilled worker into ketones which are substituted by alkyl or aryl radicals and which can then be reduced to the corresponding secondary alcohols or else can be converted by methods known to the skilled worker into tertiary alcohols substituted by alkyl or aryl radicals.

Abbreviations frequently used:

M            molar

	DMF	N,N-dimethylformamide
	eq	equivalents
	DIPEA	diisopropylethylamine
	MTBE	tert-butyl methyl ether
5	NaCl	sodium chloride
	sat.	saturated
	NMP	N-methylpyrrolidinone
	dba	dibenzylideneacetone
	NaOtBu	sodium tert-butoxide
10	BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

The following examples serve to explain the invention in more detail:

15 General procedure for synthesizing the compounds of the general formula IV by reacting pyrimidines II with tryptamines III

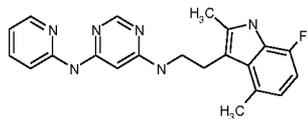
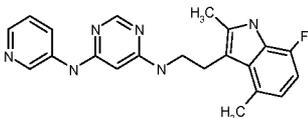
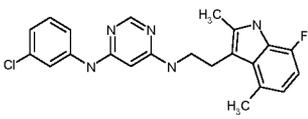
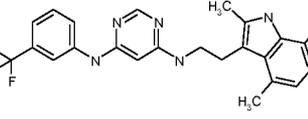
The appropriate tryptamine III is introduced 0.3 M into DMF, 1.2 eq of dichloropyrimidine II and 4 eq of DIPEA are added, and the mixture is stirred at room temperature until conversion of the tryptamine III is complete. The reaction  
20 mixture is poured into water, extracted several times with MTBE and washed with sat. NaCl solution, and the solvent is removed in vacuo. Purification takes place by column chromatography on silica gel with a hexane/ethyl acetate gradient, and the compounds of the general formula IV are obtained.

25 (6-Chloropyrimidin-4-yl)-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]amine IVa  
NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  = 2.23 (3H), 2.54 (3H), 2.92 (2H), 3.41 (2H), 8.25 (1H)

30 (6-Chloro-2-methylpyrimidin-4-yl)-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-  
amine IVb  
NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  = 2.27 (6H), 2.59 (3H), 2.91 (2H), 3.37 (2H), 8.25 (1H)

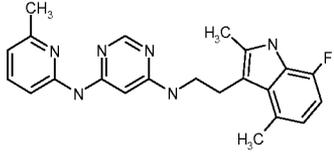
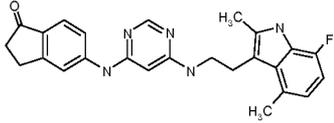
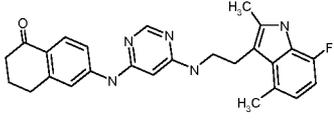
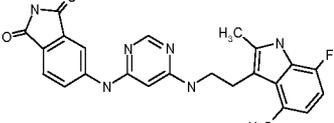
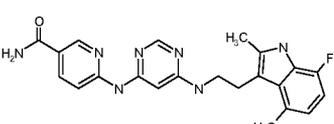
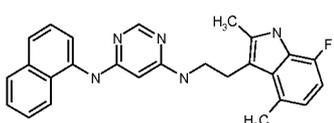
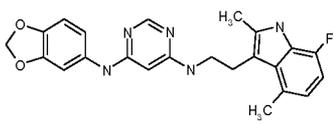
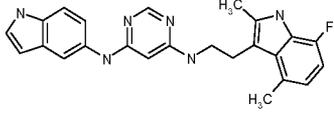
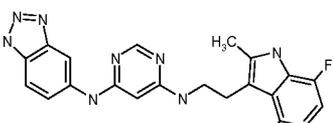
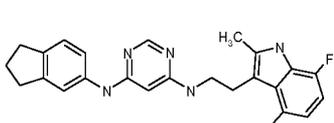
General procedure for synthesizing compounds of the general formula I by Hartwig-Buchwald coupling of the compounds of the type IV with amines V

- The appropriate compound IV is introduced 0.2 M into NMP, 1.5 eq of amine V (0.4 M in NMP), 0.2 eq of palladium catalyst Pd<sub>2</sub>(dba)<sub>3</sub> (0.014 M in NMP), 2.5 eq of NaOtBu (1 M in NMP) and 0.6 eq of rac-BINAP (0.1 M in NMP) are added, and the reaction mixture is heated at 150°C for 1 hour. After cooling, the reaction mixture is concentrated in vacuo and purified by means of preparative HPLC (analytical 4-channel MUX system with CTC Pal injector, Waters 1525 pumps, Waters 2488 UV detector and Waters ZQ 2000 single quad MS detector, column X-Bridge RP C18 4.6x50 3.5µm; detection wavelength 214 nm; flow rate 2 ml/min; eluents A: 0.1% TFA in H<sub>2</sub>O, B 0.1% TFA in ACN; gradient in each case based on B: 1% to 99% (5') to 99% (1') to 1% (0.25') to 1% (1.75'), MS: (M+H)<sup>+</sup>).
- The following compounds were synthesized by way of example according to this general reaction procedure: 1 - 143.

Example	Structure	HPLC Retention time	MW (calc.)	MW (found)
1		3.34	376.4369	377
2		2.56	376.4369	377
3		3.54	409.8939	411
4		3.77	443.4459	444

5		3.49	393.4389	394
6		2.52	390.4637	391
7		3.46	375.4488	376
8		3.41	405.4746	406
9		3.39	405.4746	406
10		3.54	405.4746	406
11		3.67	409.8939	411
12		3.59	381.4962	382
13		2.81	418.5173	420
14		3.17	377.425	378

15		3.52	389.4756	390
16		3.46	419.5014	421
17		3.95	465.5732	467
18		2.96	442.4997	443
19		3.22	446.5313	448
20		3.63	403.5024	405
21		3.84	443.4459	444
22		3.89	465.5732	467
23		2.94	537.6416	539
24		3.02	560.6551	562

25		3.42	390.4637	391
26		3.24	429.4966	430
27		3.36	443.5234	445
28		2.92	444.4679	445
29		2.99	419.4618	420
30		3.74	425.5086	427
31		3.56	419.4578	420
32		3.33	414.4857	415
33		2.81	416.4619	417
34		3.89	415.5134	417

35		3.11	444.4679	445
36		3.23	418.4737	419
37		3.31	459.4828	460
38		3.12	379.4408	380
39		3.03	426.4967	427
40		2.64	426.4967	427
41		3.42	426.4967	427
42		3.22	458.4947	459
43		3.01	417.45	418
44		2.9	393.4676	394
45		3.3	483.4709	484

46		3.09	443.4878	444
47		2.99	454.5277	456
48		2.96	415.4738	416
49		3.17	415.4738	416
50		3.81	426.4967	427
51		3.11	432.5249	434
52		3.94	431.556	433
53		3.79	444.434	445
54		3.77	426.4967	427
55		3.26	414.4857	415
56		3.61	405.4786	406

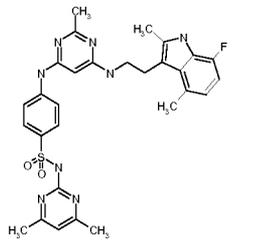
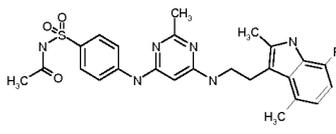
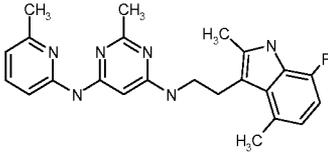
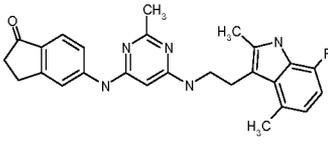
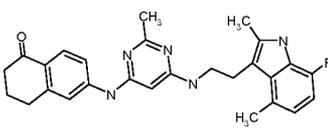
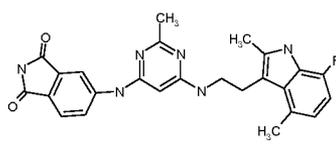
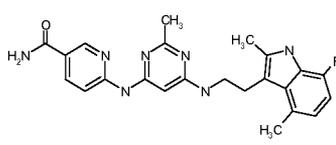
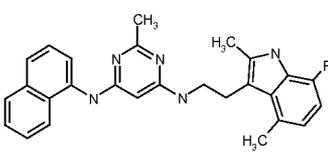
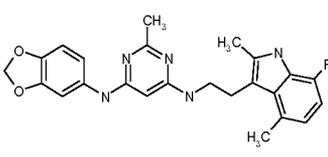
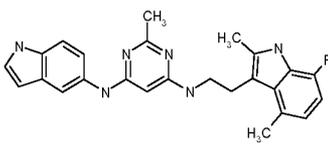
57		3.43	433.4846	434
58		3,94	467,5454	469
59		3.21	457.5066	459
60		3.26	446.5517	448
61		3.85	381.4962	382
62		4.2	465.5732	467
63		3.48	390.4637	391
64		2.64	390.4637	391
65		3.86	423.9207	425

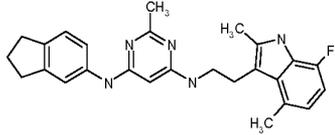
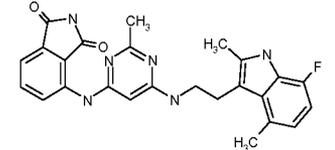
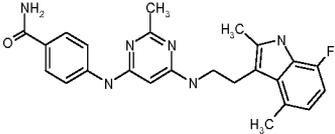
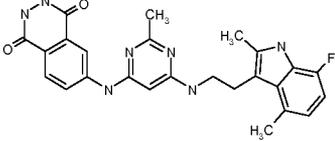
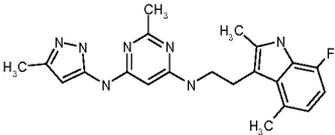
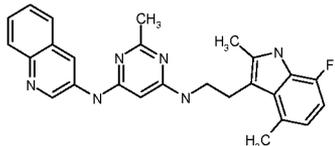
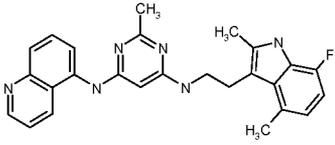
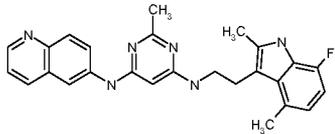
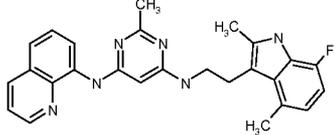
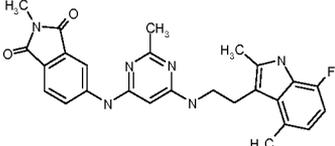
66		3.99	457.4727	458
67		3.53	407.4657	408
68		3.52	407.4657	408
69		3.61	457.4727	458
70		2.96	390.4637	391
71		3,69	417,5292	419
72		2.82	404.4905	405
73		2.57	404.4905	405
74		2.77	404.4905	405
75		3.53	389.4756	390

76		3.56	419.5014	421
77		3.62	419.5014	421
78		3.79	419.5014	421
79		3.73		425
80		3.77	395.523	397
81		3.01	432.5441	434
82		3.16	391.4518	392
83		3.61	403.5024	405
84		3.54	433.5282	435
85		3.36	410.5187	412

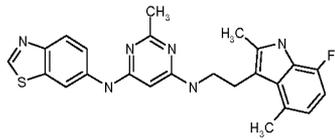
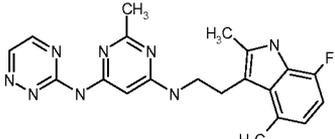
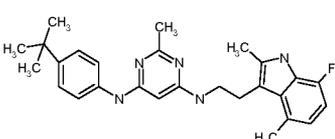
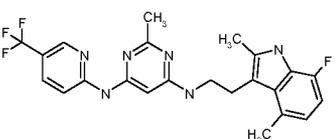
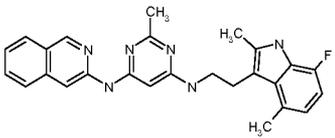
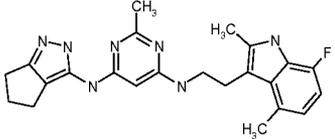
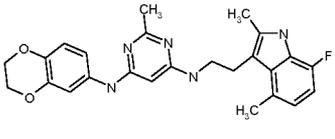
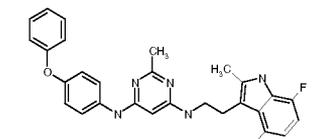
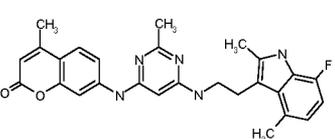
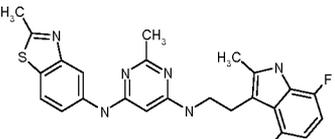
86		2.64	459.57	461
87		3.99	479.6	481
88		3.24	460.5581	462
89		3.15	472.6087	474
90		3.12	456.5265	458
91		3.06	446.5273	448
92		3.61	421.4925	422
93		4.26	409.5498	411
94		3.76	421.4925	422

95		3.84	471.4995	472
96		3.73	417.5292	419
97		3.97	471.4995	472
98		3.83	457.4727	458
99		4.04	479.6	481
100		3.99	479.6	481
101		3.09	446.5273	448
102		3.04	551.6684	553
103		3.11	546.6283	548

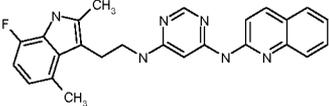
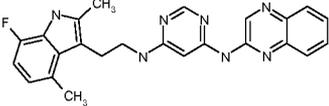
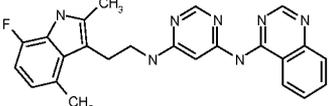
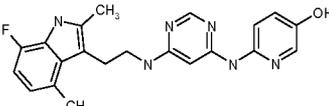
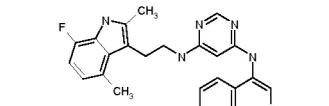
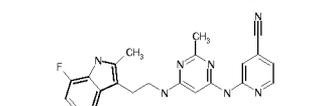
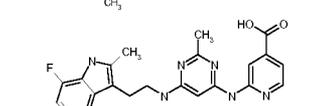
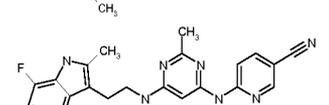
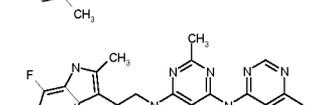
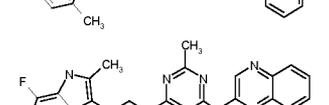
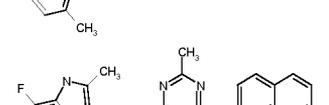
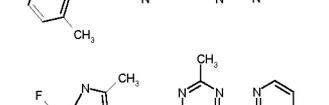
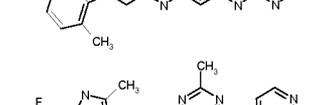
104		3.17	574.6819	576
105		3.22	510.5913	512
106		3.66	404.4905	405
107		3.24	443.5234	445
108		3.52	457.5502	459
109		3.14	458.4947	459
110		3.07	433.4886	434
111		3.73	439.5354	441
112		3.57	433.4846	434
113		3.44	428.5125	430

114		3.86	429.5402	431
115		3.24	458.4947	459
116		3.38	432.5005	434
117		3.49	473.5096	475
118		3.42	393.4676	394
119		3.34	440.5235	442
120		2.71	440.5235	442
121		2.69	440.5235	442
122		3.61	440.5235	442
123		3.4	472.5215	474

124		3.11	431.4768	432
125		3.04	407.4944	408
126		3.29	497.4977	498
127		3.29	457.5146	459
128		3.28	420.4895	421
129		2.96	392.4399	393
130		3.09	468.5545	470
131		3.26	429.5006	431
132		3.16	429.5006	431
133		3.76	440.5235	442

134		3.34	446.5517	448
135		3.11	392.4399	393
136		4.08	445.5828	447
137		3.86	458.4608	459
138		3.97	440.5235	442
139		3.49	419.5054	421
140		3.49	447.5114	449
141		3.98	481.5722	483
142		3.37	471.5334	473
143		3.39	460.5785	462

144		0.89	391,443	392
145		1.02	390,459	391
146		1.05	390,459	391
147		0.97	401,442	402
148		0.94	377,42	378
149		0.88	421,43	422
150		0.98	401,442	402
151		0.93	392,431	393
152		0.9	420,442	421
153		0.93	420,442	421
154		0.91	420,442	421
155		0.93	482,576	483
156		0.98	392,431	393
157		0.89	377,42	378

158		1.1	426,491	427
159		1.08	427,479	428
160		0.98	427,479	428
161		0.8	392,431	393
162		0.82	426,491	427
163		0.85	415,468	416
164		0.82	434,468	435
165		0.83	415,468	416
166		0.83	441,506	442
167		0.9	441,506	442
168		1.0	440,518	441
167		0.77	391,447	392
168		0.9	391,447	392

### Biological Examples:

#### 1. Detection of the antagonism of the human prostaglandin E<sub>2</sub> (subtype EP<sub>2</sub>) receptor signal

##### 1.1 Principle of detection

- 5 The binding of PGE<sub>2</sub> to the EP<sub>2</sub> subtype of the human PGE<sub>2</sub> receptor induces activation of membrane-associated adenylate cyclases and leads to the formation of cAMP. In the presence of the phosphodiesterase inhibitor IBMX, cAMP which has accumulated due to this stimulation and been released by cell lysis is employed in a competitive detection method. In this assay, the cAMP in  
10 the lysate competes with cAMP-XL665 for binding of an Eu cryptate-labelled anti-cAMP antibody.

This results, in the absence of cellular cAMP, in a maximum signal which derives from coupling of this antibody to the cAMP-XL665 molecule. After excitation at  
15 337 nm, this results in a FRET (fluorescence resonance energy transfer)-based, long-lived emission signal at 665 nm (and at 620 nm). The two signals are measured in a suitable measuring instrument with a time lag, i.e. after the background fluorescence has declined. Any increase in the low FRET signal caused by prostaglandin E<sub>2</sub> addition (measured as well ratio change =  
20  $\text{emission}_{665 \text{ nm}} / \text{emission}_{620 \text{ nm}} * 10\,000$ ) shows the effect of antagonists.

##### 1.2. Detection method

###### 1.2.1 Antagonism assay (data for each well of a 384-well plate):

The substance solutions (0.75 µl) introduced into an assay plate and 30%  
25 DMSO are dissolved in 16 µl of a KRSEB+IBMX stimulation solution (1 X Krebs-Ringer Bicarbonate Buffer; Sigma-Aldrich # K-4002; including 750 µM 3-isobutyl-1-methylxanthine Sigma-Aldrich # I-7018), and then 15 µl thereof are transferred into a media-free cell culture plate which has been washed with KRSEB shortly beforehand.

30 After preincubation at room temperature (RT) for 30 minutes, 5 µl of a 4 x PGE<sub>2</sub> solution (11 nM) are added, and incubation is carried out in the presence of the agonist at RT for a further 60 min (volume: ~20 µl) before the reaction is then stopped by adding 5 µl of lysis buffer and incubated at RT for a further 20 min (volume: ~25 µl). The cell lysate is then transferred into a measuring plate and  
35 measured in accordance with the manufacturer's information (cyclic AMP kit Cisbio International # 62AMPPEC).

###### 1.2.2 Agonism assay (data for each well of a 384-well plate):

The substance solutions (0.75  $\mu$ l) introduced into an assay plate and 30% DMSO are dissolved in 16  $\mu$ l of a KRSE+IBMX stimulation solution (1 X Krebs-Ringer Bicarbonate Buffer; Sigma-Aldrich # K-4002; including 750  $\mu$ M 3-isobutyl-  
5 1-methylxanthine Sigma-Aldrich # I-7018), and then 15  $\mu$ l thereof are transferred into a media-free cell culture plate which has been washed with KRSE shortly beforehand.

After incubation at room temperature (RT; volume: ~15  $\mu$ l) for 60 minutes, the reaction is then stopped by adding 5  $\mu$ l of lysis buffer and incubated at RT for a  
10 further 20 min (volume: ~20  $\mu$ l). The cell lysate is then transferred into a measuring plate and measured in accordance with the manufacturer's information (cyclic AMP kit Cisbio International # 62AMPPEC).

## 15 2. The EP<sub>2</sub> subtype of the PGE<sub>2</sub> receptor and the preovulatory cumulus expansion

### 2.1. Background:

In the preovulatory antral follicle, the oocyte is surrounded by cumulus cells  
20 which form a dense ring of cells around the oocyte. After the LH peak (lutening hormone), a series of processes is activated and leads to a large morphological change in this ring of cells composed of cumulus cells. In this case, the cumulus cells form an extracellular matrix which leads to so-called cumulus expansion (Vanderhyden *et al.* Dev Biol. 1990 Aug;140(2):307-317). This cumulus  
25 expansion is an important component of the ovulatory process and of the subsequent possibility of fertilization.

Prostaglandins, and here prostaglandin E<sub>2</sub>, whose synthesis is induced by the LH peak, are of crucial importance in cumulus expansion. Prostanoid EP<sub>2</sub> knockout mice (Hizaki *et al.* Proc Natl Acad Sci U S A. 1999 Aug  
30 31;96(18):10501-6.) show a markedly reduced cumulus expansion and severe subfertility, demonstrating the importance of the prostanoid EP<sub>2</sub> receptor for this process.

### 2.2 Cumulus expansion assay *in vitro*

35 Folliculogenesis is induced in immature female mice at an age of 14-18 days by a single dose (intraperitoneal) of 5-10 I.U. of PMSG (Pregnant Mare Serum Gonadotropine; Sigma G-4877, Lot 68H0909). 47-50 hours after the injection,

the ovaries are removed and the cumulus-oocyte complexes are removed. The cumulus complex is not yet expanded at this stage.

The cumulus-oocyte complexes are then incubated with prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) (0.3 μM), vehicle control (ethanol) or test substances for 20-24 hours.

- 5 Medium: alpha-MEM medium with 0.1 mM IBMX, pyruvates (0.23 mM) glutamines (2 mM), pen/strep 100 IU/ml pen. and 100 μg/ml strep.) and HSA (8 mg/ml)). Cumulus expansion is then established through the division into four stages (according to Vanderhyden *et al.* Dev Biol. 1990 Aug;140(2):307-317).

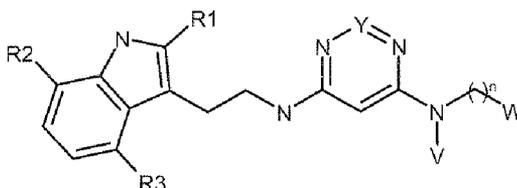
10

Table 1: Example of the biological activity of the compounds of the invention (measured by the cAMP antagonism assay):

Substance of Example	Antagonism [IC <sub>50</sub> , μM]
6	1.6
17	1.4

**Claims:**

1. A compound of the formula I



5

where

Y is a CH group or a C(C<sub>1</sub>-C<sub>4</sub>-alkyl) group,

10 V is a hydrogen, a C<sub>1</sub>-C<sub>4</sub>-alkyl group,

n is 0, 1 or 2,

15 W is a 6-10-membered, mono- or bicyclic aryl ring which is in each case unsubstituted or optionally substituted once to three times, a 5-10-membered, mono- or bicyclic heteroaryl ring which is in each case unsubstituted or optionally substituted once to three times,

20 an 8-12-membered aryl- or heteroaryl-cycloalkyl or -cycloalkenyl group which is in each case unsubstituted or optionally substituted once to three times,

an 8-12-membered aryl- or heteroaryl-heterocyclyl or -heterocyclenyl group which is in each case unsubstituted or optionally substituted once to three times,

25 a 3-12-membered, mono-, bi- or tricyclic cycloalkyl radical which is in each case unsubstituted or optionally substituted once,

30 where the substituents are linked either directly or via a spacer U to W and may be selected from the group of halogen, cyano, R<sup>4</sup>, OR<sup>4</sup>, OC(O)R<sup>4</sup>, S(O)<sub>n</sub>R<sup>4</sup>, where n is 0, 1, 2, SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, SO<sub>2</sub>NR<sup>5</sup>C(O)R<sup>4</sup>, NR<sup>4</sup>R<sup>5</sup>, NR<sup>5</sup>C(O)R<sup>4</sup>,

$\text{NR}^5\text{SO}_2\text{R}^4$ ,  $\text{C}(\text{O})\text{NR}^5\text{SO}_2\text{R}^4$ ,  $\text{C}(\text{OH})\text{R}^4\text{R}^5$ ,  $\text{C}(\text{O})\text{R}^4$ ,  
 $\text{C}(\text{NOH})\text{R}^4$ ,  $\text{CO}_2\text{R}^4$ ,  $\text{C}(\text{O})\text{NR}^4\text{R}^5$ ,

or

in the case where  $n = 0$  together with V is a pyrrolidine, piperidine,  
 5 morpholine or thiomorpholine residue which is in each case  
 unsubstituted or optionally substituted once,

or else

in the case where  $n = 0$  together with V is a piperazine residue,  
 which is unsubstituted or optionally N-substituted,

10 where the substituents are linked either directly or via a  
 spacer U to W and may be selected from the group of  
 halogen, cyano,  $\text{R}^4$ ,  $\text{OR}^4$ ,  $\text{OC}(\text{O})\text{R}^4$ ,  $\text{S}(\text{O})_n\text{R}^4$ , where  $n$  is 0,  
 1, 2,  $\text{SO}_2\text{NR}^4\text{R}^5$ ,  $\text{SO}_2\text{NR}^5\text{C}(\text{O})\text{R}^4$ ,  $\text{NR}^4\text{R}^5$ ,  $\text{NR}^5\text{C}(\text{O})\text{R}^4$ ,  
 $\text{NR}^5\text{SO}_2\text{R}^4$ ,  $\text{C}(\text{O})\text{NR}^5\text{SO}_2\text{R}^4$ ,  $\text{C}(\text{OH})\text{R}^4\text{R}^5$ ,  $\text{C}(\text{O})\text{R}^4$ ,  
 15  $\text{C}(\text{NOH})\text{R}^4$ ,  $\text{CO}_2\text{R}^4$ ,  $\text{C}(\text{O})\text{NR}^4\text{R}^5$ ,

U is a  $\text{C}_1$ - $\text{C}_4$ -alkylene,  $\text{C}_2$ - $\text{C}_4$ -alkenylidene,  $\text{C}_2$ - $\text{C}_4$ -alkynylidene,  
 O- $\text{C}_1$ - $\text{C}_4$ -alkylene,  $\text{C}(\text{O})$ - $\text{C}_1$ - $\text{C}_4$ -alkylene,  $\text{S}(\text{O})_n$ - $\text{C}_1$ - $\text{C}_4$ -alkylene,  
 where  $n$  is 0, 1, 2,  $\text{N}(\text{R}^5)$ - $\text{C}_1$ - $\text{C}_4$ -alkylene,  $\text{C}(\text{O})$ - $\text{N}(\text{R}^5)$ - $\text{C}_1$ - $\text{C}_4$ -  
 20 alkylene,  $\text{N}(\text{R}^5)$ - $\text{C}(\text{O})$ - $\text{C}_1$ - $\text{C}_4$ -alkylene spacer,

$\text{R}^1$  is a  $\text{C}_1$ - $\text{C}_4$ -alkyl group or cyano,

$\text{R}^2$  is a hydrogen, halogen, cyano, a  $\text{C}_1$ - $\text{C}_4$ -alkyl group,  
 25

$\text{R}^3$  is a hydrogen, halogen, cyano, a  $\text{C}_1$ - $\text{C}_4$ -alkyl group,

$\text{R}^4$  is a hydrogen, a  $\text{C}_1$ - $\text{C}_4$ -alkyl group, a  $\text{C}_2$ - $\text{C}_4$ -alkenyl group, a  $\text{C}_2$ - $\text{C}_4$ -  
 alkynyl group, a  $\text{C}_3$ - $\text{C}_6$ -cycloalkyl group, a  $\text{CH}_2$ - $\text{C}_3$ - $\text{C}_6$ -cycloalkyl  
 30 group, a 6-membered aryl ring, a 5-6-membered heteroaryl ring or  
 a  $\text{CH}_2$ -aryl or heteroaryl group, where the aryl radical is  
 6-membered and the heteroaryl radical is 5 or 6-membered,

R<sup>5</sup> is a hydrogen, a C<sub>1</sub>-C<sub>4</sub>-alkyl group and

R<sup>4</sup>, R<sup>5</sup> together form a 3-6-membered cycloalkyl or a heteroatom-containing ring,

5 and the isomers, diastereomers, enantiomers and salts thereof, and cyclodextrin clathrates.

2. A compound as claimed in claim 1, where  
where

10

Y is a CH group or a C(C<sub>1</sub>-C<sub>4</sub>-alkyl) group,

V is a hydrogen, a CH<sub>3</sub> group,

15

n is 0, 1 or 2,

W is a 6-10-membered, mono- or bicyclic aryl ring which is in each case unsubstituted or optionally substituted once to three times, a 5-10-membered, mono- or bicyclic heteroaryl ring which is in each case unsubstituted or optionally substituted once to three times,  
an 8-12-membered aryl- or heteroaryl-cycloalkyl or -cycloalkenyl group which is in each case unsubstituted or optionally substituted once to three times,

25

an 8-12-membered aryl- or heteroaryl-heterocyclyl or -heterocyclenyl group which is in each case unsubstituted or optionally substituted once to three times,  
a 3-6 membered cycloalkyl radical which is in each case unsubstituted or optionally substituted once,

30

where the substituents are linked either directly or via a spacer U to W and may be selected from the group of halogen, cyano, R<sup>4</sup>, OR<sup>4</sup>, OC(O)R<sup>4</sup>, S(O)<sub>n</sub>R<sup>4</sup>, where n is 0, 1, 2, SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, SO<sub>2</sub>NR<sup>5</sup>C(O)R<sup>4</sup>, NR<sup>4</sup>R<sup>5</sup>, NR<sup>5</sup>C(O)R<sup>4</sup>, NR<sup>5</sup>SO<sub>2</sub>R<sup>4</sup>, C(O)NR<sup>5</sup>SO<sub>2</sub>R<sup>4</sup>, C(OH)R<sup>4</sup>R<sup>5</sup>, C(O)R<sup>4</sup>,  
35 C(NO<sub>2</sub>)R<sup>4</sup>, CO<sub>2</sub>R<sup>4</sup>, C(O)NR<sup>4</sup>R<sup>5</sup>,

or

in the case where  $n = 0$  together with V is a pyrrolidine, piperidine, morpholine or thiomorpholine residue which is in each case unsubstituted or optionally substituted once,

5

or else

in the case where  $n = 0$  together with V is a piperazine radical, which is unsubstituted or optionally N-substituted,

where the substituents are linked either directly or via a spacer U to W and may be selected from the group of

10

halogen, cyano,  $R^4$ ,  $OR^4$ ,  $OC(O)R^4$ ,  $S(O)_nR^4$ , where  $n$  is 0, 1, 2,  $SO_2NR^4R^5$ ,  $SO_2NR^5C(O)R^4$ ,  $NR^4R^5$ ,  $NR^5C(O)R^4$ ,  $NR^5SO_2R^4$ ,  $C(O)NR^5SO_2R^4$ ,  $C(OH)R^4R^5$ ,  $C(O)R^4$ ,  $C(NOHR^4)$ ,  $CO_2R^4$ ,  $C(O)NR^4R^5$ ,

15

U

is a  $C_1$ - $C_4$ -alkylene,  $C_2$ - $C_4$ -alkenylidene,  $C_2$ - $C_4$ -alkynylidene,  $O$ - $C_1$ - $C_4$ -alkylene,  $C(O)$ - $C_1$ - $C_4$ -alkylene,  $S(O)_n$ - $C_1$ - $C_4$ -alkylene, where  $n$  is 0, 1, 2,  $N(R^5)$ - $C_1$ - $C_4$ -alkylene,  $C(O)$ - $N(R^5)$ - $C_1$ - $C_4$ -alkylene,  $N(R^5)$ - $C(O)$ - $C_1$ - $C_4$ -alkylene spacer,

20

$R^1$

is a  $C_1$ - $C_4$ -alkyl group or cyano,

$R^2$

is a hydrogen, halogen, cyano, a  $C_1$ - $C_4$ -alkyl group,

$R^3$

is a hydrogen, halogen, cyano, a  $C_1$ - $C_4$ -alkyl group,

25

$R^4$

is a hydrogen, a  $C_1$ - $C_4$ -alkyl group, a  $C_2$ - $C_4$ -alkenyl group, a  $C_2$ - $C_4$ -alkynyl group, a  $C_3$ - $C_6$ -cycloalkyl group, a  $CH_2$ - $C_3$ - $C_6$ -cycloalkyl group, a 6-membered aryl ring, a 5-6-membered heteroaryl ring or a  $CH_2$ -aryl or heteroaryl group, where the aryl radical is 6-membered and the heteroaryl radical is 5 or 6-membered,

30

$R^5$

is a hydrogen, a  $C_1$ - $C_4$ -alkyl group,

35

$R^4$ ,  $R^5$

together form a 3-6-membered cycloalkyl or a heteroatom-containing ring.

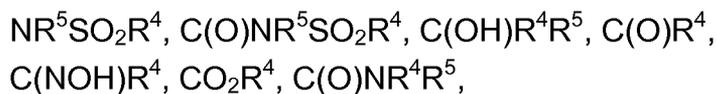
3. A compound as claimed in claim 1-2, where

Y is a CH group or a C(C<sub>1</sub>-alkyl) group,

5 V is a hydrogen, a CH<sub>3</sub> group,

n is 0, 1 or 2,

10 W is a 6-10-membered, mono- or bicyclic aryl ring which is in each case unsubstituted or optionally substituted once to three times, a 5-10-membered, mono- or bicyclic heteroaryl ring which is in each case unsubstituted or optionally substituted once to three times,  
15 an 8-12-membered aryl- or heteroaryl-cycloalkyl or -cycloalkenyl group which is in each case unsubstituted or optionally substituted once to three times,  
an 8-12-membered aryl- or heteroaryl-heterocyclyl or  
-heterocyclenyl group which is in each case unsubstituted or optionally substituted once to three times,  
20 a 3-6-membered cycloalkyl radical which is in each case unsubstituted or optionally substituted once, where the substituents are linked either directly or via a spacer U to W and may be selected from the group of halogen, cyano, R<sup>4</sup>, OR<sup>4</sup>, OC(O)R<sup>4</sup>, S(O)<sub>n</sub>R<sup>4</sup>, where n is 0, 1, 2, SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, SO<sub>2</sub>NR<sup>5</sup>C(O)R<sup>4</sup>, NR<sup>4</sup>R<sup>5</sup>, NR<sup>5</sup>C(O)R<sup>4</sup>, NR<sup>5</sup>SO<sub>2</sub>R<sup>4</sup>, C(O)NR<sup>5</sup>SO<sub>2</sub>R<sup>4</sup>, C(OH)R<sup>4</sup>R<sup>5</sup>, C(O)R<sup>4</sup>, NR<sup>5</sup>C(O)R<sup>4</sup>, CO<sub>2</sub>R<sup>4</sup>, C(O)NR<sup>4</sup>R<sup>5</sup>,  
25 or  
in the case where n = 0 together with V is a pyrrolidine, piperidine, morpholine or thiomorpholine residue which is in each case  
30 unsubstituted or optionally substituted once,  
or else  
in the case where n = 0 together with V is a piperazine residue which is unsubstituted or optionally N-substituted,  
35 where the substituents are linked either directly or via a spacer U to W and may be selected from the group of halogen, cyano, R<sup>4</sup>, OR<sup>4</sup>, OC(O)R<sup>4</sup>, S(O)<sub>n</sub>R<sup>4</sup>, where n is 0, 1, 2, SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, SO<sub>2</sub>NR<sup>5</sup>C(O)R<sup>4</sup>, NR<sup>4</sup>R<sup>5</sup>, NR<sup>5</sup>C(O)R<sup>4</sup>,



- 5 U is a C<sub>1</sub>-C<sub>4</sub>-alkylene, C<sub>2</sub>-C<sub>4</sub>-alkenylidene, C<sub>2</sub>-C<sub>4</sub>-alkynylidene, O-C<sub>1</sub>-C<sub>4</sub>-alkylene, C(O)-C<sub>1</sub>-C<sub>4</sub>-alkylene, S(O)<sub>n</sub>-C<sub>1</sub>-C<sub>4</sub>-alkylene, where n is 0, 1, 2, N(R<sup>5</sup>)-C<sub>1</sub>-C<sub>4</sub>-alkylene, C(O)-N(R<sup>5</sup>)-C<sub>1</sub>-C<sub>4</sub>-alkylene, N(R<sup>5</sup>)-C(O)-C<sub>1</sub>-C<sub>4</sub>-alkylene spacer,
- 10 R<sup>1</sup> is a C<sub>1</sub>-alkyl group or cyano,
- R<sup>2</sup> is a hydrogen, halogen, cyano, a C<sub>1</sub>-alkyl group,
- R<sup>3</sup> is a hydrogen, halogen, cyano, a C<sub>1</sub>-alkyl group,
- 15 R<sup>4</sup> is a hydrogen, a C<sub>1</sub>-C<sub>4</sub>-alkyl group, a C<sub>2</sub>-C<sub>4</sub>-alkenyl group, a C<sub>2</sub>-C<sub>4</sub>-alkynyl group, a C<sub>3</sub>-C<sub>6</sub>-cycloalkyl group, a CH<sub>2</sub>-C<sub>3</sub>-C<sub>6</sub>-cycloalkyl group, a 6-membered aryl ring, a 5-6-membered heteroaryl ring or a CH<sub>2</sub>-aryl or heteroaryl group, where the aryl radical is 6-membered and the heteroaryl radical is 5 or 6-membered,
- 20 R<sup>5</sup> is a hydrogen, a C<sub>1</sub>-C<sub>4</sub>-alkyl group and
- R<sup>4</sup>, R<sup>5</sup> together form a 3-6-membered cycloalkyl or a heteroatom-containing ring.

25

4. A compound as claimed in the preceding claims selected from a group which comprises the following compounds:

1. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-pyridin-2-ylpyrimidine-4,6-diamine
- 30 2. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-pyridin-3-ylpyrimidine-4,6-diamine
3. N-(3-Chlorophenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
4. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(3-trifluoromethylphenyl)-
- 35 pyrimidine-4,6-diamine

5. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-fluorophenyl)-pyrimidine-4,6-diamine
6. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-pyridin-3-ylmethylpyrimidine-4,6-diamine
- 5 7. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-phenylpyrimidine-4,6-diamine
8. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(2-methoxyphenyl)-pyrimidine-4,6-diamine
9. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(3-methoxyphenyl)-  
10 pyrimidine-4,6-diamine
10. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-methoxyphenyl)-pyrimidine-4,6-diamine
11. N-(4-Chlorophenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
- 15 12. N-Cyclohexyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]pyrimidine-4,6-diamine
13. N-(4-Dimethylaminophenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
14. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-pyrazin-2-ylpyrimidine-4,6-  
20 diamine
15. N-Benzyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]pyrimidine-4,6-diamine
16. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-methoxybenzyl)-pyrimidine-4,6-diamine
- 25 17. N-Biphenyl-2-ylmethyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
18. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-[1,2,4]triazol-1-ylphenyl)pyrimidine-4,6-diamine
19. [2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-[6-(2,3,5,6-tetrahydro-  
30 [1,2']bipyrazinyl-4-yl)pyrimidin-4-yl]amine
20. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-methylbenzyl)-pyrimidine-4,6-diamine

21. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-trifluoromethylphenyl)-pyrimidine-4,6-diamine
22. N-Biphenyl-3-ylmethyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
- 5 23. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-N-thiazol-2-ylbenzenesulfonamide
24. N-(4,6-Dimethylpyrimidin-2-yl)-4-{6-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}benzenesulfonamide
25. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(6-methylpyridin-2-yl)-  
10 pyrimidine-4,6-diamine
26. 5-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-indan-1-one
27. 6-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-3,4-dihydro-2H-naphthalen-1-one
- 15 28. 5-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-isoindole-1,3-dione
29. 6-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-nicotinamide
30. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-naphthalen-1-yl-  
20 pyrimidine-4,6-diamine
31. N-Benzo[1,3]dioxol-5-yl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
32. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-indol-5-yl)-pyrimidine-4,6-diamine
- 25 33. N-(1H-Benzotriazol-5-yl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-pyrimidine-4,6-diamine
34. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-indan-5-ylpyrimidine-4,6-diamine
35. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-  
30 isoindole-1,3-dione
36. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-benzamide

37. 6-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-  
2,3-dihydrophthalazine-1,4-dione
38. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(5-methyl-2H-pyrazol-3-  
yl)pyrimidine-4,6-diamine
- 5 39. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-quinolin-3-ylpyrimidine-  
4,6-diamine
40. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-quinolin-5-ylpyrimidine-  
4,6-diamine
41. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-quinolin-8-ylpyrimidine-  
10 4,6-diamine
42. 5-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-  
2-methylisoindole-1,3-dione
43. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-pyrazolo[3,4-  
d]pyrimidin-4-yl)pyrimidine-4,6-diamine
- 15 44. N-(2,5-Dimethyl-2H-pyrazol-3-yl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-  
yl)ethyl]pyrimidine-4,6-diamine
45. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(2-trifluoromethyl-1H-  
benzoimidazol-5-yl)pyrimidine-4,6-diamine
46. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-[3-(1H-tetrazol-5-yl)-  
20 phenyl]pyrimidine-4,6-diamine
47. 3-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-  
benzenesulfonamide
48. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-indazol-5-yl)-  
pyrimidine-4,6-diamine
- 25 49. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-indazol-6-yl)-  
pyrimidine-4,6-diamine
50. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-isoquinolin-1-yl-  
pyrimidine-4,6-diamine
51. N-Benzothiazol-6-yl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-  
30 pyrimidine-4,6-diamine
52. N-(4-tert-Butylphenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-  
pyrimidine-4,6-diamine

53. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(5-trifluoromethylpyridin-2-yl)pyrimidine-4,6-diamine
54. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-isoquinolin-3-yl-pyrimidine-4,6-diamine
- 5 55. (4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}phenyl)acetonitrile
56. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(2,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)pyrimidine-4,6-diamine
57. N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]pyrimidine-4,6-diamine
- 10 58. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-phenoxyphenyl)-pyrimidine-4,6-diamine
59. 7-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]pyrimidin-4-ylamino}-4-methylchromen-2-one
- 15 60. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(2-methylbenzothiazol-5-yl)pyrimidine-4,6-diamine
61. [2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl](2-methyl-6-piperidin-1-yl-pyrimidin-4-yl)amine
62. N-Biphenyl-4-yl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
- 20 63. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyridin-2-yl-pyrimidine-4,6-diamine
64. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyridin-3-yl-pyrimidine-4,6-diamine
- 25 65. N-(3-Chlorophenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
66. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(3-trifluoromethylphenyl)pyrimidine-4,6-diamine
67. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-fluorophenyl)-2-methylpyrimidine-4,6-diamine
- 30 68. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(2-fluorophenyl)-2-methylpyrimidine-4,6-diamine

69. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(2-trifluoromethylphenyl)pyrimidine-4,6-diamine
70. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyridin-4-yl-pyrimidine-4,6-diamine
- 5 71. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-phenethyl-pyrimidine-4,6-diamine
72. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyridin-2-ylmethylpyrimidine-4,6-diamine
73. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyridin-3-ylmethylpyrimidine-4,6-diamine
- 10 74. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyridin-4-ylmethylpyrimidine-4,6-diamine
75. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-phenyl-pyrimidine-4,6-diamine
- 15 76. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(2-methoxyphenyl)-2-methylpyrimidine-4,6-diamine
77. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(3-methoxyphenyl)-2-methylpyrimidine-4,6-diamine
78. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-methoxyphenyl)-2-methylpyrimidine-4,6-diamine
- 20 79. N-(4-Chlorophenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
80. N-Cyclohexyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
- 25 81. N-(4-Dimethylaminophenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
82. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-pyrazin-2-yl-pyrimidine-4,6-diamine
83. N-Benzyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
- 30 84. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(4-methoxybenzyl)-2-methylpyrimidine-4,6-diamine

85. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(3-methylisothiazol-5-yl)pyrimidine-4,6-diamine
86. [2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-[2-methyl-6-(4-pyridin-2-ylpiperazin-1-yl)pyrimidin-4-yl]amine
- 5 87. N-Biphenyl-2-ylmethyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
88. [2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-[2-methyl-6-(4-pyrimidin-2-ylpiperazin-1-yl)pyrimidin-4-yl]amine
89. [6-(4-Benzylpiperazin-1-yl)-2-methylpyrimidin-4-yl][2-(7-fluoro-2,4-dimethyl-10 1H-indol-3-yl)ethyl]amine
90. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(4-[1,2,4]triazol-1-ylphenyl)pyrimidine-4,6-diamine
91. N-(4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}phenyl)acetamide
- 15 92. N-(2-Fluorobenzyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
93. N-Cyclohexylmethyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
94. N-(4-Fluorobenzyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-20 methylpyrimidine-4,6-diamine
95. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(3-trifluoromethylbenzyl)pyrimidine-4,6-diamine
96. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(4-methylbenzyl)pyrimidine-4,6-diamine
- 25 97. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(4-trifluoromethylbenzyl)pyrimidine-4,6-diamine
98. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(4-trifluoromethylphenyl)pyrimidine-4,6-diamine
99. N-Biphenyl-4-ylmethyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-30 methylpyrimidine-4,6-diamine
100. N-Biphenyl-3-ylmethyl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine

101. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-N-methylbenzamide
102. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-N-thiazol-2-ylbenzenesulfonamide
- 5 103. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-N-pyrimidin-2-ylbenzenesulfonamide
104. N-(4,6-Dimethylpyrimidin-2-yl)-4-{6-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}benzenesulfonamide
105. N-Acetyl-4-{6-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-  
10 methylpyrimidin-4-ylamino}benzenesulfonamide
106. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(6-methylpyridin-2-yl)pyrimidine-4,6-diamine
107. 5-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}indan-1-one
- 15 108. 6-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-3,4-dihydro-2H-naphthalen-1-one
109. 5-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}isoindole-1,3-dione
110. 6-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-  
20 methylpyrimidin-4-ylamino}nicotinamide
111. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-naphthalen-1-ylpyrimidine-4,6-diamine
112. N-Benzo[1,3]dioxol-5-yl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
- 25 113. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-indol-5-yl)-2-methylpyrimidine-4,6-diamine
114. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-indan-5-yl-2-methylpyrimidine-4,6-diamine
115. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methyl-  
30 pyrimidin-4-ylamino}isoindole-1,3-dione
116. 4-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}benzamide

117. 6-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-2,3-dihydrophthalazine-1,4-dione
118. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(5-methyl-2H-pyrazol-3-yl)pyrimidine-4,6-diamine
- 5 119. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-quinolin-3-ylpyrimidine-4,6-diamine
120. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-quinolin-5-ylpyrimidine-4,6-diamine
121. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-quinolin-6-ylpyrimidine-4,6-diamine
- 10 122. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-quinolin-8-ylpyrimidine-4,6-diamine
123. 5-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-2-methylisoindole-1,3-dione
- 15 124. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)pyrimidine-4,6-diamine
125. N-(2,5-Dimethyl-2H-pyrazol-3-yl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
126. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(2-trifluoromethyl-1H-benzimidazol-5-yl)pyrimidine-4,6-diamine
- 20 127. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-[3-(1H-tetrazol-5-yl)phenyl]pyrimidine-4,6-diamine
128. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(6-methoxypyridin-3-yl)-2-methylpyrimidine-4,6-diamine
- 25 129. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-[1,3,5]triazin-2-ylpyrimidine-4,6-diamine
130. 3-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}benzenesulfonamide
131. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-indazol-5-yl)-2-methylpyrimidine-4,6-diamine
- 30 132. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-(1H-indazol-6-yl)-2-methylpyrimidine-4,6-diamine

133. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-isoquinolin-1-yl-2-methylpyrimidine-4,6-diamine
134. N-Benzothiazol-6-yl-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
- 5 135. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-[1,2,4]triazin-3-ylpyrimidine-4,6-diamine
136. N-(4-tert-Butylphenyl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
137. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(5-trifluoromethylpyridin-2-yl)pyrimidine-4,6-diamine
- 10 138. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-N'-isoquinolin-3-yl-2-methylpyrimidine-4,6-diamine
139. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(2,4,5,6-tetrahydrocyclopentapyrazol-3-yl)pyrimidine-4,6-diamine
- 15 140. N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-N'-[2-(7-fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methylpyrimidine-4,6-diamine
141. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(4-phenoxyphenyl)pyrimidine-4,6-diamine
142. 7-{6-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethylamino]-2-methylpyrimidin-4-ylamino}-4-methylchromen-2-one
- 20 143. N-[2-(7-Fluoro-2,4-dimethyl-1H-indol-3-yl)ethyl]-2-methyl-N'-(2-methylbenzothiazol-5-yl)pyrimidine-4,6-diamine

5. The use of the compounds as claimed in claims 1-4 for the manufacture of medicaments which comprise at least one of the compounds of the formula I.

25

6. A medicament as set forth in claim 5 with suitable formulating substances and carriers.

7. The use of the medicaments as set forth in claim 5 and 6, wherein the medicament is used for the treatment and prophylaxis of disorders.

30

8. The use of the medicaments as claimed in claims 5 and 6 for the treatment and prophylaxis of disorders connected with the EP<sub>2</sub> receptor.

9. The use of the medicaments as claimed in claims 5 and 6 for the treatment and prophylaxis of fertility impairments.
10. The use of the medicaments as claimed in claims 5 and 6 for the treatment and prophylaxis of painful menstruation.
11. The use of the medicaments as claimed in claims 5 and 6 for the treatment and prophylaxis of endometriosis.
- 10 12. The use of the medicaments as claimed in claims 5 and 6 for modulating the EP<sub>2</sub> receptor.
13. The use of the medicaments as claimed in claims 5 and 6 for the treatment and prophylaxis of pain.
- 15 14. The use of the compounds as claimed in claims 1-4 for the manufacture of pharmaceutical compositions with suitable formulating substances and carriers for controlling fertility/contraception.
- 20 15. The use of the medicaments as claimed in claims 5 and 6 for the treatment and prophylaxis of osteoporosis.
16. The use of the medicaments as claimed in claims 5 and 6 for the treatment and prophylaxis of cancer.
- 25 17. The use of the medicaments as claimed in claims 5 and 6 for the treatment and prophylaxis of inflammatory disorders such as, for example, Crohn's disease.
- 30 18. The use of the compounds as claimed in claims 1-4 in the form of a pharmaceutical product for enteral, parenteral, vaginal and oral administration.