1,5-Diphenylpyrazoles

BACKGROUND OF THE INVENTION

The invention was based on the object of finding novel compounds having valuable properties, in particular those which can be used for the preparation of medicaments.

The present invention relates to compounds in which the inhibition, regulation and/or modulation of HSP90 plays a role, furthermore to pharmaceutical compositions which comprise these compounds, and to the use of the compounds for the treatment of diseases in which HSP90 plays a role.

The correct folding and conformation of proteins in cells is ensured by molecular chaperones and is critical for the regulation of the equilibrium between protein synthesis and degradation. Chaperones are important for the regulation of many central functions of cells, such as, for example, cell proliferation and apoptosis (Jolly and Morimoto, 2000; Smith et al., 1998; Smith, 2001).

Heat shock proteins (HSPs)

The cells of a tissue react to external stress, such as, for example, heat, hypoxia, oxidative stress, or toxic substances, such as heavy metals or alcohols, with activation of a number of chaperones which are known under the term "heat shock proteins" (HSPs).

The activation of HSPs protects the cell against damage initiated by such stress factors, accelerates the restoration of the physiological state and results in a stress-tolerant state of the cell.

Besides this originally discovered protective mechanism promoted by HSPs against external stress, further important chaperone functions have also been described in the course of time for individual HSPs

under normal stress-free conditions. Thus, various HSPs regulate, for example, correct folding, intracellular localisation and function or regulated degradation of a number of biologically important proteins of cells.

HSPs form a gene family with individual gene products whose cellular expression, function and localisation differs in different cells. The naming and classification within the family is carried out on the basis of their molecular weight, for example HSP27, HSP70, and HSP90.

Some human diseases are based on incorrect protein folding (see review, for example, Tytell et al., 2001; Smith et al., 1998). The development of therapies which engages in the mechanism of the chaperone-dependent protein folding could therefore be useful in such cases. For example, incorrectly folded proteins result in aggregation of protein with neurodegenerative progression in the case of Alzheimer's disease, prion diseases or Huntington's syndrome. Incorrect protein folding may also result in loss of wild-type function, which can have the consequence of incorrectly regulated molecular and physiological function.

HSPs are also ascribed great importance in tumour diseases. There are, for example, indications that the expression of certain HSPs correlates with the stage of progression of tumours (Martin et al., 2000; Conroy et al., 1996; Kawanishi et al., 1999; Jameel et al., 1992; Hoang et al., 2000; Lebeau et al., 1991).

The fact that HSP90 plays a role in a number of central oncogenic signalling pathways in the cell and certain natural products having cancer-inhibiting activity target HSP90 has led to the concept that inhibition of the function of HSP90 would be sensible in the treatment of tumour diseases. An HSP90 inhibitor, 17- allylamino-17-demethoxygeldanamycin (17AAG), a derivative of geldanamycin, is currently undergoing clinical trials.

HSP90

HSP90 represents approximately 1-2% of the total cellular protein mass. It is usually in the form of a dimer in the cell and is associated with a multiplicity of proteins, so-called co-chaperones (see, for example, Pratt, 1997). HSP90 is essential for the vitality of cells (Young et al., 2001) and plays a key role in the response to cellular stress by interaction with many proteins whose native folding has been modified by external stress, such as, for example, heat shock, in order to restore the original folding or to prevent aggregation of the proteins (Smith et al.,1998).

There are also indications that HSP90 is of importance as buffer against the effects of mutations, presumably through correction of incorrect protein folding caused by the mutation (Rutherford and Lindquist, 1998).

In addition, HSP90 also has a regulatory importance. Under physiological conditions, HSP90, together with its homologue in the endoplasmatic reticulum, GRP94, plays a role in the cell balance for ensuring the stability of the conformation and maturing of various client key proteins. These can be divided into three groups: receptors for steroid hormones, Ser/Thr or tyrosine kinases (for example ERBB2, RAF-1, CDK4 and LCK) and a collection of various proteins, such as, for example, mutated p53 or the catalytic subunit of telomerase hTERT. Each of these proteins takes on a key role in the regulation of physiological and biochemical processes of cells.

The preserved HSP90 family in humans consists of four genes, cytosolic HSP90α, the inducible HSP90β isoform (Hickey et al., 1989), GRP94 in the endoplasmatic reticulum (Argon et al., 1999) and HSP75/TRAP1 in the mitochondrial matrix (Felts et al., 2000). It is assumed that all members of the family have a similar mode of action, but, depending on their localisation in the cell, bind to different client proteins. For example, ERBB2 is a specific client protein of GRP94 (Argon et al., 1999), while the type 1 receptor of tumour necrosis factor (TNFR1) or the retinoblastoma protein

(Rb) have been found to be clients of TRAP1 (Song et al., 1995; Chen et al., 1996).

HSP90 is involved in a number of complex interactions with a large number of client proteins and regulatory proteins (Smith, 2001). Although precise molecular details have not yet been clarified, biochemical experiments and investigations with the aid of X-ray crystallography in recent years have increasingly been able to decipher details of the chaperone function of HSP90 (Prodromou et al., 1997; Stebbins et al., 1997). Accordingly, HSP90 is an ATP-dependent molecular chaperone (Prodromou et al, 1997), with dimerisation being important for ATP hydrolysis. The binding of ATP results in the formation of a toroidal dimer structure, in which the two N-terminal domains come into close contact with one another and act as a switch in the conformation (Prodromou and Pearl, 2000).

Known HSP90 inhibitors

The first class of HSP90 inhibitors to be discovered were benzoquinone ansamycins with the compounds herbimycin A and geldanamycin. Originally, the reversion of the malignant phenotype in fibroblasts which had been induced by transformation with the v-Src oncogene was detected with them (Uehara et al., 1985).

Later, a strong antitumoural activity was demonstrated in vitro (Schulte et al., 1998) and in vivo in animal models (Supko et al., 1995).

Immune precipitation and investigations on affinity matrices then showed that the principal mechanism of action of geldanamycin involves binding to HSP90 (Whitesell et al., 1994; Schulte and Neckers, 1998). In addition, X-ray crystallographic studies have shown that geldanamycin competes for the ATP binding site and inhibits the intrinsic ATPase activity of HSP90 (Prodromou et al., 1997; Panaretou et al., 1998). This prevents the forma-

tion of the multimeric HSP90 complex, with its property of functioning as chaperone for client proteins. As a consequence, client proteins are degraded via the ubiquitin-proteasome pathway.

The geldanamycin derivative 17- allylamino-17-demethoxygeldanamycin (17AAG) showed an unchanged property in the inhibition of HSP90, the degradation of client proteins and antitumoural activity in cell cultures and in xenograft tumour models (Schulte et al, 1998; Kelland et al, 1999), but had significantly lower liver cytotoxicity than geldanamycin (Page et all 1997).17AAG is currently undergoing phase I/II clinical trials.

Radicicol, a macrocyclic antibiotic, likewise exhibited revision of the v-Src and v-Ha-Ras-induced malignant phenotype of fibroblasts (Kwon et all 1992; Zhao et al, 1995). Radicicol degrades a large number of signal proteins as a consequence of HSP90 inhibition (Schulte et al., 1998). X-ray crystallographic studies have shown that radicicol likewise binds to the N-terminal domain of HSP90 and inhibits the intrinsic ATPase activity (Roe et al., 1998).

Antibiotics of the coumarine type, as is known, bind to the ATP binding site of the HSP90 homolog DNA gyrase in bacteria. The coumarine, Novobiocin, binds to the carboxy-terminal end of HSP90, i.e. to a different site in HSP90 than the benzoquinone-ansamycins and radicicol, which bind to the N-terminal end of HSP90 (Marcu et al., 2000b).

The inhibition of HSP90 by novobiocin results in degradation of a large number of HSP90-dependent signal proteins (Marcu et al., 2000a).

The degradation of signal proteins, for example ERBB2, was demonstrated using PU3, an HSP90 inhibitor derived from purines. PU3 causes cell cycle arrest and differentiation in breast cancer cell lines (Chiosis et al., 2001).

HSP90 as therapeutic target

Due to the participation of HSP90 in the regulation of a large number of signalling pathways which have crucial importance in the phenotype of a tumour, and the discovery that certain natural products exert their biological effect through inhibition of the activity of HSP90, HSP90 is currently being tested as a novel target for the development of a tumour therapeutic agent (Neckers et al., 1999).

The principal mechanism of action of geldanamycin, 17AAG, and radicicol includes the inhibition of the binding of ATP to the ATP binding site at the N-terminal end of the protein and the resultant inhibition of the intrinsic ATPase activity of HSP90 (see, for example, Prodromou et al., 1997; Stebbins et al., 1997; Panaretou et al., 1998). Inhibition of the ATPase activity of HSP90 prevents the recruitment of co-chaperones and favours the formation of an HSP90 heterocomplex, which causes client proteins to undergo degradation via the ubiquitin-proteasome pathway (see, for example, Neckers et al., 1999; Kelland et al., 1999). The treatment of tumour cells with HSP90 inhibitors results in selective degradation of important proteins having fundamental importance for processes such as cell proliferation, regulation of the cell cycle and apoptosis. These processes are frequently deregulated in tumours (see, for example, Hostein et al., 2001). An attractive rationale for the development of an inhibitor of HSP90 is that a strong tumour-therapeutic action can be achieved by simultaneous degradation of a plurality of proteins which are associated with the transformed phenotype.

In detail, the present invention relates to compounds which inhibit, regulate and/or modulate HSP90, to compositions which comprise these compounds, and to methods for the use thereof for the treatment of HSP90-induced diseases, such as tumour diseases, viral diseases, such as, for ex-

ample, hepatitis B (Waxman, 2002); immune suppression in transplants (Bijlmakers, 2000 and Yorgin, 2000); inflammation-induced diseases (Bucci, 2000), such as rheumatoid arthritis, asthma, multiple sclerosis, type 1 diabetes, lupus erythematosus, psoriasis and inflammatory bowel disease; cystic fibrosis (Fuller, 2000); diseases associated with angiogenesis (Hur, 2002 and Kurebayashi, 2001), such as, for example, diabetic retinopathy, haemangiomas, endometriosis and tumour angiogenesis; infectious diseases; autoimmune diseases; ischaemia; promotion of nerve regeneration (Rosen et al., WO 02/09696; Degranco et al., WO 99/51223; Gold, US 6,210,974 B1); fibrogenetic diseases, such as, for example, dermatosclerosis, polymyositis, systemic lupus, cirrhosis of the liver, keloid formation, interstitial nephritis and pulmonary fibrosis (Strehlow, WO 02/02123).

The invention also relates to the use of the compounds according to the invention for the protection of normal cells against toxicity caused by chemotherapy, and to the use in diseases where incorrect protein folding or aggregation is a principal causal factor, such as, for example, scrapie, Creutzfeldt-Jakob disease, Huntington's or Alzheimer's (Sittler, Hum. Mol. Genet., 10, 1307, 2001; Tratzelt et al., Proc. Nat. Acad. Sci., 92, 2944, 1995; Winklhofer et al., J. Biol. Chem., 276, 45160, 2001). WO 01/72779 describes purine compounds and the use thereof for the treatment of GRP94 (homologue or paralogue of HSP90)-induced diseases, such as tumour diseases, where the cancerous tissue includes a sarcoma or carcinoma selected from the group consisting of fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumour, leiosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, syringocarcinoma, sebaceous cell carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinomas, bone mar-

row carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonic carcinoma, Wilm's tumour, cervical cancer, testicular tumour, lung carcinoma, small-cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, haemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukaemia, lymphoma, multiple myeloma, Waldenström's macroglobulinaemia and heavy-chain disease.

WO 01/72779 furthermore discloses the use of the compounds mentioned therein for the treatment of viral diseases, where the viral pathogen is selected from the group consisting of hepatitis type A, hepatitis type B, hepatitis type C, influenza, varicella, adenovirus, herpes simplex type I (HSV-I), herpes simplex type II (HSV-II), cattle plague, rhinovirus, echovirus, rotavirus, respiratory syncytial virus (RSV), papillomavirus, papovavirus, cytomegalovirus, echinovirus, arbovirus, huntavirus, Coxsackie virus, mumps virus, measles virus, rubella virus, polio virus, human immunodeficiency virus type I (HIV-I) and human immunodeficiency virus type II (HIV-II). WO 01/72779 furthermore describes the use of the compounds mentioned therein for GRP94 modulation, where the modulated biological GRP94 activity causes an immune reaction in an individual, protein transport from the endoplasmatic reticulum, recovery from hypoxic/anoxic stress, recovery from malnutrition, recovery from heat stress, or combinations thereof, and/or where the disorder is a type of cancer, an infectious disease, a disorder associated with disrupted protein transport from the endoplasmatic reticulum, a disorder associated with ischaemia/reperfusion, or combinations thereof, where the the disorder associated with ischaemia/reperfusion is a consequence of cardiac arrest, asystolia and delayed ventricular arrhythmia, heart operation, cardiopulmonary bypass operation, organ transplant, spinal cord trauma, head trauma, stroke, thromboembolic

stroke, haemorrhagic stroke, cerebral vasospasm, hypotonia, hypoglycaemia, status epilepticus, an epileptic fit, anxiety, schizophrenia, a neurodegenerative disorder, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) or neonatal stress.

Finally, WO 01/72779 describes the use of an effective amount of a GRP94 protein modulator for the preparation of a medicament for changing a subsequent cellular reaction to an ischaemic state in a tissue site in an individual, by treatment of the cells at the tissue site with the GRP94 protein modulator in order that the GRP94 activity in cells is increased to such an extent that a subsequent cellular reaction to an ischaemic state is changed, where the subsequent ischaemic condition is preferably the consequence of cardiac arrest, asystolia and delayed ventricular arrhythmia, heart operation, cardiopulmonary bypass operation, organ transplant, spinal cord trauma, head trauma, stroke, thromboembolic stroke, haemorrhagic stroke, cerebral vasospasm, hypotonia, hypoglycaemia, status epilepticus, an epileptic fit, anxiety, schizophrenia, a neurodegenerative disorder, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) or neonatal stress, or where the tissue site is the donor tissue for a transplant.

A. Kamal et al. in Trends in Molecular Medicine, Vol. 10 No. 6 June 2004, describe therapeutic and diagnostic applications of HSP90 activation, inter alia for the treatment of diseases of the central nervous system and of cardiovascular diseases.

The identification of small compounds which specifically inhibit, regulate and/or modulate HSP90 is therefore desirable and an aim of the present invention.

It has been found that the compounds according to the invention and salts thereof have very valuable pharmacological properties while being well tolerated.
In particular, they exhibit HSP90-inhibiting properties.

The present invention therefore relates to compounds according to the invention as medicaments and/or medicament active compounds in the treatment and/or prophylaxis of the said diseases and to the use of compounds according to the invention for the preparation of a pharmaceutical for the treatment and/or prophylaxis of the said diseases and also to a process for the treatment of the said diseases which comprises the administration of one or more compounds according to the invention to a patient in need of such an administration.

The host or patient may belong to any mammal species, for example a primate species, particularly humans; rodents, including mice, rats and hamsters; rabbits; horses, cows, dogs, cats, etc. Animal models are of interest for experimental investigations, where they provide a model for the treatment of a human disease.

PRIOR ART

WO 00/53169 describes HSP90 inhibition with coumarine or a coumarine derivative.
WO 03/041643 A2 discloses HSP90-inhibiting zearalanol derivatives.
Other HSP90-inhibiting pyrazole derivatives which are substituted in the 3- or 5-position by an aromatic radical are disclosed in WO 2004/050087 A1 and WO 2004/056782 A1.
WO 03/055860 A1 describes 3,4-diarylpyrazoles as HSP90 inhibitors.
Purine derivatives having HSP90-inhibiting properties are disclosed in WO 02/36075 A2.

Further literature:

Argon Y and Simen BB. 1999 "Grp94, an ER chaperone with protein and peptide binding properties", Semin. Cell Dev. Biol., Vol. 10, pp. 495-505.

Bijlmakers M-JJE, Marsh M. 2000 "Hsp90 is essential for the synthesis and subsequent membrane association, but not the maintenance, of the Src-kinase p56lck", Mol. Biol. Cell, Vol. 11*(5)*, pp. 1585-1595.

Bucci M; Roviezzo F; Cicala C; Sessa WC, Cirino *G.* 2000 "Geldanamycin, an inhibitor of heat shock protein 90 (Hsp90) mediated signal transduction has anti-inflammatory effects and interacts with glucocorticoid receptor in vivo", Brit. J. Pharmacol., Vol 131(1), pp. 13-16.

Carreras CW, Schirmer A, Zhong Z, Santi VS. 2003 "Filter binding assay for the geldanamycin-heat shock protein 90 interaction", Analytical Biochem., Vol 317, pp 40-46.

Chen C-F, Chen Y, Dai KD, Chen P-L, Riley DJ and Lee W-H. 1996 "A new member of the hsp90 family of molecular chaperones interacts with the retinoblastoma protein during mitosis and after heat shock", Mol. Cell. Biol., Vol. 16, pp. 4691-4699.

Chiosis G, Timaul MN, Lucas B, Munster PN, Zheng FF, Sepp-Lozenzino L and Rosen N. 2001 "A small molecule designed to bind to the adenine nucleotide pocket of HSP90 causes Her2 degradation and the growth arrest and differentiation of breast cancer cells", Chem. Biol., Vol. 8, pp. 289-299.

Chiosis G, Lucas B, Shtil A, Huezo H, Rosen N 2002 "Development of a purine-scaffold novel class of HSP90 binders that inhibit the proliferation of cancer cells and induce the degradation of her2 tyrosine kinase". Bio-organic Med. Chem., Vol 10, pp 3555-3564.

Conroy SE and Latchman DS. 1996 "Do heat shock proteins have a role in breast cancer?", Brit. J. Cancer, Vol. 74, pp. 717-721.

Felts SJ, Owen BAL, Nguyen P, Trepel J, Donner DB and Toft DO. 2000 "The HSP90-related protein TRAP1 is a mitochondrial protein with distinct functional properties", J. Biol. Chem., Vol. 5, pp. 3305-331 2.

Fuller W, Cuthbert AW. 2000 "Post-translational disruption of the delta F508 cystic fibrosis transmembrane conductance regulator (CFTR)-molecular Chaperone complex with geldanamycin stabilises delta F508 CFTR in the rabbit reticulocyte lysate", J. Biol. Chem., Vol. 275(48), pp. 37462-37468.

Hickey E, Brandon SE, Smale G, Lloyd D and Weber LA. 1999 "Sequence and regulation of a gene encoding a human 89-kilodalton heat shock protein", Mol. Cell. Biol., Vol. 9, pp. 2615-2626.

Hoang AT, Huang J, Rudra-Gonguly N, Zheng J, Powell WC, Rabindron SK, Wu C and Roy-Burman P. 2000 "A novel association between the human heat shock transcription factor 1 (HSF1) and prostate adenocarcinoma, Am. J. Pathol., Vol. 156, pp. 857-864.

Hostein I, Robertson D, Di Stefano F, Workman P and Clarke PA. 2001 "Inhibition of signal transduction by the HSP90 inhibitor 17-allylamino-1 7-demethoxygeldanamycin results in cytostasis and apoptosis", Cancer Res., Vol. 61, pp. 4003-4009.

Hur E, Kim H-H, Choi SM, Kim JH, Yim S, Kwon HJ, Choi Y, Kim DK, Lee M-0, Park H. 2002 "Reduction of hypoxia-induced transcription through the repression of hypoxia-inducible factor-1α/aryl hydrocarbon receptor nuclear translocator DNA binding by the 90-kDa heat-shock protein inhibitor radicicol", Mol. Pharmacol., Vol 62(5), pp. 975-982.

Jameel A, Skilton RA, Campbell TA, Chander SK, Coombes RC and Luqmani YA. 1992 "Clinical

Jolly C and Morimoto RI. 2000 "Role of the heat shock response and molecular chaperones in oncogenesis and cell death", J. Natl. Cancer Inst., Vol. 92, pp. 1564-1572.

Kawanishi K, Shiozaki H, Doki Y, Sakita I, Inoue M, Yano M, Tsujinata T, Shamma A and Monden M. 1999 "Prognostic significance of heat shock proteins 27 and 70 in patients with squamous cell carcinoma of the esophagus", Cancer, Vol. 85, pp. 1649-1657.

Kelland LR, Abel G, McKeage MJ, Jones M, Goddard PM, Valenti M, Murrer BA, and Harrap KR. 1993 "Preclinical antitumour evaluation of bis-acetalo-amino-dichloro-cyclohexylamine platinum (IV): an orally active platinum drug", Cancer Research, Vol. 53, pp. 2581 - 2586.

Kelland LR, Sharp SY, Rogers PM, Myers TG and Workman P. 1999 "DT-diaphorase expression and tumor cell sensitivity to 17-allylamino, 17-demethoxygeldanamycin, an inhibitor of heat shock protein 90", J. Natl. Cancer Inst., Vol. 91, pp. 1940-1949.

Kurebayashi J, Otsuki T, Kurosumi M, Soga S, Akinaga S, Sonoo, H. 2001 "A radicicol derivative, KF58333, inhibits expression of hypoxia-inducible factor-1α and vascular endothelial growth factor, angiogenesis and growth

of human breast cancer xenografts", Jap. J. Cancer Res.,Vol. 92(12), 1342-1351.

Kwon HJ, Yoshida M, Abe K, Horinouchi S and Bepple T. 1992 "Radicicol, an agent inducing the reversal of transformed phentoype of src-transformed fibroblasts, Biosci., Biotechnol., Biochem., Vol. 56, pp. 538-539.

Lebeau J, Le Cholony C, Prosperi MT and Goubin G. 1991 "Constitutive overexpression of 89 kDa heat shock protein gene in the HBL100 mammary cell line converted to a tumorigenic phenotype by the EJE24 Harvey-ras oncogene", Oncogene, Vol. 6, pp. 1125-1132.

Marcu MG, Chadli A, Bouhouche I, Catelli M and Neckers L. 2000a "The heat shock protein 90 antagonist novobiocin interacts with a previously unrecognised ATP-binding domain in the carboxyl terminus of the chaperone", J. Biol. Chem., Vol. 275, pp. 37181-37186.

Marcu MG, Schulte TW and Neckers L. 2000b "Novobiocin and related coumarins and depletion of heat shock protein 90-dependent signaling proteins", J. Natl. Cancer Inst., Vol. 92, pp. 242-248.

Martin KJ, Kritzman BM, Price LM, Koh B, Kwan CP, Zhang X, MacKay A, O'Hare MJ, Kaelin CM, Mutter GL, Pardee AB and Sager R. 2000 "Linking gene expression patterns to therapeutic groups in breast cancer", Cancer Res., Vol. 60, pp. 2232-2238.

Neckers L, Schulte TW and Momnaaugh E. 1999 "Geldanamycin as a potential anti-cancer agent: its molecular target and biochemical activity", Invest. New Druqs, Vol. 17, pp. 361-373.

Page J, Heath J, Fulton R, Yalkowsky E, Tabibi E, Tomaszewski J, Smith A and Rodman L. 1997 "Comparison of geldanamycin (NSC-122750) and 17-allylaminogeldanamycin (NSC-330507D) toxicity in rats", Proc. Am. Assoc. Cancer Res., Vol. 38, pp. 308.

Panaretou B, Prodromou C, Roe SM, OBrien R, Ladbury JE, Piper PW and Pearl LH. 1998 "ATP binding and hydrolysis are essential to the function of the HSP90 molecular chaperone in vivo", EMBO J., Vol. 17, pp. 4829-4836.

Pratt WB. 1997 "The role of the HSP90-based chaperone system in signal transduction by nuclear receptors and receptors signalling via MAP kinase", Annu. Rev. Pharmacol. Toxicol., Vol. 37, pp. 297-326.

Prodromou C, Roe SM, O'Brien R, Ladbury JE, Piper PW and Pearl LH. 1997 "Identification and structural characterisation of the ATP/ADP-binding site in the HSP90 molecular chaperone", Cell, Vol. 90, pp. 65-75.

Prodromou C, Panaretou B, Chohan S, Siligardi G, O'Brien R, Ladbury JE, Roe SM, Piper PW and Pearl LH. 2000 "The ATPase cycle of HSP90 drives a molecular "clamp" via transient dimerisation of the N-terminal domains", EMBO J., Vol. 19, pp. 4383-4392.

Roe SM, Prodromou C, O'Brien R, Ladbury JE, Piper PW and Pearl LH. 1999 "Structural basis for inhibition of the HSP90 molecular chaperone by the antitumour antibiotics radicicol and geldanamycin", J. Med. Chem., Vol. 42, pp. 260-266.

Rutherford SL and Lindquist S. 1998 "HSP90 as a capacitor for morphological evolution. Nature, Vol. 396, pp. 336-342.

Schulte TW, Akinaga S, Murakata T, Agatsuma T, Sugimoto S, Nakano H, Lee YS, Simen BB, Argon Y, Felts S, Toft DO, Neckers LM and Sharma SV. 1999 "Interaction of radicicol with members of the heat shock protein 90 family of molecular chaperones", Mol. Endocrinoloqy, Vol. 13, pp. 1435-1448.

Schulte TW, Akinaga S, Soga S, Sullivan W, Sensgard B, Toft D and Neckers LM. 1998 "Antibiotic radicicol binds to the N-terminal domain of HSP90 and shares important biologic activities with geldanamcyin", Cell Stress and Chaperones, Vol. 3, pp. 100-108.

Schulte TW and Neckers LM. 1998 "The benzoquinone ansamycin 17-allylamino-17-demethoxygeldanamcyin binds to HSP90 and shares important biologic activities with geldanamycin", Cancer Chemother. Pharmacol., Vol. 42, pp. 273-279.

Smith DF. 2001 "Chaperones in signal transduction", in: Molecular chaperones in the cell (P Lund, ed.; Oxford University Press, Oxford and NY), pp. 165-178.

Smith DF, Whitesell L and Katsanis E. 1998 "Molecular chaperones: Biology and prospects for pharmacological intervention", Pharmacological Reviews, Vol. 50, pp. 493-513.

Song HY, Dunbar JD, Zhang YX, Guo D and Donner DB. 1995 "Identification of a protein with homology to hsp90 that binds the type 1 tumour necrosis factor receptor", J. Biol. Chem., Vol. 270, pp. 3574-3581.

Stebbins CE, Russo A, Schneider C, Rosen N, Hartl FU and Pavletich NP. 1997 "Crystal structure of an HSP90-geldanamcyin complex: targeting of a protein chaperone by an antitumor agent", Cell, Vol. 89, pp. 239-250.

Supko JG, Hickman RL, Grever MR and Malspeis L. 1995 "Preclinical pharmacologic evaluation of geldanamycin as an antitumour agent", Cancer Chemother. Pharmacol., Vol. 36, pp. 305-315.

Tytell M and Hooper PL. 2001 "Heat shock proteins: new keys to the development of cytoprotective therapies", Emerging Therapeutic Targets, Vol. 5, pp. 267-287.

Uehara U, Hori M, Takeuchi T and Umezawa H. 1986 "Phenotypic change from transformed to normal induced by benzoquinoid ansa-mycins accompanies inactivation of p6Osrc in rat kidney cells infected with Rous sarcoma virus", Mol. Cell. Biol., Vol. 6, pp. 21 98-2206.

Waxman, Lloyd H. Inhibiting hepatitis C virus processing and replication. (Merck & Co., Inc., USA). PCT Int. Appl. (2002), WO 0207761

Whitesell L, Mimnaugh EG, De Costa B, Myers CE and Neckers LM. 1994 "Inhibition of heat shock protein HSP90-pp60v-src heteroprotein complex formation by benzoquinone ansamycins: essential role for stress proteins in oncogenic transformation", Proc. Natl. Acad. Sci. USA., Vol. 91, pp. 8324-8328.

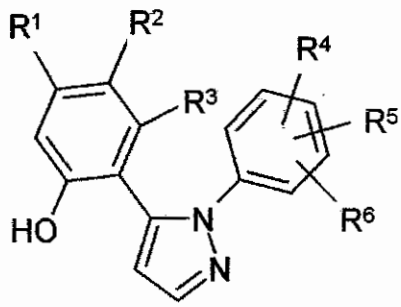
Yorgin et al. 2000 "Effects of geldanamycin, a heat-shock protein 90-binding agent, on T cell function and T cell nonreceptor protein tyrosine kinases", J. Immunol., Vol 164(6), pp. 2915-2923.

Young JC, Moarefi I and Hartl FU. 2001 "HSP90: a specialised but essential protein-folding tool", J. Cell. Biol., Vol. 154, pp. 267-273.

Zhao JF, Nakano H and Sharma S. 1995 "Suppression of RAS and MOS transformation by radicicol", Oncoqene, Vol. 11, pp. 161 -173.

SUMMARY OF THE INVENTION

The invention relates to compounds of the formula I



I

in which

R^1 denotes OH, OCH_3, OCF_3, $OCHF_2$, OBzl, OAc, p-methoxybenzyloxy, SH, $S(O)_mCH_3$, SO_2NH_2, Hal, CF_3 or CH_3,

R^2, R^3 each, independently of one another, denote H, Hal, CN, NO_2, A, Alk, $(CH_2)_nAr$, $(CH_2)_nHet$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, COOAr, COOHet, $CONH_2$, CONHA, CONAA', CONHAr, CONAAr, $CON(Ar)_2$, CONHHet, $CON(Het)_2$, NH_2, NHA, NHAr, NHHet, NAA', NHCOA, NACOA', NHCOAr, NHCOHet, NHCOOA, NHCOOAr, NHCOOHet, NHCONHA, NHCONHAr, NHCONHHet, OH, OA, OAr, OHet, SH, $S(O)_mA$, $S(O)_mAr$, $S(O)_mHet$, SO_2NH_2, SO_2NHA, SO_2NAA', SO_2NHAr, SO_2NAAr, SO_2NHHet, $SO_2N(Ar)_2$, $SO_2N(Het)_2$, $CONH(CH_2)_oHet$, $NH(CH_2)_oHet$, $O(CH_2)_oAr$, $S(O)_m(CH_2)_oHet$, $S(O)_m(CH_2)_oAr$, $(CH_2)_oCH(Ar)CH_3$, $CONAR^{12}$, $SO_2NA(CH_2CONAA')$,

$SO_2NH(CH_2Ar)$, $SO_2NA[(CH_2)_oCN]$, $SO_2NA(CH_2Ar)$, $(CH_2)_oNHAr$, $(CH_2)_oNAAr$, $(CH_2)_oOAr$, $(CH_2)_oS(O)_mAr$, CH=CH-Ar, CHO, COA or R^{12},

R^4, R^5, R^6 each, independently of one another, denote H, Hal, CN, NO_2, A, Alk, $(CH_2)_nAr$, $(CH_2)_nHet$, COOH, COOA, COOAr, COO-Het, $CONH_2$, CONHA, CONAA', CONHAr, CONAAr, $CON(Ar)_2$, CONHHet, $CON(Het)_2$, NH_2, NHA, NHAr, NHHet, NAA', NHCOA, NACOA', NHCOAr, NHCOHet, NHCOOA, NHCOOAr, NHCOOHet, NHCONHA, NHCONHAr, NHCONHHet, OH, OA, OAr, OHet, SH, $S(O)_mA$, $S(O)_mAr$, $S(O)_mHet$, SO_2NH_2, SO_2NHA, SO_2NAA', SO_2NHAr, SO_2NAAr, SO_2NHHet, $SO_2N(Ar)_2$, $SO_2N(Het)_2$, $CONH(CH_2)_oAr$, $NHCO(CH_2)_oAr$, $NHCO(CH_2)_oOA$ or $O(CH_2)_oHet$,

R^4 and R^5 together also denote OCH_2O or OCH_2CH_2O,

A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH, NR^8 and/or by -CH=CH- groups and/or, in addition, 1-5 H atoms may be replaced by F, Cl, Br and/or R^7,

Alk or cyclic alkyl having 3-7 C atoms,

A and A' together also denote an alkylene chain having 2, 3, 4, 5 or 6 C atoms, which may be substituted by CH_2OH, CH_2Br, CH_2NEt_2,

and/or in which a CH_2 group may be replaced by O, S, SO, SO_2, N, NH, NR^8, $NCOR^8$ or $NCOOR^8$,

Alk denotes alkenyl having 2-6 C atoms,

R^7 denotes $COOR^9$, $CONR^9R^{10}$, NR^9R^{10}, $NHCOR^9$, $NHCOOR^9$ or OR^9,

R^8 denotes cycloalkyl having 3-7 C atoms,

cycloalkylalkylene having 4-10 C atoms,

Alk or

unbranched or branched alkyl having 1-6 C atoms, in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl,

R^9, R^{10} each, independently of one another, denote H or alkyl having 1-5 C atoms, in which 1-3 CH_2 groups may be replaced by O, S, SO, SO_2, NH, NMe or NEt and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl,

R^9 and R^{10} together also denote an alkylene chain having 2, 3, 4, 5 or 6 C atoms, in which a CH_2 group may be replaced by O, S, SO, SO_2, NH, NR^8, $NCOR^8$ or $NCOOR^8$,

Ar denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR^{11}, $N(R^{11})_2$, NO_2, CN, phenyl, $CON(R^{11})_2$, $NR^{11}COA$, $NR^{11}CON(R^{11})_2$, $NR^{11}SO_2A$, COR^{11}, $NR^{11}CO(CH_2)_oR^{11}$, $SO_2N(R^{11})_2$, $S(O)_mA$, $-[C(R^{11})_2]_n-COOR^{11}$ and/or $-O[C(R^{11})_2]_o-COOR^{11}$,

Het denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono-, di- or trisubstituted by Hal, A, OR^{11}, $N(R^{11})_2$, NO_2, CN, $COOR^{11}$, $CON(R^{11})_2$, $NR^{11}COA$, $NR^{11}SO_2A$, COR^{11}, SO_2NR^{11}, $S(O)_mA$, =S, $=NR^{11}$ and/or =O (carbonyl oxygen),

R^{11} denotes H or A,

R^{12} denotes cycloalkyl having 3-7 C atoms or cycloalkylalkylene having 4-12 C atoms,

Hal denotes F, Cl, Br or I,

m denotes 0, 1 or 2,

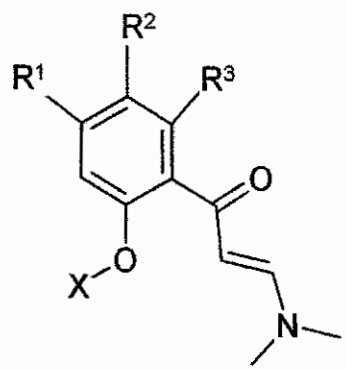
n denotes 0, 1, 2, 3 or 4,

o denotes 1, 2 or 3,

and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

The invention relates to the compounds of the formula I and salts thereof and to a process for the preparation of compounds of the formula I according to Claims 1-16 and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, characterised in that

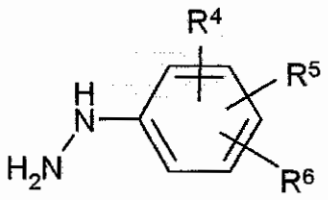
a) a compound of the formula II



II

in which R^1, R^2 and R^3 have the meanings indicated in Claim 1, and X denotes H or methyl,

is reacted with a compound of the formula III



III

in which R^4, R^5 and R^6 have the meanings indicated in Claim 1,

the resultant compound in which X denotes methyl is subsequently, if desired, converted into a compound of the formula I in which X denotes H by ether cleavage,

and/or in that one or more radical(s) R^1,R^2, R^3, R^4 and/or R^5 in a compound of the formula I are converted into one or more radical(s) R^1,R^2, R^3, R^4 and/or R^5

by, for example,

i) reducing a nitro group to an amino group,

ii) hydrolysing an ester group to a carboxyl group,

iii) converting an amino group into an alkylated amine by reductive amination,

iv) converting a carboxyl group into a sulfonamidocarbonyl group,

v) converting an acid chloride into an amide,

and/or

a base or acid of the formula I is converted into one of its salts.

The invention also relates to the stereoisomers (E, Z isomers) and the hydrates and solvates of these compounds. Solvates of the compounds are taken to mean adductions of inert solvent molecules onto the compounds which form owing to their mutual attractive force. Solvates are, for example, mono- or dihydrates or alcoholates.

Pharmaceutically usable derivatives are taken to mean, for example, the salts of the compounds according to the invention and also so-called prodrug compounds.

Prodrug derivatives are taken to mean compounds of the formula I which have been modified with, for example, alkyl or acyl groups, sugars or oligopeptides and which are rapidly cleaved in the organism to give the effective compounds according to the invention.

These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example, in Int. J. Pharm. 115, 61-67 (1995).

The expression "effective amount" means the amount of a medicament or pharmaceutical active compound which causes a biological or medical response which is sought or desired, for example, by a researcher or physician in a tissue, system, animal or human.

In addition, the expression "therapeutically effective amount" means an amount which, compared with a corresponding subject who has not received this amount, has the following consequence:

improved healing treatment, healing, prevention or elimination of a disease, a disease picture, a disease state, a complaint, a disorder or of side effects or also the reduction in the progress of a disease, a complaint or a disorder.

The term "therapeutically effective amount" also encompasses the amounts which are effective for increasing normal physiological function.

The invention also relates to mixtures of the compounds of the formula I according to the invention, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000.

These are particularly preferably mixtures of stereoisomeric compounds.

For all radicals which occur more than once, their meanings are independent of one another.

Above and below, the radicals and parameters R^1, R^2, R^3, R^4 and R^5 have the meanings indicated for the formula I, unless expressly indicated otherwise.

A or A' preferably denotes alkyl, is unbranched (linear) or branched, and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 C atoms. A or A' particularly preferably

denotes denotes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1- , 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1- , 2- , 3- or 4-methylpentyl, 1,1- , 1,2- , 1,3- , 2,2- , 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl.

A or A' very particularly preferably denotes alkyl having 1, 2, 3, 4, 5 or 6 C atoms, preferably ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, trifluoromethyl, pentafluoroethyl or 1,1,1-trifluoroethyl.

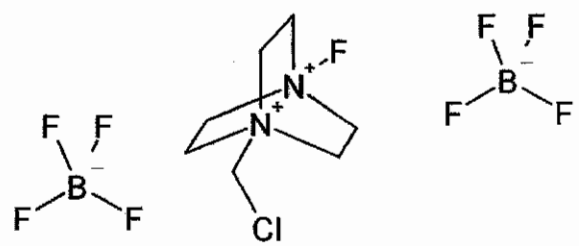
A or A' also denotes cycloalkyl. Cycloalkyl preferably denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

A or A' also denotes Alk. Alk denotes alkenyl having 2-6 C atoms, such as, for example, vinyl or propenyl.

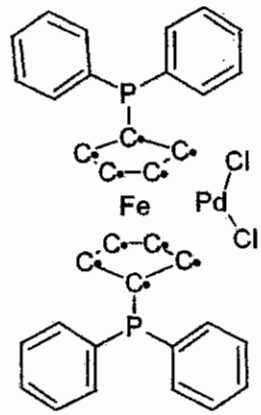
Cycloalkylalkylene denotes, for example, cyclopropylmethyl or cyclopentylmethyl.

Ac denotes acetyl, Bzl denotes benzyl, Ms denotes $-SO_2CH_3$.

Selectfluor/F-TEDA-BF4/1(1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetra-fluoroborate)) =



$PdCl_2$(dppf) denotes [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II):



R^1 preferably denotes OH, OCH_3 or SH, particularly preferably OH or OCH_3, furthermore also OCF_3, $OCHF_2$.

R^2, R^3 preferably each, independently of one another, denote H, Hal, A, $(CH_2)_nAr$, $(CH_2)_nHet$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, $CONH_2$, CONHA, CONAA', CONHAr, CONHHet, NH_2, NHA, NHAr, NHHet, NAA', $S(O)_mA$, $S(O)_mAr$, SO_2NH_2, SO_2NHA, SO_2NAA', SO_2NHAr, SO_2NAAr, SO_2NHHet, $CONH(CH_2)_oHet$, $NH(CH_2)_oHet$, $O(CH_2)_oAr$, $S(O)_m(CH_2)_oHet$, $S(O)_m(CH_2)_oAr$, $(CH_2)_oCH(Ar)CH_3$, $CONAR^{12}$, $SO_2NA(CH_2CONAA')$, $SO_2NH(CH_2Ar)$, $SO_2NA[(CH_2)_oCN]$, $SO_2NA(CH_2Ar)$, $(CH_2)_oNHAr$, $(CH_2)_oNAAr$, $(CH_2)_oOAr$, $(CH_2)_oS(O)_mAr$, CH=CH-Ar or R^{12}, where R^3 particularly preferably denotes H.

R^2 particularly preferably denotes H; Hal, such as, for example, Cl, Br or I; A, such as, for example, methyl or ethyl; SO_2NAA', CONAA', SO_2NHA, where A, A' each, independently of one another, denotes unbranched or branched alkyl having 1-6 C atoms, in which, in addition, 1-5 H atoms may be replaced by F, Cl and/or Br,
or cyclic alkyl having 3-7 C atoms,
and where A and A' together also denote an alkylene chain having 3, 4, 5 or 6 C atoms, which may be substituted by CH_2OH, CH_2Br or CH_2NEt_2, and/or in which a CH_2 group may be replaced by O, N, NH or NA;

R^2 furthermore particularly preferably denotes SO_2NH_2, fluorophenylaminosulfonyl, phenylaminosulfonyl, benzylaminosulfonyl, pyridylaminosulfonyl, phenylthio, benzyl, phenylsulfonyl, phenyl, 2-phenylethyl, 2-(pyridyl)ethyl, fluorophenyl, 2-phenylvinyl, 2-carboxyethyl, 2-(methoxycarbonyl)ethyl, 2-(fluorophenyl)ethyl, $SO_2N(CH_2CH_2OH, CH_2CH_2Br)$, $SO_2NA(CH_2CH_2CN)$, $SO_2NA(CH_2CH_2Br)$, $SO_2NA(CH_2CONAA')$ or $SO_2NA(CH_2phenyl)$.

R^4, R^5, R^6 preferably each, independently of one another, denote H, Hal, CN, NO_2, A, $(CH_2)_nAr$, COOH, COOA, $CONH_2$, CONHA, CONAA', CONHAr, NH_2, NHA, NAA', NHCOA, NHCOAr, NHCOHet, OH, OA, SO_2NH_2, SO_2NHA, SO_2NAA', $CONH(CH_2)_oAr$, $NHCO(CH_2)_oAr$, $NHCO(CH_2)_oOA$ or $O(CH_2)_oHet$.

R^4 particularly preferably denotes H.

R^5 particularly preferably denotes H, F, Cl, CN or A, such as, for example, methyl, ethyl or trifluoromethyl.

R^6 particularly preferably denotes H, NHCOA, NH_2, NO_2, COOH, Fl, Cl, Br, A, OA, OH, CN, SO_2NH_2, COOA, 4-[2-(4-methylpiperazin-1-yl)ethoxy]-phenyl, benzyl, benzoylamino, benzylcarbonylamino, pyridylcarbonylamino or methoxyethylcarbonylamino,

where A preferably denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-5 H atoms may be replaced by F, Cl and/or Br.

R^7 preferably denotes $COOR^9$, such as, for example, COOH or $COOCH_3$; $CONR^9R^{10}$, such as, for example, $CONH_2$; NR^9R^{10}, such as, for example, amino, methylamino or dimethylamino; $NHCOR^9$, $NHCOOR^9$ or OR^9, such as, for example, hydroxyl or methoxy;

R^8 preferably denotes cyclopentyl, cyclohexyl, methyl, ethyl, propyl or butyl.

R^9, R^{10} preferably each, independently of one another, denote H or alkyl having 1-5 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl.

Ar denotes, for example, phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-(N-methylaminocarbonyl)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N,N-dimethylaminocarbonyl)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-(methylsulfonamido)phenyl, o-, m- or p-(methylsulfonyl)phenyl, o-, m- or p-cyanophenyl, o-, m- or p-ureidophenyl, o-, m- or p-formylphenyl, o-, m- or p-acetylphenyl, o-, m- or p-aminosulfonylphenyl, o-, m- or p-carboxyphenyl, o-, m- or p-carboxymethylphenyl, o-, m- or p-carboxymethoxyphenyl, further preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-chloro-, 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-5-chloro- or 2-amino-6-chlorophenyl, 2-nitro-4-N,N-dimethylamino- or 3-nitro-4-N,N-dimethylaminophenyl, 2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-trimethoxyphenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-chloro-4-acetamidophenyl, 3-fluoro-4-methoxyphenyl, 3-amino-6-methylphenyl, 3-chloro-4-acetamidophenyl or 2,5-dimethyl-4-chlorophenyl.

Ar preferably denotes, for example, phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR^{11}, $N(R^{11})_2$, $NR^{11}COA$, $NR^{11}CO(CH_2)_oR^{11}$, and/or $-[C(R^{11})_2]_n-COOR^{11}$, where R^{11} denotes H or A,

such as, for example, methyl. Ar very particularly preferably denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal and/or A.

Het denotes, irrespective of further substitutions, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or 5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7- benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, further preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

The heterocyclic radicals may also be partially or fully hydrogenated.

Het can thus also denote, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or 5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-

pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-,-2-,-3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8- 3,4-dihydro-2H-benzo-1,4-oxazinyl, further preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 3,4-(difluoromethylenedioxy)phenyl, 2,3-dihydrobenzofuran-5- or 6-yl, 2,3-(2-oxomethylenedioxy)phenyl or also 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl or 2,3-dihydro-2-oxofuranyl.

Het preferably denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 2 N and/or O atoms, which may be unsubstituted or mono-, di- or trisubstituted by A, Hal, OH and/or OA.

Het particularly preferably denotes a monocyclic saturated heterocycle having 1 to 2 N and/or O atoms, which may be unsubstituted or mono- or disubstituted by A.

In a further embodiment, Het very particularly preferably denotes pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl.

In a further embodiment, Het particularly preferably denotes furyl, thienyl, pyrrolyl, imidazolyl, pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, indolyl, pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl, each of which is unsubstituted or mono-, di- or trisubstituted by A, Hal, OH and/or OA.

In a very particularly preferred embodiment, Het denotes pyridyl, piperidinyl or piperazinyl.

The compounds of the formula I may have one or more chiral centres and therefore occur in various stereoisomeric forms. The formula I encompasses all these forms.

Particular preference is given to compounds of the formula I selected from the group

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-(*N*-isopropyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[2-(2-fluorophenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxy-5-bromophenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxy-5-chlorophenyl)-1-(2-fluorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxy-5-bromophenyl)-1-(2-ethylphenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-{4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-1*H*-pyrazole,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

Accordingly, the invention relates, in particular, to the compounds of the formula I in which at least one of the said radicals has one of the preferred meanings indicated above. Some preferred groups of compounds may be expressed by the following sub-formulae Ia to Il, which conform to the formula I and in which the radicals not designated in greater detail have the meaning indicated for the formula I, but in which

in Ia R^1 denotes OH, OCH_3 or SH;

in Ib R^2, R^3 each, independently of one another, denote H, Hal, A, $(CH_2)_nAr$, $(CH_2)_nHet$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$,

$CONH_2$, CONHA, CONAA', CONHAr, CONHHet, NH_2, NHA, NHAr, NHHet, NAA', $S(O)_mA$, $S(O)_mAr$, SO_2NH_2, SO_2NHA, SO_2NAA', SO_2NHAr, SO_2NAAr, SO_2NHHet, $CONH(CH_2)_oHet$, $NH(CH_2)_oHet$, $O(CH_2)_oAr$, $S(O)_m(CH_2)_oHet$, $S(O)_m(CH_2)_oAr$, $(CH_2)_oCH(Ar)CH_3$, $CONAR^{12}$, $SO_2NA(CH_2CONAA')$, $SO_2NH(CH_2Ar)$, $SO_2NA[(CH_2)_oCN]$, $SO_2NA(CH_2Ar)$, $(CH_2)_oNHAr$, $(CH_2)_oNAAr$, $(CH_2)_oOAr$, $(CH_2)_oS(O)_mAr$ or R^{12};

in Ic R^4, R^5, R^6 each, independently of one another, denote H, Hal, CN, NO_2, A, $(CH_2)_nAr$, COOH, COOA, $CONH_2$, CONHA, CONAA', CONHAr, NH_2, NHA, NAA', NHCOA, NHCOAr, NHCOHet, OH, OA, SO_2NH_2, SO_2NHA, SO_2NAA', $CONH(CH_2)_oAr$, $NHCO(CH_2)_oAr$, $NHCO(CH_2)_oOA$ or $O(CH_2)_oHet$;

in Id A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH, NR^8 and/or by -CH=CH- groups and/or, in addition, 1-5 H atoms may be replaced by F, Cl, Br and/or R^7,
Alk or cyclic alkyl having 3-7 C atoms,

A and A' together also denote an alkylene chain having 2, 3, 4, 5 or 6 C atoms, which may be substituted by CH_2OH, CH_2Br or CH_2NEt_2,
and/or in which a CH_2 group may be replaced by O, N, NH or NR^8;

in Ie A, A' each, independently of one another, denote unbranched or branched alkyl having 1-6 C atoms, in

which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH and/or by -CH=CH- groups and/or, in addition, 1-5 H atoms may be replaced by F, Cl and/or Br,

Alk or cyclic alkyl having 3-7 C atoms;

in If R^7 denotes $COOR^9$, $CONR^9R^{10}$, NR^9R^{10}, $NHCOR^9$, $NHCOOR^9$ or OR^9;

in Ig R^8 denotes unbranched or branched alkyl having 1-6 C atoms;

in Ih R^9, R^{10} each, independently of one another, denote H or alkyl having 1-5 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl;

in Ii A, A' each, independently of one another, denote unbranched or branched alkyl having 1-6 C atoms, in which 1-5 H atoms may be replaced by F, Cl and/or Br, or cyclic alkyl having 3-7 C atoms;

in Ij Ar denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR^{11}, $N(R^{11})_2$, $NR^{11}COA$, $NR^{11}CO(CH_2)_oR^{11}$, and/or $-[C(R^{11})_2]_n-COOR^{11}$;

in Ik Het denotes a mono- or bicyclic saturated or aromatic heterocycle having 1 to 2 N and/or O atoms, which may be mono- or disubstituted by A;

in Il R^1 denotes OH, OCH_3 or SH,

R^2, R^3 each, independently of one another, denote H, Hal, A, $(CH_2)_nAr$, $(CH_2)_nHet$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, $CONH_2$, CONHA, CONAA', CONHAr, CONHHet, NH_2, NHA, NHAr, NHHet, NAA', $S(O)_mA$, $S(O)_mAr$, SO_2NH_2, SO_2NHA, SO_2NAA', SO_2NHAr, SO_2NAAr, SO_2NHHet, $CONH(CH_2)_oHet$, $NH(CH_2)_oHet$, $O(CH_2)_oAr$, $S(O)_m(CH_2)_oHet$, $S(O)_m(CH_2)_oAr$, $(CH_2)_oCH(Ar)CH_3$, $CONAR^{12}$, $SO_2NA(CH_2CONAA')$, $SO_2NH(CH_2Ar)$, $SO_2NA[(CH_2)_oCN]$, $SO_2NA(CH_2Ar)$, $(CH_2)_oNHAr$, $(CH_2)_oNAAr$, $(CH_2)_oOAr$, $(CH_2)_oS(O)_mAr$ or R^{12},

R^4, R^5, R^6 each, independently of one another, denote H, Hal, CN, NO_2, A, $(CH_2)_nAr$, COOH, COOA, $CONH_2$, CONHA, CONAA', CONHAr, NH_2, NHA, NAA', NHCOA, NHCOAr, NHCOHet, OH, OA, SO_2NH_2, SO_2NHA, SO_2NAA', $CONH(CH_2)_oAr$, $NHCO(CH_2)_oAr$, $NHCO(CH_2)_oOA$ or $O(CH_2)_oHet$,

R^4 and R^5 together also denote OCH_2O or OCH_2CH_2O,

A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH, NR^8 and/or by -CH=CH- groups and/or, in addition, 1-5 H atoms may be replaced by F, Cl, Br and/or R^7,
Alk or cyclic alkyl having 3-7 C atoms,

A and A' together also denote an alkylene chain having 2, 3, 4, 5 or 6 C atoms, which may be substituted by CH_2OH, CH_2Br or CH_2NEt_2,
and/or in which a CH_2 group may be replaced by O, N, NH or NR^8,

R^7	denotes $COOR^9$, $CONR^9R^{10}$, NR^9R^{10}, $NHCOR^9$, $NHCOOR^9$ or OR^9,
R^8	denotes unbranched or branched alkyl having 1-6 C atoms,
R^9, R^{10}	each, independently of one another, denote H or alkyl having 1-5 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl,
Ar	denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR^{11}, $N(R^{11})_2$, $NR^{11}COA$, $NR^{11}CO(CH_2)_oR^{11}$, and/or $-[C(R^{11})_2]_n-COOR^{11}$,
Het	denotes a mono- or bicyclic saturated or aromatic heterocycle having 1 to 2 N and/or O atoms, which may be mono- or disubstituted by A,
R^{11}	denotes H or A,
R^{12}	denotes cycloalkyl having 3-7 C atoms or cycloalkyl-alkylene having 4-12 C atoms,
Hal	denotes F, Cl, Br or I,
m	denotes 0, 1 or 2,
n	denotes 0, 1, 2, 3 or 4,
o	denotes 1, 2 or 3;

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

The compounds according to the invention and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use may

also be made here of variants known per se which are not mentioned here in greater detail.

If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds according to the invention.

The starting compounds are generally known. If they are novel, however, they can be prepared by methods known per se.

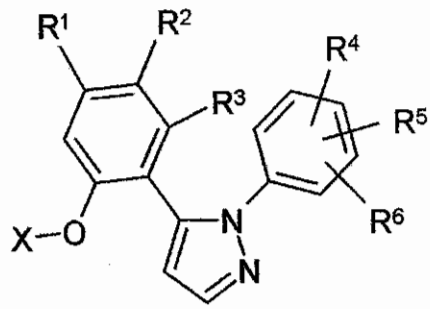
Compounds of the formula I can preferably be obtained by reacting a compound of the formula II with a hydrazide of the formula III.
The reaction generally gives the 1,5-diphenylpyrazole derivative. The 1,3-diphenyl derivative may form as by-product.

The reaction is carried out by methods which are known to the person skilled in the art.
Reaction is firstly carried out in a suitable solvent.
Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether, ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

Particularly preferred solvents are alcohols, such as, for example, isopropanol or ethanol.

Depending on the conditions used, the reaction time is between a few minutes and 14 days, the reaction temperature is between about -30° and 140°, normally between -10° and 110°, in particular between about 20° and about 100°.

In the resultant compound of the formula I



I

in which X denotes H or methyl,
the ether cleavage is optionally carried out by methods which are known to the person skilled in the art.
The reaction is carried out in a suitable solvent, as indicated above, preferably by addition of boron tribromide.
The reaction is particularly preferably carried out in dichloromethane at a reaction temperature between about -30° and 50°, normally between -20° and 20°, in particular between about -15° and about 0°.

This gives compounds of the formula I in which X denotes H.

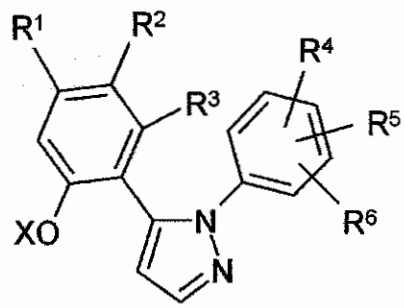
It is furthermore possible to convert a compound of the formula I into another compound of the formula I by converting one or more radical(s) R^1, R^2, R^3, R^4 and/or R^5 into one or more other radicals R^1, R^2, R^3, R^4 and/or

R^5, for example by reducing nitro groups to amino groups, for example by hydrogenation on Raney nickel or Pd/carbon in an inert solvent, such as methanol or ethanol, and/or

converting an ester group into a carboxyl group and/or converting an amino group into an alkylated amine by reductive amination and/or esterifying carboxyl groups by reaction with alcohols and/or converting acid chlorides into an acid amide by reaction with an amine.

Furthermore, free amino groups can be acylated in a conventional manner using an acid chloride or anhydride or alkylated using an unsubstituted or substituted alkyl halide, advantageously in an inert solvent, such as dichloromethane or THF, and/or in the presence of a base, such as triethylamine or pyridine, at temperatures between -60 and +30°.

The invention also relates to intermediate compounds of the formula I-I



I-I

in which

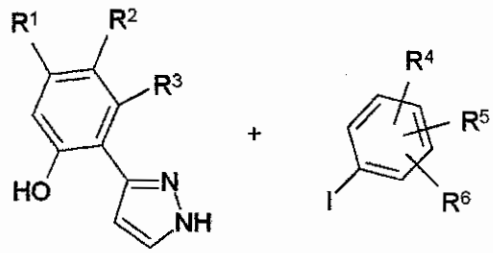
R^1	denotes OCH_3, OBzl, OAc, p-methoxybenzyloxy or I,
R^2, R^3	denote H
R^4, R^5, R^6	each, independently of one another, denote H, Hal, CN, NO_2, A, COOH, COOA, NH_2, OH, OA or SO_2NH_2,
X	denotes CH_3, Bzl, Ac or p-methoxybenzyl,

A denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl,
or cyclic alkyl having 3-7 C atoms,

and salts thereof.

Alternative processes for the preparation of compounds of the formula I:

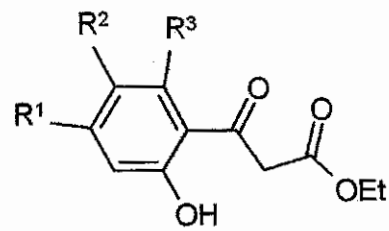
1. Arylation of pyrazoles using substituted phenyl iodides



II-1 II-2

Literature:
Fr. Demande, 2840303, 05 Dec 2003;
U.S. Pat. Appl. Publ., 2003236413, 25 Dec 2003;

2.



III-1 + III

3. Other processes for the preparation of 1,5-diarylpyrazoles are described by

a) Zhu, Jiuxiang; Song, Xueqin; Lin, Ho-Pi; Young, Donn C.; Yan, Shunqi; Marquez, Victor E.; Chen, Ching-Shih. College of Pharmacy,

Division of Medicinal Chemistry and Pharmacognosy, The Ohio State University, Columbus, OH, USA. Journal of the National Cancer Institute (2002), 94(23), 1745-1757.

b) Pal, Manojit; Madan, Manjula; Padakanti, Srinivas; Pattabiraman, Vijaya R.; Kalleda, Srinivas; Vanguri, Akhila; Mullangi, Ramesh; Mamidi, N. V. S. Rao; Casturi, Seshagiri R.; Malde, Alpeshkumar; Gopalakrishnan, B.; Yeleswarapu, Koteswar R. Discovery-Chemistry and Discovery-Biology, Dr Reddy's Laboratories Ltd., Hyderabad, India. Journal of Medicinal Chemistry (2003), 46(19).

Pharmaceutical salts and other forms

The said compounds according to the invention can be used in their final non-salt form. On the other hand, the present invention also encompasses the use of these compounds in the form of their pharmaceutically acceptable salts, which can be derived from various organic and inorganic acids and bases by procedures known in the art. Pharmaceutically acceptable salt forms of the compounds of the formula I are for the most part prepared by conventional methods. If the compound of the formula I contains a carboxyl group, one of its suitable salts can be formed by reacting the compound with a suitable base to give the corresponding base-addition salt. Such bases are, for example, alkali metal hydroxides, including potassium hydroxide, sodium hydroxide and lithium hydroxide; alkaline earth metal hydroxides, such as barium hydroxide and calcium hydroxide; alkali metal alkoxides, for example potassium ethoxide and sodium propoxide; and various organic bases, such as piperidine, diethanolamine and N-methylglutamine. The aluminium salts of the compounds of the formula I are likewise included. In the case of certain compounds of the formula I, acid-addition salts can be formed by treating these compounds with pharmaceutically acceptable organic and inorganic acids, for example hydrogen halides, such as hydrogen chloride, hydrogen bromide or hydrogen iodide, other mineral acids and corresponding salts thereof, such as sulfate,

nitrate or phosphate and the like, and alkyl- and monoarylsulfonates, such as ethanesulfonate, toluenesulfonate and benzenesulfonate, and other organic acids and corresponding salts thereof, such as acetate, trifluoroacetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate and the like. Accordingly, pharmaceutically acceptable acid-addition salts of the compounds of the formula I include the following: acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, isobutyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, palmoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, phthalate, but this does not represent a restriction.

Furthermore, the base salts of the compounds according to the invention include aluminium, ammonium, calcium, copper, iron(III), iron(II), lithium, magnesium, manganese(III), manganese(II), potassium, sodium and zinc salts, but this is not intended to represent a restriction. Of the above-mentioned salts, preference is given to ammonium; the alkali metal salts sodium and potassium, and the alkaline earth metal salts calcium and magnesium. Salts of the compounds of the formula I which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, also including naturally occurring substituted amines, cyclic amines, and basic ion exchanger resins, for example arginine, betaine, caffeine, chloroprocaine,

choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris-(hydroxymethyl)methylamine (tromethamine), but this is not intended to represent a restriction.

Compounds of the present invention which contain basic nitrogen-containing groups can be quaternised using agents such as (C_1-C_4)alkyl halides, for example methyl, ethyl, isopropyl and tert-butyl chloride, bromide and iodide; di(C_1-C_4)alkyl sulfates, for example dimethyl, diethyl and diamyl sulfate; (C_{10}-C_{18})alkyl halides, for example decyl, dodecyl, lauryl, myristyl and stearyl chloride, bromide and iodide; and aryl(C_1-C_4)alkyl halides, for example benzyl chloride and phenethyl bromide. Both water- and oil-soluble compounds according to the invention can be prepared using such salts.

The above-mentioned pharmaceutical salts which are preferred include acetate, trifluoroacetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate, meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate and tromethamine, but this is not intended to represent a restriction.

The acid-addition salts of basic compounds of the formula I are prepared by bringing the free base form into contact with a sufficient amount of the desired acid, causing the formation of the salt in a conventional manner. The free base can be regenerated by bringing the salt form into contact

with a base and isolating the free base in a conventional manner. The free base forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free base forms thereof.

As mentioned, the pharmaceutically acceptable base-addition salts of the compounds of the formula I are formed with metals or amines, such as alkali metals and alkaline earth metals or organic amines. Preferred metals are sodium, potassium, magnesium and calcium. Preferred organic amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methyl-D-glucamine and procaine.

The base-addition salts of acidic compounds according to the invention are prepared by bringing the free acid form into contact with a sufficient amount of the desired base, causing the formation of the salt in a conventional manner. The free acid can be regenerated by bringing the salt form into contact with an acid and isolating the free acid in a conventional manner. The free acid forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free acid forms thereof.

If a compound according to the invention contains more than one group which is capable of forming pharmaceutically acceptable salts of this type, the invention also encompasses multiple salts. Typical multiple salt forms include, for example, bitartrate, diacetate, difumarate, dimeglumine, diphosphate, disodium and trihydrochloride, but this is not intended to represent a restriction.

With regard to that stated above, it can be seen that the expression "pharmaceutically acceptable salt" in the present connection is taken to mean an active compound which comprises a compound of the formula I in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active compound compared with the free form of the active compound or any other salt form of the active compound used earlier. The pharmaceutically acceptable salt form of the active compound can also provide this active compound for the first time with a desired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active compound with respect to its therapeutic efficacy in the body.

Compounds of the formula I according to the invention may be chiral owing to their molecular structure and may accordingly occur in various enantiomeric forms. They can therefore exist in racemic or in optically active form.

Since the pharmaceutical activity of the racemates or stereoisomers of the compounds according to the invention may differ, it may be desirable to use the enantiomers. In these cases, the end product or even the intermediates can be separated into enantiomeric compounds by chemical or physical measures known to the person skilled in the art or even employed as such in the synthesis.

In the case of racemic amines, diastereomers are formed from the mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids, such as the R and S forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitably N-protected amino acids (for example N-benzoylproline or N-benzenesulfonylproline), or the various optically active camphorsulfonic acids. Also advantageous is chromatographic enantiomer resolution with the aid of an optically active resolving agent (for example dinitrobenzoylphenylglycine, cellulose triacetate or other derivatives

of carbohydrates or chirally derivatised methacrylate polymers immobilised on silica gel). Suitable eluents for this purpose are aqueous or alcoholic solvent mixtures, such as, for example, hexane/isopropanol/ acetonitrile, for example in the ratio 82:15:3.

The invention furthermore relates to the use of the compounds and/or physiologically acceptable salts thereof for the preparation of a medicament (pharmaceutical composition), in particular by non-chemical methods. They can be converted into a suitable dosage form here together with at least one solid, liquid and/or semi-liquid excipient or adjuvant and, if desired, in combination with one or more further active compounds.

The invention furthermore relates to medicaments comprising at least one compound according to the invention and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

Pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active compound per dosage unit. Such a unit can comprise, for example, 0.1 mg to 3 g, preferably 1 mg to 700 mg, particularly preferably 5 mg to 100 mg, of a compound according to the invention, depending on the disease condition treated, the method of administration and the age, weight and condition of the patient, or pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active compound per dosage unit. Preferred dosage unit formulations are those which comprise a daily dose or part-dose, as indicated above, or a corresponding fraction thereof of an active compound. Furthermore, pharmaceutical formulations of this type can be prepared using a process which is generally known in the pharmaceutical art.

Pharmaceutical formulations can be adapted for administration via any desired suitable method, for example by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) methods. Such formulations can be prepared using all processes known in the pharmaceutical art by, for example, combining the active compound with the excipient(s) or adjuvant(s).

Pharmaceutical formulations adapted for oral administration can be administered as separate units, such as, for example, capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or foam foods; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Thus, for example, in the case of oral administration in the form of a tablet or capsule, the active-ingredient component can be combined with an oral, non-toxic and pharmaceutically acceptable inert excipient, such as, for example, ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing it with a pharmaceutical excipient comminuted in a similar manner, such as, for example, an edible carbohydrate, such as, for example, starch or mannitol. A flavour, preservative, dispersant and dye may likewise be present.

Capsules are produced by preparing a powder mixture as described above and filling shaped gelatine shells therewith. Glidants and lubricants, such as, for example, highly disperse silicic acid, talc, magnesium stearate, calcium stearate or polyethylene glycol in solid form, can be added to the powder mixture before the filling operation. A disintegrant or solubiliser, such as, for example, agar-agar, calcium carbonate or sodium carbonate, may likewise be added in order to improve the availability of the medicament after the capsule has been taken.

In addition, if desired or necessary, suitable binders, lubricants and disintegrants as well as dyes can likewise be incorporated into the mixture. Suitable binders include starch, gelatine, natural sugars, such as, for example, glucose or beta-lactose, sweeteners made from maize, natural and synthetic rubber, such as, for example, acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. The lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. The disintegrants include, without being restricted thereto, starch, methylcellulose, agar, bentonite, xanthan gum and the like. The tablets are formulated by, for example, preparing a powder mixture, granulating or dry-pressing the mixture, adding a lubricant and a disintegrant and pressing the entire mixture to give tablets. A powder mixture is prepared by mixing the compound comminuted in a suitable manner with a diluent or a base, as described above, and optionally with a binder, such as, for example, carboxymethylcellulose, an alginate, gelatine or polyvinylpyrrolidone, a dissolution retardant, such as, for example, paraffin, an absorption accelerator, such as, for example, a quaternary salt, and/or an absorbent, such as, for example, bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting it with a binder, such as, for example, syrup, starch paste, acadia mucilage or solutions of cellulose or polymer materials and pressing it through a sieve. As an alternative to granulation, the powder mixture can be run through a tableting machine, giving lumps of non-uniform shape which are broken up to form granules. The granules can be lubricated by addition of stearic acid, a stearate salt, talc or mineral oil in order to prevent sticking to the tablet casting moulds. The lubricated mixture is then pressed to give tablets. The compounds according to the invention can also be combined with a free-flowing inert excipient and then pressed directly to give tablets without carrying out the granulation or dry-pressing steps. A transparent or opaque protective layer

consisting of a shellac sealing layer, a layer of sugar or polymer material and a gloss layer of wax may be present. Dyes can be added to these coatings in order to be able to differentiate between different dosage units.

Oral liquids, such as, for example, solution, syrups and elixirs, can be prepared in the form of dosage units so that a given quantity comprises a prespecified amount of the compounds. Syrups can be prepared by dissolvng the compound in an aqueous solution with a suitable flavour, while elixirs are prepared using a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersion of the compound in a non-toxic vehicle. Solubilisers and emulsifiers, such as, for example, ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavour additives, such as, for example, peppermint oil or natural sweeteners or saccharin, or other artificial sweeteners and the like, can likewise be added.

The dosage unit formulations for oral administration can, if desired, be encapsulated in microcapsules. The formulation can also be prepared in such a way that the release is extended or retarded, such as, for example, by coating or embedding of particulate material in polymers, wax and the like.

The compounds according to the invention and salts, solvates and physiologically functional derivatives thereof can also be administered in the form of liposome delivery systems, such as, for example, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from various phospholipids, such as, for example, cholesterol, stearylamine or phosphatidylcholines.

The compounds according to the invention and the salts, solvates and physiologically functional derivatives thereof can also be delivered using monoclonal antibodies as individual carriers to which the compound mole-

cules are coupled. The compounds can also be coupled to soluble polymers as targeted medicament carriers. Such polymers may encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidophenol, polyhydroxyethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. The compounds may furthermore be coupled to a class of biodegradable polymers which are suitable for achieving controlled release of a medicament, for example polylactic acid, poly-epsilon-caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydroxypyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration can be administered as independent plasters for extended, close contact with the epidermis of the recipient. Thus, for example, the active compound can be delivered from the plaster by iontophoresis, as described in general terms in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compounds adapted for topical administration can be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For the treatment of the eye or other external tissue, for example mouth and skin, the formulations are preferably applied as topical ointment or cream. In the case of formulation to give an ointment, the active compound can be employed either with a paraffinic or a water-miscible cream base. Alternatively, the active compound can be formulated to give a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical application to the eye include eye drops, in which the active compound is dissolved or suspended in a suitable carrier, in particular an aqueous solvent.

Pharmaceutical formulations adapted for topical application in the mouth encompass lozenges, pastilles and mouthwashes.

Pharmaceutical formulations adapted for rectal administration can be administered in the form of suppositories or enemas.

Pharmaceutical formulations adapted for nasal administration in which the carrier substance is a solid comprise a coarse powder having a particle size, for example, in the range 20-500 microns, which is administered in the manner in which snuff is taken, i.e. by rapid inhalation via the nasal passages from a container containing the powder held close to the nose. Suitable formulations for administration as nasal spray or nose drops with a liquid as carrier substance encompass active-ingredient solutions in water or oil.

Pharmaceutical formulations adapted for administration by inhalation encompass finely particulate dusts or mists, which can be generated by various types of pressurised dispensers with aerosols, nebulisers or insufflators.

Pharmaceutical formulations adapted for vaginal administration can be administered as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions comprising antioxidants, buffers, bacteriostatics and solutes, by means of which the formulation is rendered isotonic with the blood of the recipient to be treated; and aqueous and non-aqueous sterile suspensions, which may comprise suspension media and thickeners. The formulations can be administered in

single-dose or multidose containers, for example sealed ampoules and vials, and stored in freeze-dried (lyophilised) state, so that only the addition of the sterile carrier liquid, for example water for injection purposes, immediately before use is necessary.

Injection solutions and suspensions prepared in accordance with the recipe can be prepared from sterile powders, granules and tablets.

It goes without saying that, in addition to the above particularly mentioned constituents, the formulations may also comprise other agents usual in the art with respect to the particular type of formulation; thus, for example, formulations which are suitable for oral administration may comprise flavours.

A therapeutically effective amount of a compound of the present invention depends on a number of factors, including, for example, the age and weight of the human or animal, the precise disease condition which requires treatment, and its severity, the nature of the formulation and the method of administration, and is ultimately determined by the treating doctor or vet. However, an effective amount of a compound according to the invention is generally in the range from 0.1 to 100 mg/kg of body weight of the recipient (mammal) per day and particularly typically in the range from 1 to 10 mg/kg of body weight per day. Thus, the actual amount per day for an adult mammal weighing 70 kg is usually between 70 and 700 mg, where this amount can be administered as an individual dose per day or usually in a series of part-doses (such as, for example, two, three, four, five or six) per day, so that the total daily dose is the same. An effective amount of a salt or solvate or of a physiologically functional derivative thereof can be determined as the fraction of the effective amount of the compound according to the invention *per se*. It can be assumed that simi-

lar doses are suitable for the treatment of other conditions mentioned above.

The invention furthermore relates to medicaments comprising at least one compound according to the invention and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active compound.

Further medicament active compounds are preferably chemotherapeutic agents, in particular those which inhibit angiogenesis and thus inhibit the growth and spread of tumour cells; preference is given here to VEGF receptor inhibitors, including robozymes and antisense which are directed to VEGF receptors, and angiostatin and endostatin.

Examples of antineoplastic agents which can be used in combination with the compounds according to the invention generally include alkylating agents, antimetabolites; epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazin; mitoxantron or platinum coordination complexes.

Antineoplastic agents are preferably selected from the following classes: anthracyclins, vinca medicaments, mitomycins, bleomycins, cytotoxic nucleosides, epothilones, discodermolides, pteridines, diynenes and podophyllotoxins.

Particular preference is given in the said classes to, for example, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloromethotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosinarabinoside, podophyllotoxin or podophyllotoxin derivatives, such as, for example, etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine and paclitaxel. Other preferred antineoplastic agents are

selected from the group estramustine, carboplatin, cyclophosphamide, bleomycin, gemcitabine, ifosamide, melphalan, hexamethylmelamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, arabinosylcytosine, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons and interleukins.

The invention also relates to a set (kit) consisting of separate packs of

(a) an effective amount of a compound according to the invention and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
and

(b) an effective amount of a further medicament active compound.

The set comprises suitable containers, such as boxes, individual bottles, bags or ampoules. The set may, for example, comprise separate ampoules, each containing an effective amount of a compound according to the invention and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and an effective amount of a further medicament active compound in dissolved or lyophilised form.

USE

The present compounds are suitable as pharmaceutical active compounds for mammals, in particular for humans, in the treatment of diseases in which HSP90 plays a role.

The invention thus relates to the use of compounds according to Claim 1 and to pharmaceutically usable derivatives, solvates and stereoisomers,

including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of diseases in which the inhibition, regulation and/or modulation of HSP90 plays a role.

Preference is given here to SGK.

Preference is given to the use of compounds according to Claim 1 and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of tumour diseases, for example fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumour, leiosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, syringocarcinoma, sebaceous cell carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinomas, bone marrow carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonic carcinoma, Wilm's tumour, cervical cancer, testicular tumour, lung carcinoma, small-cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, haemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukaemia, lymphoma, multiple myeloma, Waldenström's macroglobulinaemia and heavy-chain disease;

viral diseases, where the viral pathogen is selected from the group consisting of hepatitis type A, hepatitis type B, hepatitis type C, influenza, varicella, adenovirus, herpes simplex type I (HSV-I), herpes simplex type II (HSV-II), cattle plague, rhinovirus, echovirus, rotavirus, respiratory syncytial virus (RSV), papillomavirus, papovavirus, cytomegalovirus, echinovirus, arbovirus, huntavirus, Coxsackie virus, mumps virus, measles

virus, rubella virus, polio virus, human immunodeficiency virus type I (HIV-I) and human immunodeficiency virus type II (HIV-II);
for immune suppression in transplants; inflammation-induced diseases, such as rheumatoid arthritis, asthma, multiple sclerosis, type 1 diabetes, lupus erythematosus, psoriasis and inflammatory bowel disease; cystic fibrosis; diseases associated with angiogenesis, such as, for example, diabetic retinopathy, haemangioma, endometriosis, tumour angiogenesis; infectious diseases; autoimmune diseases; ischaemia; promotion of nerve regeneration; fibrogenetic diseases, such as, for example, dermatosclerosis, polymyositis, systemic lupus, cirrhosis of the liver, keloid formation, interstitial nephritis and pulmonary fibrosis;

The compounds according to the invention can inhibit, in particular, the growth of cancer, tumour cells and tumour metastases and are therefore suitable for tumour therapy.

The present invention furthermore encompasses the use of the compounds according to Claim 1 according to the invention and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the protection of normal cells against toxicity caused by chemotherapy, and for the treatment of diseases in which incorrect protein folding or aggregation is a principal causal factor, such as, for example, scrapie, Creutzfeldt-Jakob disease, Huntington's or Alzheimer's.

The invention also relates to the use of the compounds according to Claim 1 according to the invention and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of diseases of the central nervous system, of cardiovascular diseases and cachexia.

In a further embodiment, the invention also relates to the use of the compounds according to Claim 1 according to the invention and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for HSP90 modulation, where the modulated biological HSP90 activity causes an immune reaction in an individual, protein transport from the endoplasmatic reticulum, recovery from hypoxic/anoxic stress, recovery from malnutrition, recovery from heat stress, or combinations thereof, and/or where the disorder is a type of cancer, an infectious disease, a disorder associated with disrupted protein transport from the endoplasmatic reticulum, a disorder associated with ischaemia/reperfusion, or combinations thereof, where the the disorder associated with ischaemia/reperfusion is a consequence of cardiac arrest, asystolia and delayed ventricular arrhythmia, heart operation, cardiopulmonary bypass operation, organ transplant, spinal cord trauma, head trauma, stroke, thromboembolic stroke, haemorrhagic stroke, cerebral vasospasm, hypotonia, hypoglycaemia, status epilepticus, an epileptic fit, anxiety, schizophrenia, a neurodegenerative disorder, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) or neonatal stress.

In a further embodiment, the invention also relates to the use of the compounds according to Claim 1 according to the invention and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of ischaemia as a consequence of cardiac arrest, asystolia and delayed ventricular arrhythmia, heart operation, cardiopulmonary bypass operation, organ transplant, spinal cord trauma, head trauma, stroke, thromboembolic stroke, haemorrhagic stroke, cerebral vasospasm, hypotonia, hypoglycaemia, status epilepticus, an epileptic fit, anxiety, schizophrenia, a neurodegenerative disorder, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) or neonatal stress.

Test method for the measurement of HSP90 inhibitors

The binding of geldanamycin or 17- allylamino-17-demethoxygeldanamycin (17AAG) to HSP90 and competitive inhibition thereof can be utilised in order to determine the inhibitory activity of the compounds according to the invention (Carreras et al. 2003, Chiosis et al. 2002).
In the specific case, a radioligand filter binding test is used. The radioligand used here is tritium-labelled 17-allylaminogeldanamycin, [3H]17AAG. This filter binding test allows a targeted search for inhibitors which interfere with the ATP binding site.

Material

Recombinant human HSP90α (E. coli expressed, 95% purity);
[3H]17AAG (17-allylaminogeldanamycin, [allylamino-2,3-^{3}H. Specific activity: 1.11x10^{12} Bq/mmol (Moravek, MT-1717);
HEPES filter buffer (50 mM HEPES, pH 7.0, 5 mM MgCl2, BSA 0.01%)
Multiscreen FB (1 µm) filter plate (Millipore, MAFBNOB 50).

Method

The 96-well microtitre filter plates are firstly irrigated and coated with 0.1% of polyethylenimine.

The test is carried out under the following conditions:

Reaction temperature 22°C

Reaction time: 30 min., shaking at 800 rpm
Test volume: 50 µl
Final concentrations:
50 mM HEPES HCl, pH 7.0, 5 mM MgCl2, 0.01% (w/v) BSA
HSP90: 1.5 µg/assay

[3H]17AAG: 0.08 µM.

At the end of the reaction, the supernatant in the filter plate is removed by suction with the aid of a vacuum manifold (Multiscreen Separation System, Millipore), and the filter is washed twice.
The filter plates are then measured in a beta counter (Microbeta, Wallac) with scintillator (Microscint 20, Packard).

"% of control" is determined from the "counts per minutes" values and the IC-50 value of a compound is calculated therefrom.

Above and below, all temperatures are indicated in°C. In the following examples, "conventional work-up" means: if necessary, water is added, the pH is adjusted, if necessary, to between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation. Rf values on silica gel; eluent: ethyl acetate/methanol 9:1.

LC-MS conditions

HP 1100 series Hewlett Packard System having the following features: ion source: electrospray (positive mode); scan: 100-1000 m/e; fragmentation voltage: 60 V; gas temperature: 300°C, DAD: 220 nm.

Flow rate: 2.4 ml/min. The splitter used reduced the flow rate for the MS to 0.75 ml/min. after the DAD.
Column: Chromolith SpeedROD RP-18e 50-4.6
Solvent: LiChrosolv quality from Merck KGaA
Solvent A: H2O (0.01% of TFA)

Solvent B: ACN (0.008% of TFA)

Gradient:

20% of B → 100% of B: 0 min to 2.8 min

100% of B: 2.8 min to 3.3 min

100% of B → 20% of B: 3.3 min to 4 min

The retention times and $M+H^+$ data indicated in the following examples are the measurement results of the LC-MS measurements.

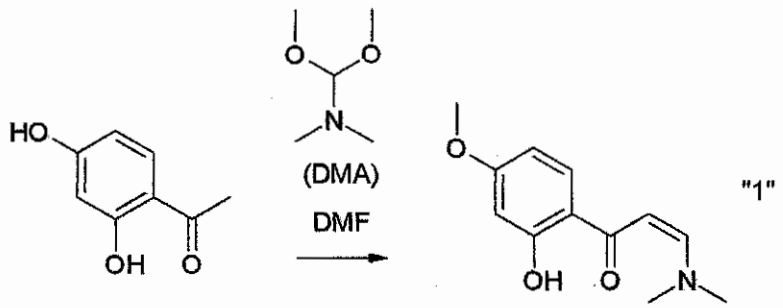
Example 1

Preparation of 5-(2-hydroxy-4-methoxyphenyl)-1-(3-nitrophenyl)-1*H*-pyrazole ("A1"):

1. Reaction of resorcinol with glacial acetic acid in the presence of boron trifluoride etherate gives 2,4-dihydroxyacetophenone.

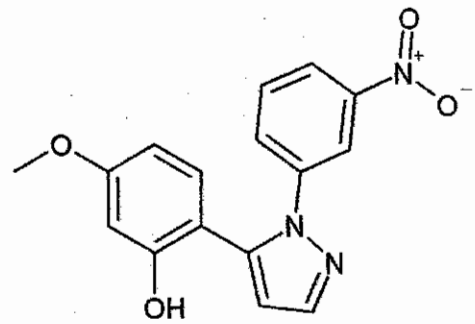
2. N,N-dimethylformamide dimethyl acetal (DMA) is added to a solution of 2,4-dihydroxyacetophenone in dimethylformamide (DMF), and the mixture is refluxed for 24 hours on a water separator.

Removal of the solvent and conventional work-up gives ("1")



3. A solution of 500 mg of "1" and 428.5 mg of (3-nitrophenyl)hydrazine hydrochloride in 20 ml of ethanol is refluxed for 16 hours. Removal of the

solvent and conventional work-up gives "A1", retention time [min] 1.776, $M+H^+$ [m/e] 312.30;



"A1"

The following compounds are obtained analogously

5-(2-hydroxy-4-methyl-5-chlorophenyl)-1-phenyl-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(3,5-dichlorophenyl)-1*H*-pyrazole, retention time [min] 2.251, $M+H^+$ [m/e] 324.15;

5-(2-hydroxy-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1*H*-pyrazole, retention time [min] 1.843, $M+H^+$ [m/e] 324.15;

5-(2-hydroxy-4-fluorophenyl)-1-(2-chloro-5-trifluoromethylphenyl)-1*H*-pyrazole, retention time [min] 2.068, $M+H^+$ [m/e] 357.71;

5-(2-hydroxy-4-fluorophenyl)-1-(2-ethylphenyl)-1*H*-pyrazole, retention time [min] 1.917, $M+H^+$ [m/e] 283.32;

5-(2-hydroxy-4-fluorophenyl)-1-(3-methoxyphenyl)-1*H*-pyrazole, retention time [min] 1.755, $M+H^+$ [m/e] 285.29;

5-(2-hydroxy-4-fluorophenyl)-1-(3-cyanophenyl)-1*H*-pyrazole, retention time [min] 1.731, $M+H^+$ [m/e] 280.27;

5-(2-hydroxy-4-fluorophenyl)-1-(3-trifluoromethylphenyl)-1*H*-pyrazole, retention time [min] 2.067, $M+H^+$ [m/e] 323.26;

5-(2-hydroxy-4-fluorophenyl)-1-(3-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.965, $M+H^+$ [m/e] 289.71;

5-(2-hydroxy-4-fluorophenyl)-1-(3-fluorophenyl)-1*H*-pyrazole, retention time [min] 1.823, $M+H^+$ [m/e] 273.25;

5-(2-hydroxy-4-fluorophenyl)-1-phenyl-1*H*-pyrazole, retention time [min] 1.729, $M+H^+$ [m/e] 255.26;

5-(2-hydroxy-4-fluorophenyl)-1-(4-trifluoromethylphenyl)-1*H*-pyrazole, retention time [min] 2.090, $M+H^+$ [m/e] 323.26;

5-(2-hydroxy-4-fluorophenyl)-1-(4-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.962, $M+H^+$ [m/e] 289.71;

5-(2-hydroxy-4-fluorophenyl)-1-(4-aminosulfonylphenyl)-1*H*-pyrazole, retention time [min] 1.376, $M+H^+$ [m/e] 334.34;

5-(2-hydroxy-4-fluorophenyl)-1-(4-carboxyphenyl)-1*H*-pyrazole, retention time [min] 1.472, $M+H^+$ [m/e] 299.27;

5-(2-hydroxy-4-fluorophenyl)-1-(4-cyanophenyl)-1*H*-pyrazole, retention time [min] 1.758, $M+H^+$ [m/e] 280.27;

5-(2-hydroxy-4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazole, retention time [min] 1.734, $M+H^+$ [m/e] 285.29;

5-(2-hydroxy-4-fluorophenyl)-1-(3-chloro-4-methylphenyl)-1*H*-pyrazole, retention time [min] 2.095, $M+H^+$ [m/e] 303.74;

5-(2-hydroxy-4-fluorophenyl)-1-(4-methylphenyl)-1*H*-pyrazole, retention time [min] 1.865, $M+H^+$ [m/e] 269.29;

5-(2-hydroxy-4-fluorophenyl)-1-(4-bromophenyl)-1*H*-pyrazole, retention time [min] 2.009, $M+H^+$ [m/e] 334.16;

5-(2-hydroxy-4-fluorophenyl)-1-(2-methoxyphenyl)-1*H*-pyrazole, retention time [min] 1.601, $M+H^+$ [m/e] 285.29;

5-(2-hydroxy-4-fluorophenyl)-1-(2-fluorophenyl)-1*H*-pyrazole, retention time [min] 1.667, $M+H^+$ [m/e] 273.25;

5-(2-hydroxy-4-fluorophenyl)-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.753, $M+H^+$ [m/e] 289.71;

5-(2-hydroxy-4-fluorophenyl)-1-(2,6-difluorophenyl)-1*H*-pyrazole, retention time [min] 1.702, $M+H^+$ [m/e] 291.24.

Example 2

Preparation of 5-(2,4-dihydroxyphenyl)-1-(3-nitrophenyl)-1*H*-pyrazole ("A2"):

124 mg of "A1" are dissolved in 3 ml of dichloromethane, and the solution is cooled to -10°. A solution of 0.475 ml of boron tribromide in 2 ml of dichloromethane is then added dropwise, and the mixture is stirred for a further 16 hours. Conventional work-up gives 77 mg of "A2", retention time [min] 1.418, $M+H^+$ [m/e] 298.27.

Example 3

The compound 5-(2-hydroxy-4-methoxyphenyl)-1-(4-nitrophenyl)-1*H*-pyrazole ("A3"), retention time [min] 1.789, $M+H^+$ [m/e] 312.30, is obtained analogously to Example 1.

Reduction of the nitro group in "A3" under standard conditions in tetrahydrofuran using 5% Pd/C and hydrogen and removal of the catalyst and solvent gives 5-(2-hydroxy-4-methoxyphenyl)-1-(4-aminophenyl)-1*H*-pyrazole ("A4"), retention time [min] 0.826, $M+H^+$ [m/e] 282.31.

An analogous procedure gives

5-(2-hydroxy-4-methoxyphenyl)-1-(2-nitrophenyl)-1*H*-pyrazole

and reduction thereof gives

5-(2-hydroxy-4-methoxyphenyl)-1-(2-aminophenyl)-1*H*-pyrazole, retention time [min] 1.123, $M+H^+$ [m/e] 282.31.

Example 4

Analogously to Example 2, ether cleavage of 5-(2-hydroxy-4-methoxyphenyl)-1-(4-aminophenyl)-1*H*-pyrazole ("A4") gives the compound 5-(2,4-

dihydroxyphenyl)-1-(4-aminophenyl)-1*H*-pyrazole ("A5"), retention time [min] 0.537, $M+H^+$ [m/e] 268.29.

Example 5

Analogously to Example 1, reaction of 367.5 mg of "1" with 500 mg of (2-fluorophenyl)hydrazine hydrochloride gives the compound 5-(2-hydroxy-4-methoxyphenyl)-1-(2-fluorophenyl)-1*H*-pyrazole ("A6").
Ether cleavage of "A6" analogously to Example 2 gives the compound 5-(2,4-dihydroxyphenyl)-1-(2-fluorophenyl)-1*H*-pyrazole ("A7"), retention time [min] 1.191, $M+H^+$ [m/e] 271.26.

The following compounds are obtained analogously to Example 1

5-(2-hydroxy-4-methoxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.725, $M+H^+$ [m/e] 301.74;

5-(2-hydroxy-4-methoxyphenyl)-1-(2,4-difluorophenyl)-1*H*-pyrazole, retention time [min] 1.683, $M+H^+$ [m/e] 303.28;

5-(2-hydroxy-4-methoxyphenyl)-1-(3,5-dichlorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(3-chloro-2-cyanophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(2,6-dichlorophenyl)-1*H*-pyrazole, retention time [min] 1.756, $M+H^+$ [m/e] 336.19;

5-(2-hydroxy-4-methoxyphenyl)-1-(2-chloro-5-trifluoromethylphenyl)-1*H*-pyrazole, retention time [min] 1.999, $M+H^+$ [m/e] 369.74;

5-(2-hydroxy-4-methoxyphenyl)-1-(2-ethylphenyl)-1*H*-pyrazole, retention time [min] 1.830, $M+H^+$ [m/e] 295.35;

5-(2-hydroxy-4-methoxyphenyl)-1-(3-methoxyphenyl)-1*H*-pyrazole, retention time [min] 1.680, $M+H^+$ [m/e] 297.33;

5-(2-hydroxy-4-methoxyphenyl)-1-(3-cyanophenyl)-1*H*-pyrazole, retention time [min] 1.650, $M+H^+$ [m/e] 292.31;

5-(2-hydroxy-4-methoxyphenyl)-1-(3-trifluoromethylphenyl)-1*H*-pyrazole, retention time [min] 2.002, M+H$^+$ [m/e] 335.30;

5-(2-hydroxy-4-methoxyphenyl)-1-(3-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.852, M+H$^+$ [m/e] 301.74;

5-(2-hydroxy-4-methoxyphenyl)-1-(3-carboxyphenyl)-1*H*-pyrazole, retention time [min] 1.371, M+H$^+$ [m/e] 311.31;

5-(2-hydroxy-4-methoxyphenyl)-1-(3-fluorophenyl)-1*H*-pyrazole, retention time [min] 1.725, M+H$^+$ [m/e] 285.29;

5-(2-hydroxy-4-methoxyphenyl)-1-(4-bromophenyl)-1*H*-pyrazole, retention time [min] 1.921, M+H$^+$ [m/e] 346.20;

5-(2-hydroxy-4-methoxyphenyl)-1-phenyl-1*H*-pyrazole, retention time [min] 1.601, M+H$^+$ [m/e] 267.30;

5-(2-hydroxy-4-methoxyphenyl)-1-(4-trifluoromethylphenyl)-1*H*-pyrazole, retention time [min] 1.997, M+H$^+$ [m/e] 335.30;

5-(2-hydroxy-4-methoxyphenyl)-1-(4-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.887, M+H$^+$ [m/e] 301.74;

5-(2-hydroxy-4-methoxyphenyl)-1-(4-aminosulfonylphenyl)-1*H*-pyrazole, retention time [min] 1.309, M+H$^+$ [m/e] 346.38;

5-(2-hydroxy-4-methoxyphenyl)-1-(4-carboxyphenyl)-1*H*-pyrazole, retention time [min] 1.409, M+H$^+$ [m/e] 311.31;

5-(2-hydroxy-4-methoxyphenyl)-1-(4-cyanophenyl)-1*H*-pyrazole, retention time [min] 1.661, M+H$^+$ [m/e] 292.31;

5-(2-hydroxy-4-methoxyphenyl)-1-(4-methoxyphenyl)-1*H*-pyrazole, retention time [min] 1.600, M+H$^+$ [m/e] 297.33;

5-(2-hydroxy-4-methoxyphenyl)-1-(3-chloro-4-methylphenyl)-1*H*-pyrazole, retention time [min] 2.002, M+H$^+$ [m/e] 315.77;

5-(2-hydroxy-4-methoxyphenyl)-1-(4-methylphenyl)-1*H*-pyrazole, retention time [min] 1.726, M+H$^+$ [m/e] 281.33;

5-(2-hydroxy-4-methoxyphenyl)-1-(2,6-difluorophenyl)-1*H*-pyrazole, retention time [min] 1.540, M+H$^+$ [m/e] 303.28;

5-(2-hydroxy-4-methoxyphenyl)-1-(4-cyano-2-nitrophenyl)-1*H*-pyrazole,
5-(2-hydroxy-4-methoxyphenyl)-1-(4-trifluoromethyl-2-nitrophenyl)-1*H*-pyrazole,
5-(2-hydroxy-4-methoxyphenyl)-1-(2-nitrophenyl)-1*H*-pyrazole, retention time [min] 1.509, $M+H^+$ [m/e] 312.30;
5-(2-hydroxy-4-methoxyphenyl)-1-(4-ethoxycarbonylphenyl)-1*H*-pyrazole, retention time [min] 1.899, $M+H^+$ [m/e] 339.36;
5-(2-hydroxy-4-methoxyphenyl)-1-(2-aminophenyl)-1*H*-pyrazole,

and ether cleavage thereof gives the following compounds

5-(2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.548, $M+H^+$ [m/e] 287.72;
5-(2,4-dihydroxyphenyl)-1-(2,4-difluorophenyl)-1*H*-pyrazole, retention time [min] 1.288, $M+H^+$ [m/e] 289.25;
5-(2,4-dihydroxyphenyl)-1-(3,5-dichlorophenyl)-1*H*-pyrazole, retention time [min] 1.807, $M+H^+$ [m/e] 322.16;
5-(2,4-dihydroxyphenyl)-1-(3-chloro-2-cyanophenyl)-1*H*-pyrazole, retention time [min] 1.726, $M+H^+$ [m/e] 312.73;
5-(2,4-dihydroxyphenyl)-1-(2,6-dichlorophenyl)-1*H*-pyrazole, retention time [min] 1.356, $M+H^+$ [m/e] 322.16;
5-(2,4-dihydroxyphenyl)-1-(2-chloro-5-trifluoromethylphenyl)-1*H*-pyrazole, retention time [min] 1.641, $M+H^+$ [m/e] 355.71;
5-(2,4-dihydroxyphenyl)-1-(2-ethylphenyl)-1*H*-pyrazole, retention time [min] 1.439, $M+H^+$ [m/e] 281.33;
5-(2,4-dihydroxyphenyl)-1-(3-hydroxyphenyl)-1*H*-pyrazole, retention time [min] 0.984, $M+H^+$ [m/e] 269.27;
5-(2,4-dihydroxyphenyl)-1-(3-cyanophenyl)-1*H*-pyrazole, retention time [min] 1.296, $M+H^+$ [m/e] 278.28;

5-(2,4-dihydroxyphenyl)-1-(3-trifluoromethylphenyl)-1*H*-pyrazole, retention time [min] 1.665, $M+H^+$ [m/e] 321.27;

5-(2,4-dihydroxyphenyl)-1-(3-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.506, $M+H^+$ [m/e] 287.72;

5-(2,4-dihydroxyphenyl)-1-(3-carboxyphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(3-fluorophenyl)-1*H*-pyrazole, retention time [min] 1.360, $M+H^+$ [m/e] 271.26;

5-(2,4-dihydroxyphenyl)-1-(4-bromophenyl)-1*H*-pyrazole, retention time [min] 1.545, $M+H^+$ [m/e] 332.17;

5-(2,4-dihydroxyphenyl)-1-phenyl-1*H*-pyrazole, retention time [min] 1.217, $M+H^+$ [m/e] 253.27;

5-(2,4-dihydroxyphenyl)-1-(4-trifluoromethylphenyl)-1*H*-pyrazole, retention time [min] 1.687, $M+H^+$ [m/e] 321.27;

5-(2,4-dihydroxyphenyl)-1-(4-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.506, $M+H^+$ [m/e] 287.72;

5-(2,4-dihydroxyphenyl)-1-(4-aminosulfonylphenyl)-1*H*-pyrazole, retention time [min] 0.936, $M+H^+$ [m/e] 332.35;

5-(2,4-dihydroxyphenyl)-1-(4-carboxyphenyl)-1*H*-pyrazole, retention time [min] 1.051, $M+H^+$ [m/e] 297.28;

5-(2,4-dihydroxyphenyl)-1-(4-cyanophenyl)-1*H*-pyrazole, retention time [min] 1.325, $M+H^+$ [m/e] 278.28;

5-(2,4-dihydroxyphenyl)-1-(4-hydroxyphenyl)-1*H*-pyrazole, retention time [min] 0.907, $M+H^+$ [m/e] 269.27;

5-(2,4-dihydroxyphenyl)-1-(3-chloro-4-methylphenyl)-1*H*-pyrazole, retention time [min] 1.638, $M+H^+$ [m/e] 301.74;

5-(2,4-dihydroxyphenyl)-1-(4-methylphenyl)-1*H*-pyrazole, retention time [min] 1.384, $M+H^+$ [m/e] 267.30;

5-(2,4-dihydroxyphenyl)-1-(2,6-difluorophenyl)-1*H*-pyrazole, retention time [min] 1.175, $M+H^+$ [m/e] 289.25;

5-(2,4-dihydroxyphenyl)-1-(4-cyano-2-nitrophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-trifluoromethyl-2-nitrophenyl)-1*H*-pyrazole,
5-(2,4-dihydroxyphenyl)-1-(2-nitrophenyl)-1*H*-pyrazole,
5-(2,4-dihydroxyphenyl)-1-(4-ethoxycarbonylphenyl)-1*H*-pyrazole,
5-(2,4-dihydroxyphenyl)-1-(2-aminophenyl)-1*H*-pyrazole, retention time [min] 0.903, $M+H^+$ [m/e] 268.29;
5-(2,4-dihydroxyphenyl)-1-(2-methylphenyl)-1*H*-pyrazole, retention time [min] 1.498, $M+H^+$ [m/e] 267.30;
5-(2,4-dihydroxy-5-bromophenyl)-1-(2-aminophenyl)-1*H*-pyrazole, retention time [min] 1.478, $M+H^+$ [m/e] 347.19;
5-(2,4-dihydroxyphenyl)-1-(3-aminophenyl)-1*H*-pyrazole, retention time [min] 0.806, $M+H^+$ [m/e] 268.29;
5-(2,4-dihydroxy-5-bromophenyl)-1-(3-aminophenyl)-1*H*-pyrazole, $M+H^+$ [m/e] 347.19;
5-(2,4-dihydroxyphenyl)-1-(3-methylphenyl)-1*H*-pyrazole, retention time [min] 1.547, $M+H^+$ [m/e] 267.30;
5-(2,4-dihydroxyphenyl)-1-(2-carboxyphenyl)-1*H*-pyrazole, retention time [min] 0.95, $M+H^+$ [m/e] 297.28;
5-(2,4-dihydroxyphenyl)-1-(4-fluorophenyl)-1*H*-pyrazole, retention time [min] 1.437, $M+H^+$ [m/e] 271.26;
5-(2,4-dihydroxy-5-bromophenyl)-1-(4-fluorophenyl)-1*H*-pyrazole, retention time [min] 1.809, $M+H^+$ [m/e] 350.16;
5-(2,4-dihydroxy-5-bromophenyl)-1-(3-methylphenyl)-1*H*-pyrazole, $M+H^+$ [m/e] 346.20.

The following compounds are obtained analogously

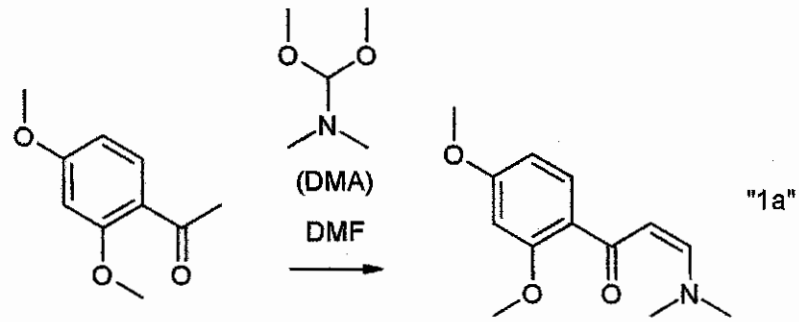
5-(2,4-dihydroxy-5-bromophenyl)-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.599, $M+H^+$ [m/e] 366.62;

5-(2,4-dihydroxy-5-chlorophenyl)-1-(2-fluorophenyl)-1*H*-pyrazole, retention time [min] 1.511, $M+H^+$ [m/e] 305.71;

5-(2,4-dihydroxy-5-bromophenyl)-1-(2-ethylphenyl)-1*H*-pyrazole, retention time [min] 1.659, $M+H^+$ [m/e] 360.23.

Example 6

1. N,N-dimethylformamide dimethyl acetal (DMA) is added to a solution of 2,4-dimethoxyacetophenone in dimethylformamide (DMF), and the mixture is refluxed for 24 hours on a water separator.
Removal of the solvent and conventional work-up gives ("1a")



2. A solution of 7.0 g of "1a" and 4.68 g of (4-nitrophenyl)hydrazine in 100 ml of ethanol is refluxed for 16 hours. Removal of the solvent and conventional work-up gives 6.6 g of 5-(2,4-dimethoxyphenyl)-1-(4-nitrophenyl)-1*H*-pyrazole ("A8").

3. Analogously to Example 3, reduction thereof using hydrogen on Pd/C gives the compound 5-(2,4-dimethoxyphenyl)-1-(4-aminophenyl)-1*H*-pyrazole ("A9").

4. Reaction of "A9" with the following acid chlorides

benzoyl chloride,
acetyl chloride,
propionyl chloride,
butyryl chloride,

pyridine-4-carbonyl chloride,

phenylacetyl chloride

under standard acylation conditions gives the following N-acyl compounds

5-(2,4-dimethoxyphenyl)-1-(4-benzoylaminophenyl)-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-(4-acetylaminophenyl)-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-(4-propionylaminophenyl)-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-[4-(butyrylamino)phenyl]-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-[4-(pyridin-4-ylcarbonylamino)phenyl]-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-[4-(phenylacetylamino)phenyl]-1*H*-pyrazole.

5. Ether cleavage thereof analogously to Example 2 gives the following compounds

5-(2,4-dihydroxyphenyl)-1-(4-benzoylaminophenyl)-1*H*-pyrazole, retention time [min] 1.734, $M+H^+$ [m/e] 372.40;

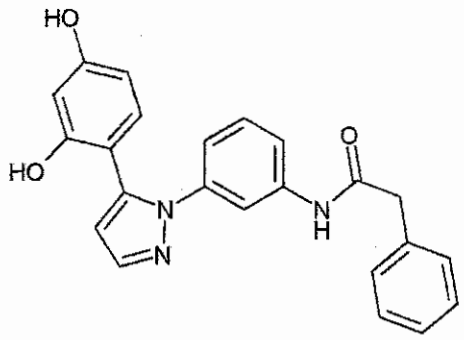
5-(2,4-dihydroxyphenyl)-1-(4-acetylaminophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-propionylaminophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-[4-(butyrylamino)phenyl]-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-[4-(pyridin-4-ylcarbonylamino)phenyl]-1*H*-pyrazole, retention time [min] 1.012, $M+H^+$ [m/e] 373.38;

5-(2,4-dihydroxyphenyl)-1-[4-(phenylacetylamino)phenyl]-1*H*-pyrazole, retention time [min] 1.495, $M+H^+$ [m/e] 386.42



The following are obtained analogously

5-(2,4-dihydroxyphenyl)-1-(3-benzoylaminophenyl)-1*H*-pyrazole, retention time [min] 1.427, $M+H^+$ [m/e] 372.40;

5-(2,4-dihydroxyphenyl)-1-[4-(pyridin-3-ylcarbonylamino)phenyl]-1*H*-pyrazole, retention time [min] 1.214, $M+H^+$ [m/e] 373.38;

5-(2,4-dihydroxyphenyl)-1-[3-(pyridin-2-ylcarbonylamino)phenyl]-1*H*-pyrazole, retention time [min] 1.683, $M+H^+$ [m/e] 373.38;

5-(2,4-dihydroxyphenyl)-1-[4-(pyridin-2-ylcarbonylamino)phenyl]-1*H*-pyrazole, retention time [min] 1.669, $M+H^+$ [m/e] 373.38;

5-(2,4-dihydroxyphenyl)-1-[3-(pyridin-3-ylcarbonylamino)phenyl]-1*H*-pyrazole, retention time [min] 1.205, $M+H^+$ [m/e] 373.38;

5-(2,4-dihydroxyphenyl)-1-[3-(pyridin-4-ylcarbonylamino)phenyl]-1*H*-pyrazole, retention time [min] 1.210, $M+H^+$ [m/e] 373.38;

5-(2,4-dihydroxyphenyl)-1-[4-(methoxyethylcarbonylamino)phenyl]-1*H*-pyrazole, $M+H^+$ [m/e] 354.38;

5-(2,4-dihydroxyphenyl)-1-[2-(pyridin-3-ylcarbonylamino)phenyl]-1*H*-pyrazole, retention time [min] 1.159, $M+H^+$ [m/e] 373.38;

5-(2,4-dihydroxyphenyl)-1-(2-benzoylaminophenyl)-1*H*-pyrazole, retention time [min] 1.875, $M+H^+$ [m/e] 372.40;

5-(2,4-dihydroxy-5-bromophenyl)-1-(2-benzoylaminophenyl)-1*H*-pyrazole, retention time [min] 2.120, $M+H^+$ [m/e] 451.30;

5-(2,4-dihydroxyphenyl)-1-[2-(benzylcarbonylamino)phenyl]-1*H*-pyrazole, retention time [min] 1.820, $M+H^+$ [m/e] 386.42;

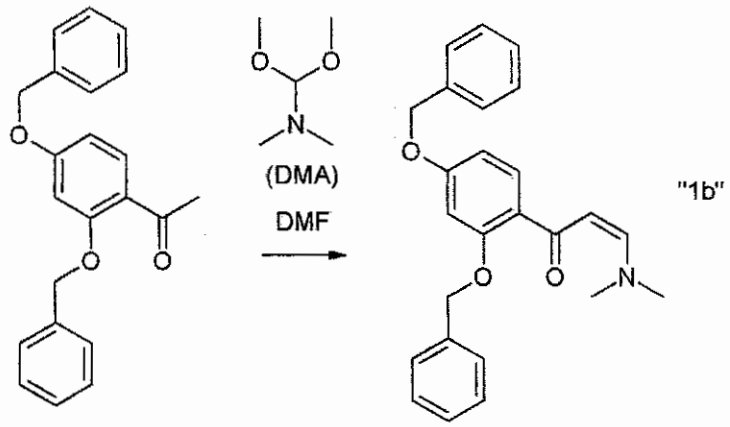
5-(2,4-dihydroxy-5-bromophenyl)-1-[2-(benzylcarbonylamino)phenyl]-1*H*-pyrazole, retention time [min] 2.079, $M+H^+$ [m/e] 465.32;

5-(2,4-dihydroxyphenyl)-1-[2-(pyridin-4-ylcarbonylamino)phenyl]-1*H*-pyrazole, retention time [min] 1.148, $M+H^+$ [m/e] 373.38.

Example 7

Instead of the methyl groups in "1a", a benzyl group may also advantageously be employed as hydroxyl-protecting group.
Alternatively, acetyl or p-methoxybenzyl can be used.

1. N,N-dimethylformamide dimethyl acetal (DMA) is added to a solution of 2,4-dibenzyloxyacetophenone in dimethylformamide (DMF), and the mixture is refluxed for 24 hours on a water separator. Removal of the solvent and conventional work-up gives ("1b")



2. A solution of "1b" and (4-carboxyphenyl)hydrazine in ethanol is refluxed for 16 hours. Removal of the solvent and conventional work-up gives 5-(2,4-dibenzyloxyphenyl)-1-(4-carboxyphenyl)-1*H*-pyrazole ("A10").

Reaction thereof with thionyl chloride under standard conditions gives 5-(2,4-dibenzyloxyphenyl)-1-(4-chlorocarbonylphenyl)-1*H*-pyrazole ("A11").

Reaction of "A11" with the following amines

benzylamine,
methylamine,
ethylamine,
propylamine,

under standard acylation conditions gives the following N-acyl compounds

5-(2,4-dibenzyloxyphenyl)-1-[4-(benzylaminocarbonyl)phenyl]-1*H*-pyrazole,
5-(2,4-dibenzyloxyphenyl)-1-[4-(methylaminocarbonyl)phenyl]-1*H*-pyrazole,
5-(2,4-dibenzyloxyphenyl)-1-[4-(ethylaminocarbonyl)phenyl]-1*H*-pyrazole,
5-(2,4-dibenzyloxyphenyl)-1-[4-(propylaminocarbonyl)phenyl]-1*H*-pyrazole.

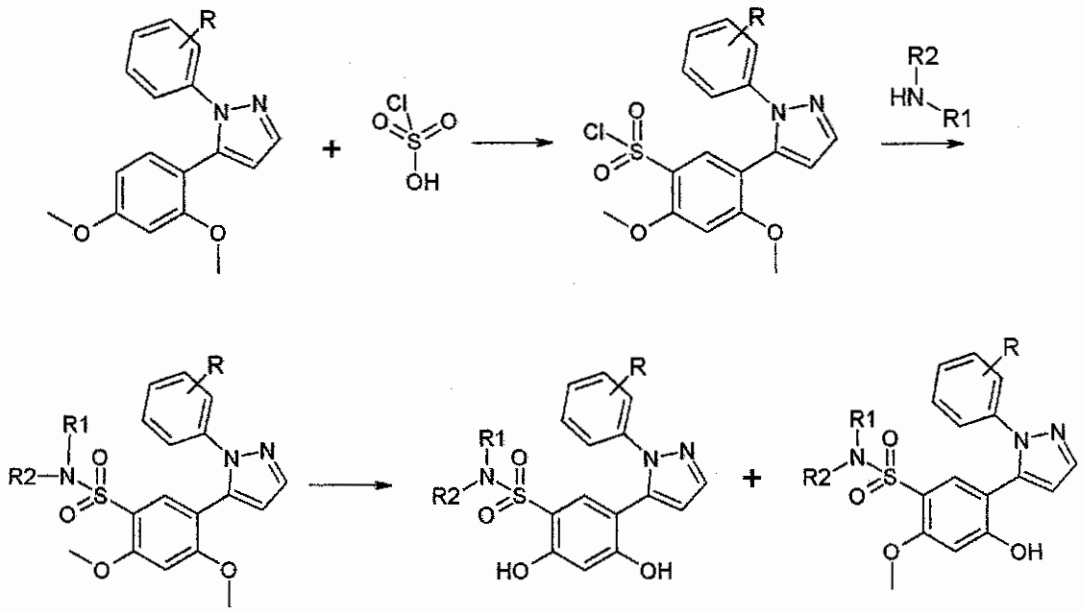
The ether cleavage is carried out using hydrogen on Pd/C analogously to Example 3. The following compounds are obtained

5-(2,4-dihydroxyphenyl)-1-[4-(benzylaminocarbonyl)phenyl]-1*H*-pyrazole,
5-(2,4-dihydroxyphenyl)-1-[4-(methylaminocarbonyl)phenyl]-1*H*-pyrazole,
5-(2,4-dihydroxyphenyl)-1-[4-(ethylaminocarbonyl)phenyl]-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-[4-(propylaminocarbonyl)phenyl]-1*H*-pyrazole.

Example 8

Synthetic scheme for the preparation of sulfonamide derivatives



Preparation of 5-(5-aminosulfonyl-2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole ("C3")

8.1 18.0 g of 5-(2,4-dimethoxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole ("B1"; obtainable analogously to Example 1) are added at -5° to 30 ml of chlorosulfonic acid, and the mixture is stirred at room temperature for a further 3 hours. The mixture is poured onto ice, the precipitated crystals are separated off and washed with water, giving 23.6 g of 5-(5-chlorosulfonyl-2,4-dimethoxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole ("B2").

8.2 20 ml of a 32% ammonia solution are added at room temperature to a solution of 413.3 mg of "B2" in 5 ml of dry methanol. The mixture is stirred overnight, approximately half of the solvent is removed, the precipitated crystals are separated off and washed with water, giving 230 mg of 5-(5-aminosulfonyl-2,4-dimethoxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole ("C1") and, as by-product, 5-(5-hydroxysulfonyl-2,4-dimethoxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole ("C2").

8.3 450 mg of "C1" are dissolved in 5 ml of dichloromethane under a nitrogen atmosphere, and the solution is cooled to -20° in a dry-ice bath. 1 ml of boron tribromide is then slowly added dropwise using a syringe via a septum, and the mixture is stirred at room temperature for a further 16 hours.

The mixture is cooled to -20°, and methanol and finally one drop of water are added dropwise. The solvent is removed at room temperature, and the residue is dissolved in 2 ml of methanol.

Separation via a 130 g RP-18 column by means of a CombiFlash COMPANION instrument gives 122 mg of "C3", retention time [min] 0.837, $M+H^+$ [m/e] 366.79.

Analogous reaction of "B2" with

N-ethyl-*N'*-methylamine,
N,N'-diethylamine,
piperidine,
aniline,
2-fluoroaniline,
3-fluoroaniline,
4-fluoroaniline,
3-aminopyridine,
3-hydroxymethylpiperidine,
N-benzyl-*N'*-methylamine,

N,N'-dimethylamine,
N-(2-hydroxyethyl)-*N'*-methylamine,
N-cyclohexyl-*N'*-methylamine,
3-methylamino-1,2-propanediol,
N-butyl-*N'*-methylamine,
N-propyl-*N'*-methylamine,
N-(2-cyanoethyl)-*N'*-methylamine,
N-isopropyl-*N'*-methylamine,
N,N'-dimethyl-2-methylaminoacetamide (sarcosine-*N,N'*-dimethyl-amide),
2-hydroxymethylpiperidine,
morpholine,
2-(*N,N'*-diethylaminomethyl)piperidine,
1-methylpiperazine,
methylamine,
4-aminopyridine

gives the compounds

5-[5-(*N*-ethyl-*N'*-methylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N,N'*-diethylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chloro-phenyl)-1*H*-pyrazole,

5-[5-(piperidine-1-sulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-phenylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chloro-phenyl)-1*H*-pyrazole,

5-{5-[*N*-(2-fluorophenyl)aminosulfonyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(3-fluorophenyl)aminosulfonyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(4-fluorophenyl)aminosulfonyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(pyridin-3-yl)aminosulfonyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(3-hydroxymethylpiperidine-1-sulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-benzyl-*N'*-methylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*,*N'*-dimethylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-(2-hydroxyethyl)-*N'*-methylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-cyclohexyl-*N'*-methylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-(2,3-dihydroxypropyl)-*N'*-methylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-butyl-*N'*-methylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-(2-cyanoethyl)-*N'*-methylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-isopropyl-*N'*-methylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(dimethylaminocarbonylmethyl)-*N'*-methylaminosulfonyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(2-hydroxymethylpiperidine-1-sulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(morpholine-4-sulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[2-(*N,N'*-diethylaminomethyl)piperidin-4-yl]sulfonyl}-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(1-methylpiperazin-4-yl)sulfonyl]-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-methylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(pyridin-4-yl)aminosulfonyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

and ether cleavage thereof gives the compounds

5-[5-(*N*-ethyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.367, $M+H^+$ [m/e] 408.88;

5-[5-(*N-N'*-diethylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.468, $M+H^+$ [m/e] 422.90;

5-[5-(piperidine-1-sulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.558, $M+H^+$ [m/e] 434.91;

5-[5-(*N*-phenylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.620, $M+H^+$ [m/e] 442.89 and

5-[5-(*N*-phenylaminosulfonyl)-2-hydroxy-4-methoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, $M+H^+$ [m/e] 456.92;

5-{5-[*N*-(2-fluorophenyl)aminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.475, $M+H^+$ [m/e] 460.88;

5-{5-[*N*-(3-fluorophenyl)aminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.502, $M+H^+$ [m/e] 460.88;

5-{5-[*N*-(4-fluorophenyl)aminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.478, $M+H^+$ [m/e] 460.88;

5-{5-[*N*-(pyridin-3-yl)aminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 0.923, $M+H^+$ [m/e] 443.99;

5-[5-(3-hydroxymethylpiperidine-1-sulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.176, $M+H^+$ [m/e] 464.94 and

5-[5-(3-bromomethylpiperidine-1-sulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, M+H$^+$ [m/e] 527.84;

5-[5-(*N*-benzyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.710, M+H$^+$ [m/e] 470.95 and

5-[5-(*N*-benzyl-*N'*-methylaminosulfonyl)-2-methoxy-4-hydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-*N'*-dimethylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.234, M+H$^+$ [m/e] 394.85;

5-[5-(*N*-(2-bromoethyl)-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.483, M+H$^+$ [m/e] 487.78;

5-[5-(*N*-cyclohexyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.738, M+H$^+$ [m/e] 462.97;

5-[5-(*N*-(2,3-dibromopropyl)-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.694, M+H$^+$ [m/e] 580.70;

5-[5-(*N*-butyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.665, M+H$^+$ [m/e] 436.93;

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.511, M+H$^+$ [m/e] 422.90;

5-{5-[*N*-(2-cyanoethyl)-*N'*-methylaminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.271, M+H$^+$ [m/e] 433.89;

5-[5-(*N*-isopropyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.412, M+H$^+$ [m/e] 422.90;

5-{5-[*N*-(dimethylaminocarbonylmethyl)-*N'*-methylaminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.044, M+H$^+$ [m/e] 465.93;

5-[5-(2-hydroxymethylpiperidine-1-sulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.159, $M+H^+$ [m/e] 464.94;

5-[5-(morpholine-4-sulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole and

5-{5-[*N*-(2-hydroxyethyl)-*N'*-(2-bromoethyl)aminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.250, $M+H^+$ [m/e] 517.80 and

5-{5-[*N*-(2-hydroxyethyl)-*N'*-(2-bromoethyl)aminosulfonyl]-2-hydroxy-4-methoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole;

5-{5-[2-(*N,N'*-diethylaminomethyl)piperidin-4-yl]sulfonyl}-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 0.967, $M+H^+$ [m/e] 520.06;

5-[5-(1-methylpiperazin-4-yl)sulfonyl]-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 0.848, $M+H^+$ [m/e] 449.93;

5-[5-(*N*-methylaminosulfonyl)-2,4-hydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.011, $M+H^+$ [m/e] 380.82;

5-{5-[*N*-(pyridin-4-yl)aminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 0.784, $M+H^+$ [m/e] 443.88.

The compounds

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole, retention time [min] 1.441, $M+H^+$ [m/e] 402.48;

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole, retention time [min] 1.395, $M+H^+$ [m/e] 406.45,

are obtained analogously

Example 9

Analogously to Example 8, reaction of 5-(5-chlorosulfonyl-2,4-dimethoxyphenyl)-1-(2-methylphenyl)-1*H*-pyrazole ("D1")

with

aniline,

benzylamine,

N,N'-diethylamine,

ethylamine,

ammonia,

gives the compounds

5-[5-(*N*-phenylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(*N*-benzylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(*N,N'*-diethylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(ethylaminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(aminosulfonyl)-2,4-dimethoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

and ether cleavage thereof gives the compounds

5-[5-(*N*-phenylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole, retention time [min] 1.438, $M+H^+$ [m/e] 422.47 and

5-[5-(*N*-phenylaminosulfonyl)-2-hydroxy-4-methoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole, retention time [min] 1.662, $M+H^+$ [m/e] 436.50;

5-[5-(*N*-benzylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole, retention time [min] 1.483, $M+H^+$ [m/e] 436.50 and

5-[5-(*N*-benzylaminosulfonyl)-2-hydroxy-4-methoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole, retention time [min] 1.702, $M+H^+$ [m/e] 436.50;

5-[5-(*N,N'*-diethylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole, retention time [min] 1.497, $M+H^+$ [m/e] 402.48 and

5-[5-(*N,N'*-diethylaminosulfonyl)-2-hydroxy-4-methoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole, retention time [min] 1.790, $M+H^+$ [m/e] 416.51;

5-[5-(ethylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole, retention time [min] 1.423, $M+H^+$ [m/e] 374.43 and

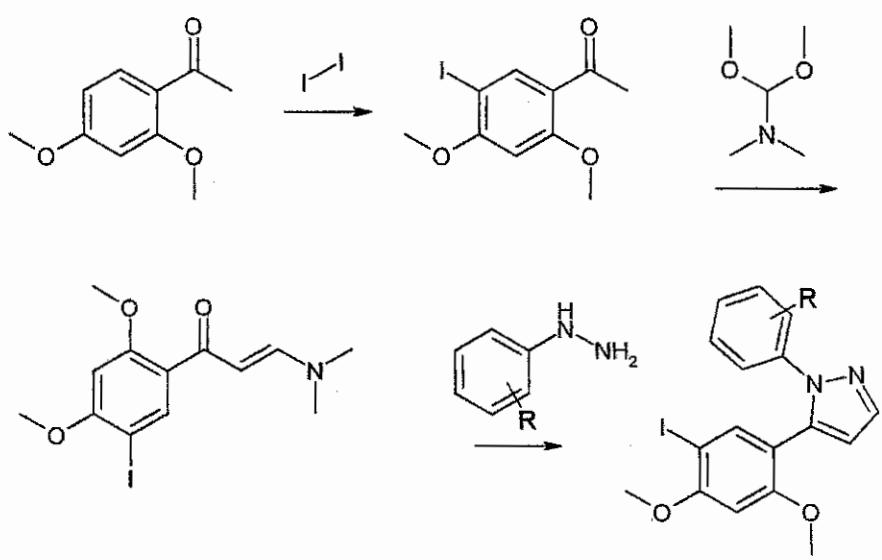
5-[5-(ethylaminosulfonyl)-2-hydroxy-4-methoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole, retention time [min] 1.156, $M+H^+$ [m/e] 388.46;

5-[5-(aminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole, retention time [min] 1.573, $M+H^+$ [m/e] 346.38 and

5-[5-(aminosulfonyl)-2-hydroxy-4-methoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole, retention time [min] 1.864, $M+H^+$ [m/e] 360.40.

Example 10

General scheme for the preparation of iodine compounds of the formula I



Preparation of 5-[5-iodo-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole:

10.1 63.45 g of iodine and subsequently 88.57 g of Selectfluor are added at room temperature to a solution of 90.1 g of 2,4-dimethoxyacetophenone in 2.5 l of acetonitrile, and the mixture is stirred for a further 2.5 hours. Conventional work-up and crystallisation from 400 ml of methanol gives 166 g of 2,4-dimethoxy-5-iodoacetophenone ("E1").

10.2 A mixture of 18.3 g of "E1" and 50 ml of *N,N*-dimethylformamide dimethyl acetal is refluxed (170°) for 16 hours on a water separator. The solvent is separated off, 100 ml of MTB ether are added, and the crystals are separated off, giving 15.5 g of (E)-3-dimethylamino-1-(5-iodo-2,4-dimethoxyphenyl)propenone ("E2").

10.3 A solution of 8.05 g of "E2" and 4.0 g of (2-chlorophenyl)hydrazine hydrochloride in 50 ml of ethanol is refluxed for 16 hours. The reaction mixture is purified by chromatography (ISCO/330 g column; petroleum ether/ethyl acetate: 10/90 to 1/1), giving 8.4 g of 5-[5-iodo-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole ("E2a").

Ether cleavage thereof using boron tribromide gives 5-[5-iodo-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole.

Analogous reaction of "E2" with

(2-fluorophenyl)hydrazine

gives the compound

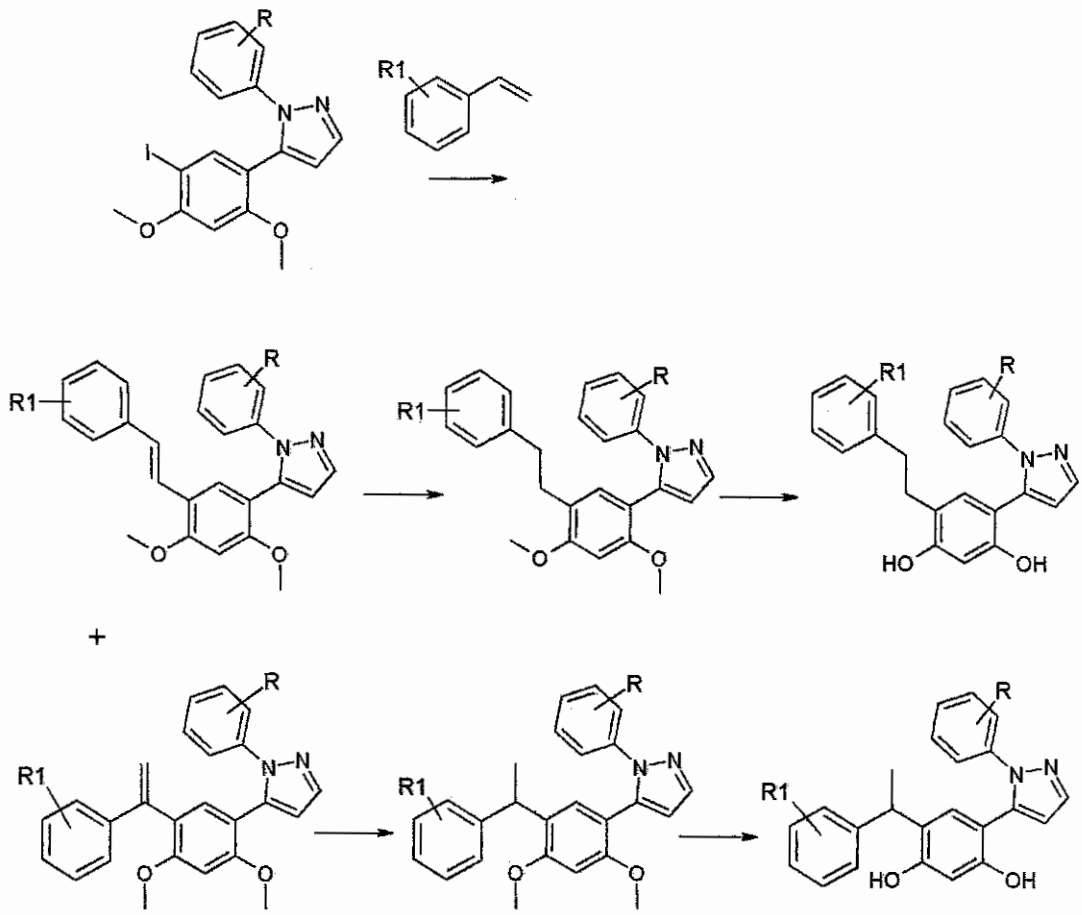
5-[5-iodo-2,4-dimethoxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole ("E3a")

and ether cleavage thereof gives

5-[5-iodo-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole ("E3"), $M+H^+$ [m/e] 397.16.

Example 11

General scheme for the preparation of compounds of the formula I by means of Heck reaction

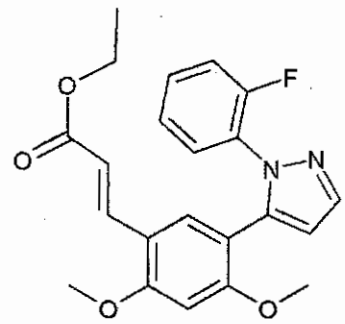


11-A

Preparation of 5-[5-carboxyethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole and 5-[5-methoxycarbonylethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole:

11.A.1 A mixture of 1.061 g of "E3a", 250.29 mg of ethyl acrylate, 0.7 ml of triethylamine, 22.45 mg of palladium(II) acetate (47% of Pd), 30.74 mg of tri-o-tolylphosphine and 5 ml of acetonitrile is irradiated in the micro-

wave for 30 minutes at 160°. Toluene is added to the reaction mixture, which is extracted a number of times with water. The organic phase is dried and evaporated. The product is purified by chromatography (ISCO/40 g column; petroleum ether/ethyl acetate: 4/1 to 1/1), giving 0.7 g of ethyl 3-{5-[2-(2-fluorophenyl)-2*H*-pyrazol-3-yl]-2,4-dimethoxyphenyl}acrylate ("E4") as isomer mixture (E/Z) in the ratio 95/5;



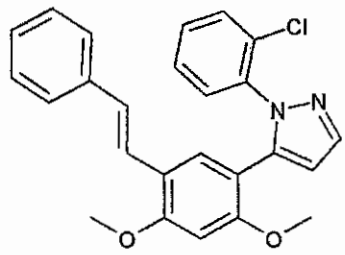
"E4".

11.A.2 A mixture of 383 mg of "E4", 400 mg of 5% Pd/C (56% of water) and 10 ml of THF is hydrogenated for 16 hours at 1.4 bar and room temperature in a BÜCHI apparatus. Removal of the catalyst and removal of the solvent gives 398.4 mg of 5-[5-(2-ethoxycarbonylethyl)-2,4-dimethoxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole ("E5").

11.A.3 Ether cleavage analogously to Example 8.3 gives a mixture of 73 mg of 5-[5-(2-carboxyethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole, $M+H^+$ [m/e] 343.33
and 356 mg of 5-[5-(2-methoxycarbonylethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole, $M+H^+$ [m/e] 357.35.

11.B

11.B.1 Analogously to Example 11.A.1, reaction of "E2a" with styrene gives the compound 5-[5-styryl-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole ("E6")



"E6".

11.B.2 Hydrogenation of "E6" gives the compound 5-[5-(2-phenylethyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole and ether cleavage thereof gives the compound 5-[5-(2-phenylethyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.872, $M+H^+$ [m/e] 391.87.

An analogous reaction gives the compounds

5-[5-styryl-2,4-dimethoxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole, hydrogenation thereof gives 5-[5-(2-phenylethyl)-2,4-dimethoxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole, and ether cleavage thereof gives 5-[5-(2-phenylethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole, $M+H^+$ [m/e] 375.41.

The compound 5-[5-(2-phenyl-2-methoxyethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole, $M+H^+$ [m/e] 405.44, is formed as by-product during the ether cleavage.

Ether cleavage of 5-[5-styryl-2,4-dimethoxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole gives 5-[5-styryl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole, $M+H^+$ [m/e] 373.40.

11.C

11.C.1 Analogously to Example 11.A.1, reaction of "E2a" with 4-vinylpyridine gives the compound 5-{5-[2-(pyridin-4-yl)vinyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole ("E7").

11.C.2 Hydrogenation of "E7" using 5% Pt/C as catalyst gives the compound 5-{5-[2-(pyridin-4-yl)ethyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole and ether cleavage thereof gives the compound 5-{5-[2-(pyridin-4-yl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.397, $M+H^+$ [m/e] 392.86.

Ether cleavage of "E7" gives the compound 5-{5-[2-(pyridin-4-yl)vinyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole.

11.D

Analogous reaction of "E2a" with 2-vinylpyridine gives the compound 5-{5-[2-(pyridin-2-yl)vinyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole ("E8").

Hydrogenation and subsequent ether cleavage thereof gives the compound 5-{5-[2-(pyridin-2-yl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 0.702, $M+H^+$ [m/e] 392.86.

11.E

Analogous reaction of "E2a" with 4-fluorostyrene gives the compounds 5-[5-(4-fluorostyryl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole ("E9") and

5-{5-[1-(4-fluorophenyl)vinyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole.

Hydrogenation and subsequent ether cleavage of "E9" gives the compound 5-{5-[2-(4-fluorophenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.882, $M+H^+$ [m/e] 409.86.

11.F

Analogous reaction of "E2a" with 3-fluorostyrene gives the compounds 5-[5-(3-fluorostyryl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole ("E10") and 5-{5-[1-(3-fluorophenyl)vinyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole.

Hydrogenation and subsequent ether cleavage of "E10" gives the compound 5-{5-[2-(3-fluorophenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.895, $M+H^+$ [m/e] 409.86.

11.G

Analogous reaction of "E2a" with 2-fluorostyrene gives the compounds 5-[5-(2-fluorostyryl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole ("E11") and 5-{5-[1-(2-fluorophenyl)vinyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole.

Hydrogenation and subsequent ether cleavage of "E11" gives the compound 5-{5-[2-(2-fluorophenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.866, $M+H^+$ [m/e] 409.86.

11.H

Hydrogenation of 700 mg of "E9" in THF with addition of 1.8 g of 5% Pt/C also gives, after 30 hours, complete dechlorination in addition to hydrogenation of the double bond. Removal of the catalyst and removal of the solvent gives 470 mg of 5-{5-[1-(4-fluorophenyl)ethyl]-2,4-dimethoxyphenyl}-1-phenyl-1*H*-pyrazole.

Ether cleavage thereof gives 5-{5-[1-(4-fluorophenyl)ethyl]-2,4-dihydroxyphenyl}-1-phenyl-1*H*-pyrazole, retention time [min] 1.874, $M+H^+$ [m/e] 375.41.

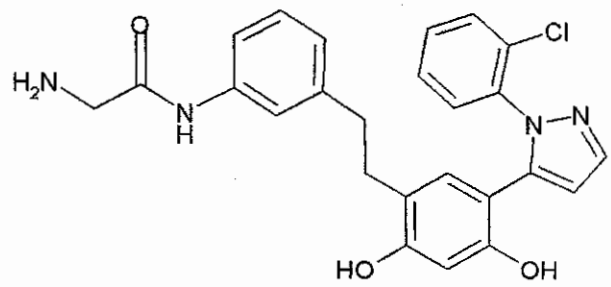
11.I.

Analogous reaction of "E2a" with 3-nitrostyrene gives the compounds 5-[5-(3-nitrostyryl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole ("E12").

Hydrogenation of "E12" gives the compound 5-{5-[2-(3-aminophenyl)-ethyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole ("E13").

Acylation of "E13" using trifluoroacetyl chloride and subsequent ether cleavage gives the compound 5-{5-[2-(3-trifluoroacetamidophenyl)ethyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole.

Reaction of "E13" with BOC-glycine and subsequent removal of the BOC group and also of the methyl ether gives

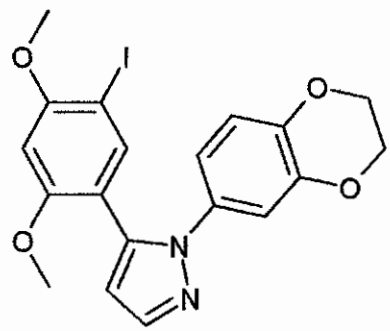


11.J

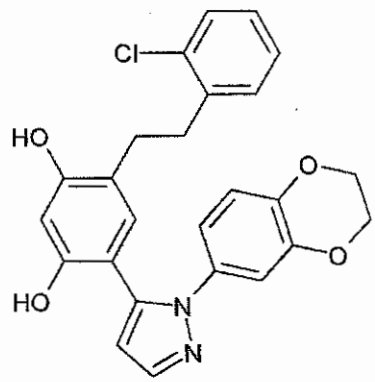
Analogous reaction of "E2a" with 3-carboxystyrene gives the compound 5-[5-(3-carboxystyryl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole and hydrogenation thereof gives 5-{5-[2-(3-carboxyphenyl)ethyl]-2,4-dimethoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole. Ether cleavage gives 5-{5-[2-(3-carboxyphenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole.

Example 12

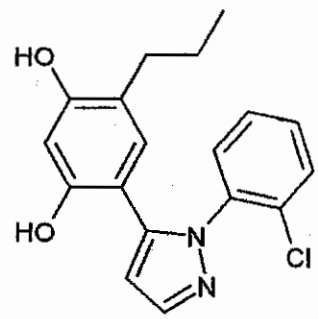
12.1 The compound 5-[5-iodo-2,4-dimethoxyphenyl]-1-(2,3-dihydro-benzo-1,4-dioxin-6-yl)-1*H*-pyrazole is obtained analogously to Example 10



Analogously to Example 11, reaction thereof with 1-chloro-2-vinylbenzene, hydrogenation and subsequent ether cleavage gives the compound 5-{5-[2-(2-chlorophenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2,3-dihydrobenzo-1,4-dioxin-6-yl)-1*H*-pyrazole



12.2 Analogous reaction of "E2a" with propene, hydrogenation and ether cleavage gives the compound 5-{5-propyl-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole



12.3 Analogous reaction of "E2a" with methylenecyclopropane, hydrogenation and ether cleavage gives the compound 5-{5-cyclopropylmethyl-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole.

12.4 Analogous reaction of 5-[5-iodo-2,4-dimethoxyphenyl]-1-(3-methylphenyl)-1*H*-pyrazole with 2-methyl-1-butene, hydrogenation and ether cleavage gives the compound 5-{5-(2-methylbutyl)-2,4-dihydroxyphenyl}-1-(3-methylphenyl)-1*H*-pyrazole.

12.5 Analogous reaction of "E2a" with 2-fluoropropene, hydrogenation and ether cleavage gives the compound 5-{5-(2-fluoropropyl)-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole.

12.6 Analogous reaction of 5-[5-iodo-2,4-dimethoxyphenyl]-1-(2,3-dihydrobenzo-1,4-dioxin-6-yl)-1*H*-pyrazole with 4-vinyltoluene, hydrogenation and ether cleavage gives the compound 5-{5-[2-(4-methylphenyl)-ethyl]-2,4-dihydroxyphenyl}-1-(2,3-dihydrobenzo-1,4-dioxin-6-yl)-1*H*-pyrazole.

12.7 Analogous reaction of "E2a" with isopropenylbenzene, hydrogenation and ether cleavage gives the compound 5-{5-(2-phenylpropyl)-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole.

12.8 Analogous reaction of 5-[5-iodo-2,4-dimethoxyphenyl]-1-(2-nitrophenyl)-1*H*-pyrazole with isopropenylbenzene, hydrogenation and ether cleavage gives the compound 5-{5-(2-phenylpropyl)-2,4-dihydroxyphenyl}-1-(2-aminophenyl)-1*H*-pyrazole.

Example 13

General reaction scheme for the preparation of compounds of the formula I in which

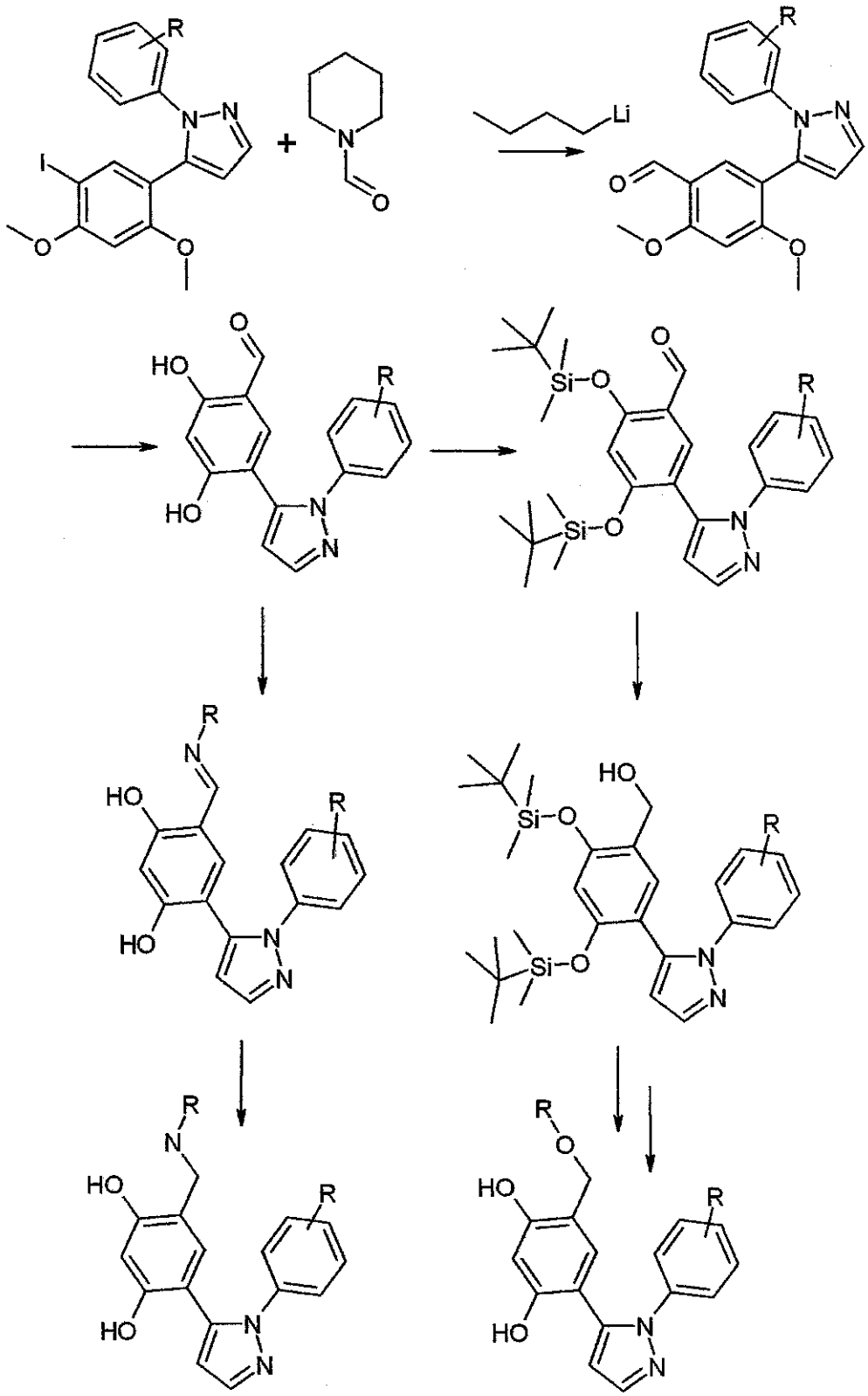
R^2 denotes $-(CH_2)_r-X-(CH)_s-R$,

R denotes Ar or Het,

X denotes NH, NA or O,

r denotes 1,

s denotes 0 or 1:

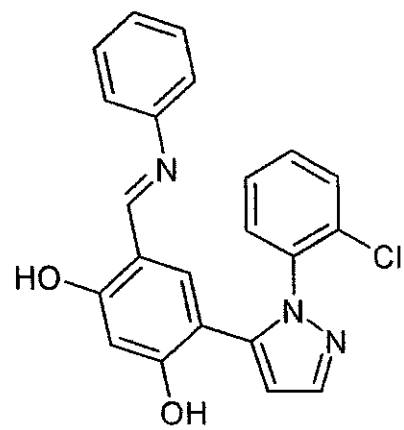

R
N
N
I
O
O
+
N
O
Li
HO
Si
HN
HO

13.A

13.A.1 A solution of 1 g of "E2a" in 10 ml of THF is cooled to -70°. 1.6 ml of butyllithium (15% solution in n-hexane) are added dropwise, during which the temperature is held between -70 and -60°. The mixture is stirred for a further 30 minutes. 0.25 ml of N-formylpiperidine is then added dropwise, and the mixture is allowed to warm to -15°. Semi-concentrated hydrochloric acid is added dropwise, and the mixture is extracted with MTB ether. The organic phases are dried. Removal of the solvent gives 5-[5-formyl-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole ("E2b").

13.A.2 Ether cleavage of "E2b" using BBr_3 gives the compound 5-[5-formyl-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole ("E2c").

13.A.3 Reaction of "E2c" with aniline (formation of the Schiff base) gives the compound



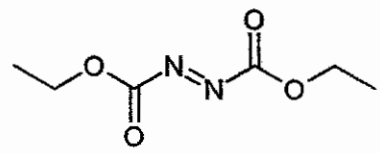
13.A.4 Reduction of the double bond under standard conditions gives 5-[5-phenylaminomethyl-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole.

The compound 5-[5-phenylaminomethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole is obtained analogously.

13.B

13.B.1 Etherification of "E2c" using *tert*-butyldimethylsilyl chloride under standard conditions gives 5-[5-formyl-2,4-di-(*tert*-butyldimethylsilyoxy)-phenyl]-1-(2-chlorophenyl)-1*H*-pyrazole ("E2d").

13.B.2 Reduction of the formyl group in "E2d" using $NaBH_4$ under standard conditions gives 5-[5-hydroxymethyl-2,4-di-(*tert*-butyldimethylsilyoxy)-phenyl]-1-(2-chlorophenyl)-1*H*-pyrazole ("E2e").

13.B.3 Reaction of "E2e", phenol, triphenylphosphine and diethyl azodicarboxylate ("DEAD")  in a Mitsunobu reaction gives the compound 5-[5-phenoxymethyl-2,4-di-(*tert*-butyl-dimethylsilyoxy)phenyl]-1-(2-chlorophenyl)-1*H*-pyrazole.
Ether cleavage thereof using HCl in dioxane gives 5-[5-phenoxymethyl-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole.

The compound 5-[5-phenoxymethyl-2,4-dihydroxyphenyl]-1-(2-fluoro-phenyl)-1*H*-pyrazole is obtained analogously.

13.C

13.C.1 Analogously to 13.B.3, reaction of "E2e" with thiophenol, PPh_3 and DEAD gives the compound 5-[5-phenylthiomethyl-2,4-di-(*tert*-butyl-dimethylsilyoxy)phenyl]-1-(2-chlorophenyl)-1*H*-pyrazole and ether cleavage thereof gives 5-[5-phenylthiomethyl-2,4-dihydroxyphenyl]-1-(2-chloro-phenyl)-1*H*-pyrazole.

The compounds

5-[5-phenylthiomethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-(4-methoxyphenylthiomethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

are obtained analogously.

Simple oxidation of 5-[5-phenylthiomethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole and

5-[5-(4-methoxyphenylthiomethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole

gives

5-[5-phenylsulfinylmethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole and

5-[5-(4-methoxyphenylsulfinylmethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole.

Oxidation of 5-[5-phenylthiomethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole and

5-[5-(4-methoxyphenylthiomethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole

using sodium perborate in acetic acid under standard conditions gives the compounds

5-[5-phenylsulfonylmethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole and

5-[5-(4-methoxyphenylsulfonylmethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole.

Example 14

14.A

14.A.1 A mixture of 440.6 mg of "E2a", 153 µl of thiophenol, 194.3 mg of copper(I) iodide, 139.6 mg of N,N-dimethylglycine hydrochloride, 651.6 mg of caesium carbonate and 4 ml of 1,4-dioxane is stirred at 90° for 50 hours. Conventional work-up gives 510 mg of 5-[5-phenylsulfanyl-2,4-dimethoxy-phenyl]-1-(2-chlorophenyl)-1*H*-pyrazole ("F1").

14.A.2 Reaction of "F1" with BBr_3 in dichloromethane gives a mixture of 5-[5-phenylsulfanyl-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.767, $M+H^+$ [m/e] 395.88
and
5-[5-phenylsulfanyl-2-hydroxy-4-methoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 2.021, $M+H^+$ [m/e] 409.91.

14.A.3 Oxidation of 5-[5-phenylsulfanyl-2-hydroxy-4-methoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole using sodium perborate in glacial acetic acid gives 5-[5-phenylsulfonyl-2-hydroxy-4-methoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, and ether cleavage thereof gives 5-[5-phenylsulfonyl-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.403, $M+H^+$ [m/e] 427.88.

14.B

14.B.1 Analogously to 14.A.1, reaction of "E2a" with
2-fluorobenzylamine,
benzyl alcohol,
(pyridin-4-yl)methanethiol,
aniline,
3-fluorophenylmethanethiol,
(pyridin-2-yl)methylamine,

4-fluorobenzyl alcohol,

gives the compounds

5-[5-(2-fluorobenzylamino)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(5-benzyloxy-2,4-dimethoxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(pyridin-4-ylmethylsulfanyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(5-phenylamino-2,4-dimethoxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(3-fluorophenylmethylsulfanyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, and simple oxidation thereof gives

5-[5-(3-fluorophenylmethylsulfinyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(pyridin-2-ylmethylamino)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(4-fluorobenzyloxy)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole.

14.B.2 Ether cleavage of the compounds obtained under 14.B.1 gives the following dihydroxypyrazole derivatives

5-[5-(2-fluorobenzylamino)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(5-benzyloxy-2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(pyridin-4-ylmethylsulfanyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(5-phenylamino-2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(3-fluorophenylmethylsulfinyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(pyridin-2-ylmethylamino)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(4-fluorobenzyloxy)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole.

14.C

Analogous reaction of 5-[5-iodo-2,4-dimethoxyphenyl]-1-phenyl-1*H*-pyrazole with 4-fluorophenylmethanethiol gives the compound

5-[5-(4-fluorophenylmethylsulfanyl)-2,4-dimethoxyphenyl]-1-phenyl-1*H*-pyrazole, and oxidation thereof using perborate gives

5-[5-(4-fluorophenylmethylsulfonyl)-2,4-dimethoxyphenyl]-1-phenyl-1*H*-pyrazole.

Ether cleavage thereof gives 5-[5-(4-fluorophenylmethylsulfonyl)-2,4-dihydroxyphenyl]-1-phenyl-1*H*-pyrazole.

Analogous reaction of 5-[5-iodo-2,4-dimethoxyphenyl]-1-(3-ethylphenyl)-1*H*-pyrazole and 3-fluorothiophenol gives the compound

5-[5-(3-fluorophenylsulfonyl)-2,4-dihydroxyphenyl]-1-(3-ethylphenyl)-1*H*-pyrazole.

14.D

Analogous reaction of 5-[5-iodo-2,4-dimethoxyphenyl]-1-(3-methylphenyl)-1*H*-pyrazole with thiophenol gives the compound

5-[5-phenylsulfanyl-2,4-dimethoxyphenyl]-1-(3-methylphenyl)-1*H*-pyrazole, and ether cleavage thereof gives

5-[5-phenylsulfanyl-2,4-dihydroxyphenyl]-1-(3-methylphenyl)-1*H*-pyrazole.

14.E

Analogous reaction of 5-[5-iodo-2,4-dimethoxyphenyl]-1-(4-nitrophenyl)-1*H*-pyrazole with 2-fluorothiophenol gives the compound

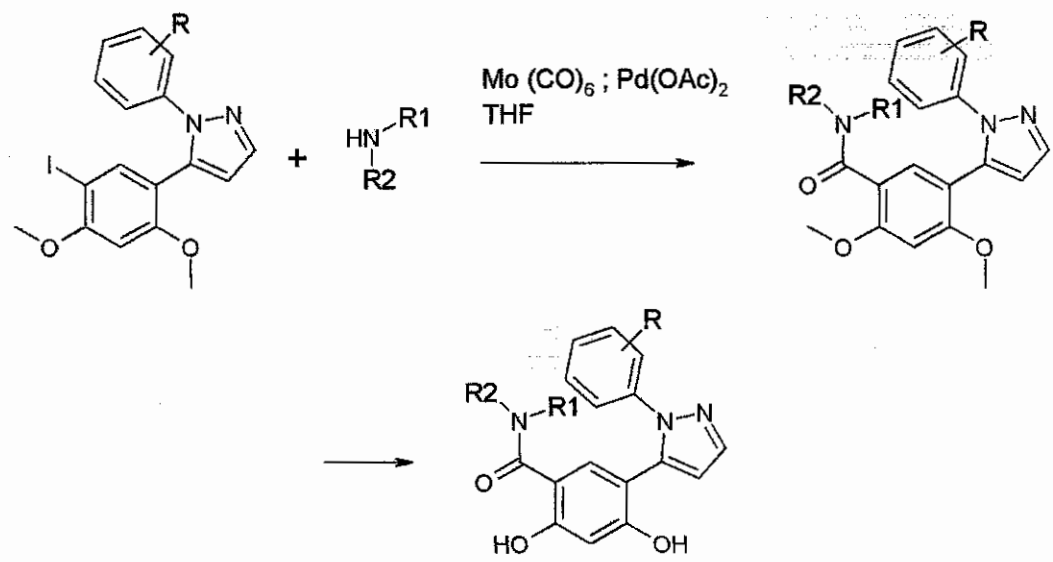
5-[5-(2-fluorophenylsulfanyl)-2,4-dimethoxyphenyl]-1-(4-nitrophenyl)-1*H*-pyrazole; monoether cleavage thereof gives

5-[5-(2-fluorophenylsulfanyl)-2-hydroxy-4-methoxyphenyl]-1-(4-nitrophenyl)-1*H*-pyrazole; and H_2 reduction thereof using Pd/C as catalyst gives the compound

5-[5-(2-fluorophenylsulfanyl)-2-hydroxy-4-methoxyphenyl]-1-(4-aminophenyl)-1*H*-pyrazole.

Example 15

General reaction scheme for the preparation of compounds of the formula I in which R^2 denotes an unsubstituted or substituted amide group



15.A

15.A.1 A mixture of 176.3 mg of "E2a", 123.6 µl of diethylamine, 3 mg of palladium(II) acetate (47% of Pd), 179.1 µl of 1,8-diaza-

bicyclo[5.4.0]undec-7-ene, 2 ml of THF and 105.6 mg of molybdenum hexacarbonyl is irradiated in the microwave for 1 hour at 120°. Conventional work-up gives 5-[5-(*N,N*-diethylaminocarbonyl)-2,4-dimethoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole ("G1").

15.A.2 Ether cleavage of "G1" using BBr_3 gives the compound 5-[5-(*N,N*-diethylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole.

15.B. Analogous reaction of "E2a" and

aniline,

methylamine,

dimethylamine,

ethylamine,

N-propyl-*N*-methylamine,

N-cyclopentyl-*N*-methylamine,

gives the compounds

5-(5-phenylaminocarbonyl-2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N,N*-dimethylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-ethylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.325, $M+H^+$ [m/e] 386.85;

5-[5-(*N*-cyclopentyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole.

15.C Analogous reaction of 5-[5-iodo-2,4-dimethoxyphenyl]-1-(2-chloro-5-fluorophenyl)-1*H*-pyrazole and C-benzo-1,3-dioxol-5-ylmethylamine gives the compound

5-{5-{*N*-[(benzo-1,3-dioxol-5-yl)methyl]aminocarbonyl}-2,4-dihydroxyphenyl}-1-(2-chloro-5-fluorophenyl)-1*H*-pyrazole.

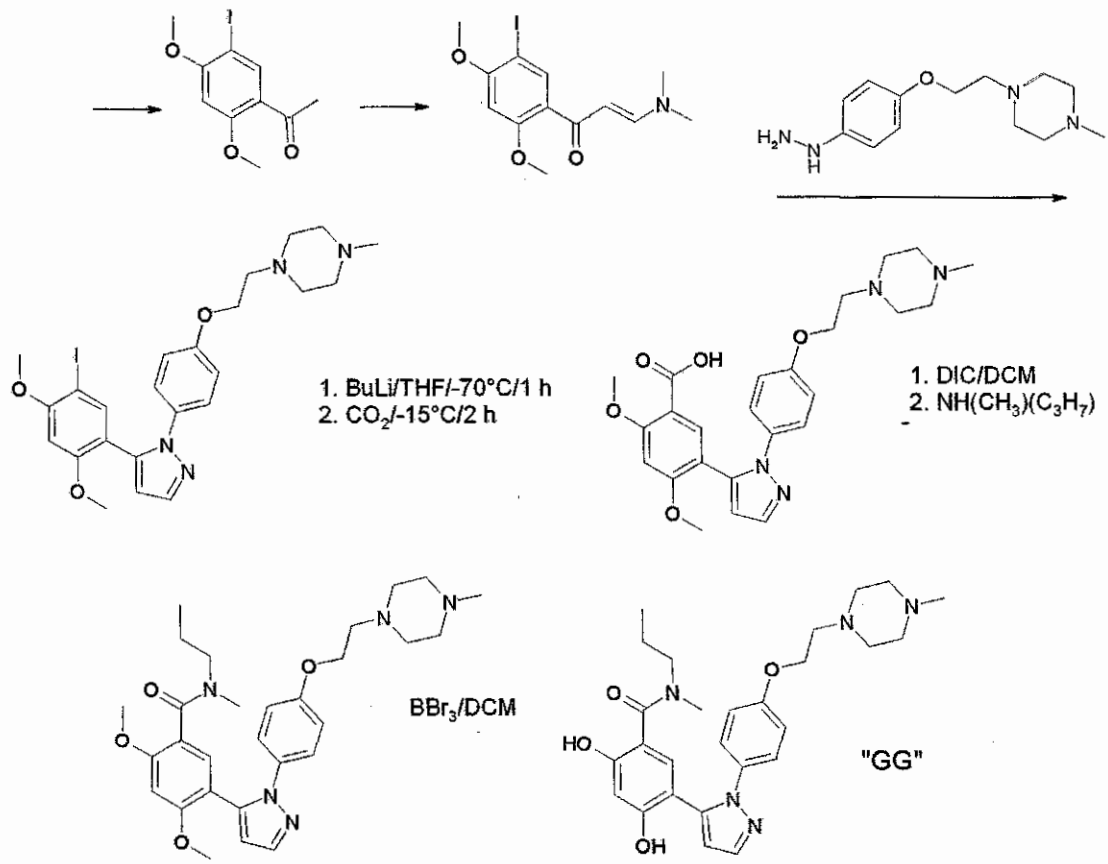
15.D Analogous reaction of 5-[5-iodo-2,4-dimethoxyphenyl]-1-(2-ethylphenyl)-1*H*-pyrazole and *N*-ethyl-*N*-methylamine gives the compound

5-[5-(*N*-ethyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-ethylphenyl)-1*H*-pyrazole.

15.E Analogous reaction of 5-[5-iodo-2,4-dimethoxyphenyl]-1-(2,3-dichlorophenyl)-1*H*-pyrazole and *N*-butyl-*N*-methylamine gives the compound

5-[5-(*N*-butyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2,3-dichlorophenyl)-1*H*-pyrazole.

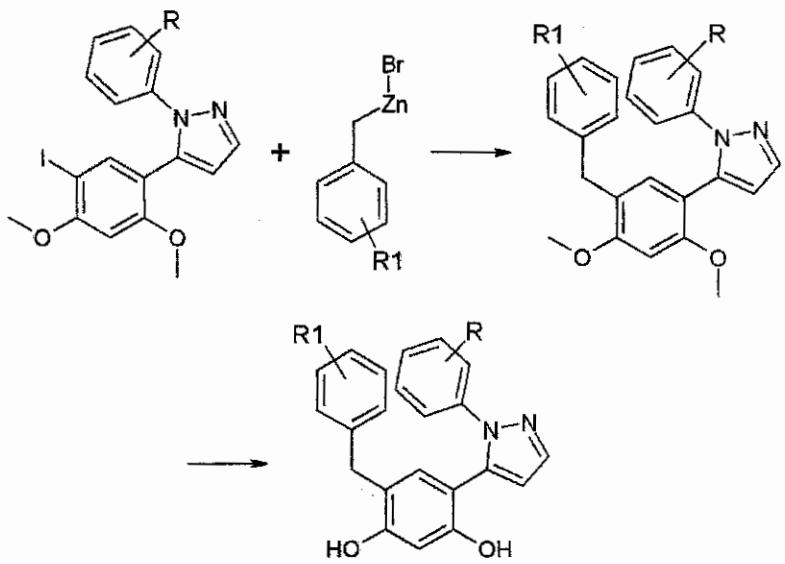
15.F The preparation of the compound 5-[5-(*N*-propyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-{4-[2-(4-methylpiperazin-1-yl)ethoxy]-phenyl}-1*H*-pyrazole ("GG") is carried out analogously to the following reaction scheme



"GG": retention time [min] 0.97, $M+H^+$ [m/e] 494.61.

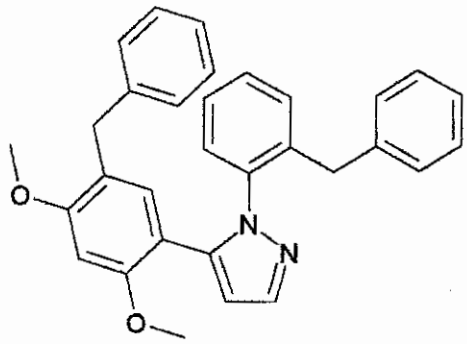
Example 16

General reaction scheme for the preparation of compounds of the formula I in which R^2 denotes an unsubstituted or substituted benzyl group

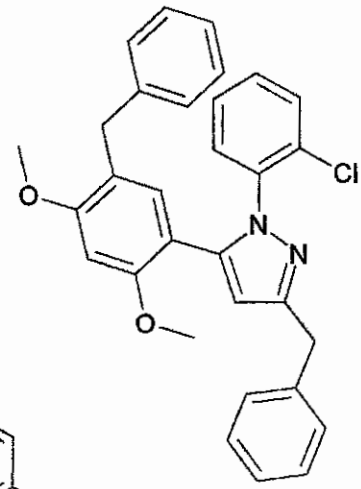


16.A

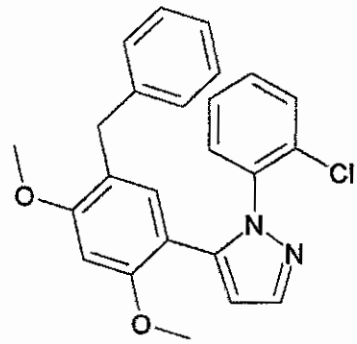
16.A.1 41 mg of $PdCl_2$(dppf) are added to 2.5 ml of benzyl zinc bromide (0.5M in THF), and the mixture is stirred for 5 minutes at room temperature under an argon atmosphere. A solution of 440.6 mg of "E2a" in 3 ml of THF is subsequently added dropwise, and the mixture is stirred at 45° for a further 30 minutes, then at 65° for 1 hour. The mixture is cooled, poured into saturated NH_4Cl solution and subjected to conventional work-up, giving a mixture of 3 compounds, which are separated by chromatography (ISCO/120 g column; petroleum ether/ethyl acetate: 95/5 to 60/40), giving 185 mg of "H1", 188 mg of "H2" and 190 mg of "H3"



"H1"



"H2"



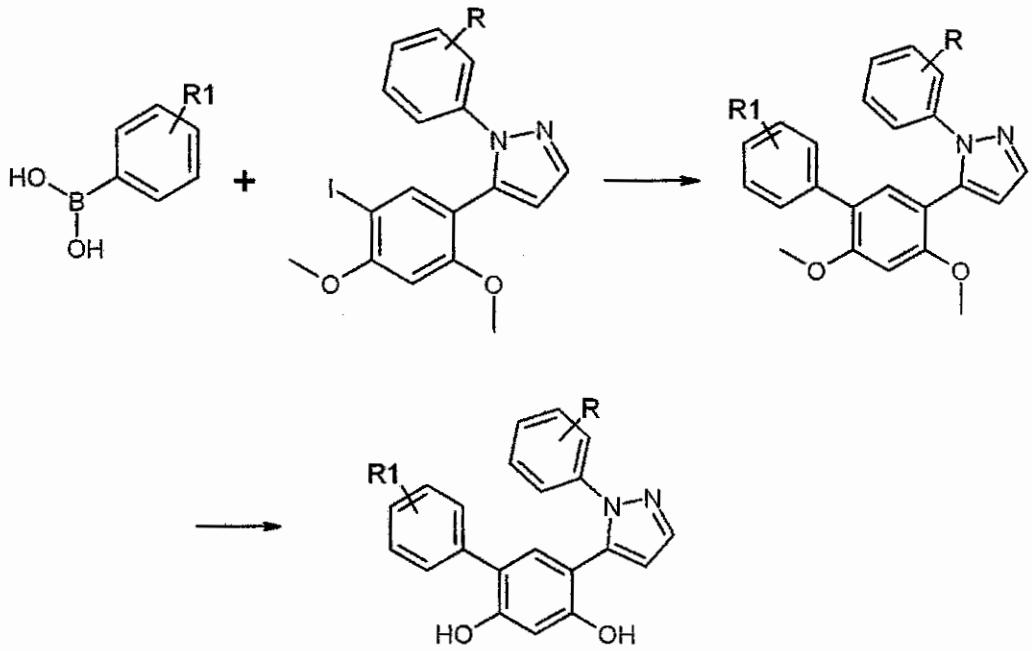
"H3"

16.A.2 Ether cleavage of "H1" using BBr_3 gives the compound 5-(5-benzyl-2,4-dihydroxyphenyl)-1-(2-benzylphenyl)-1*H*-pyrazole, $M+H^+$ [m/e] 433.52.

16.A.3 Ether cleavage of "H3" using BBr_3 gives the compound 5-(5-benzyl-2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.741, $M+H^+$ [m/e] 377.84.

Example 17

General reaction scheme for the preparation of compounds of the formula I in which R^2 denotes an unsubstituted or substituted phenyl group



17.A

17.A.1 A mixture of 170.7 mg of benzeneboronic acid, 616.9 mg of "E2a", 10 ml of propanol, 1.79 mg of palladium(II) acetate, 3.1 mg of triphenylphosphine, 2 ml of sodium carbonate solution and 1.2 ml of water is refluxed for 16 hours under an N_2 atmosphere. The mixture is cooled and subjected to conventional work-up, giving 5-(5-phenyl-2,4-dimethoxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole ("K1").

17.A.2 Ether cleavage of "K1" using BBr_3 gives the compound 5-(5-phenyl-2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole, retention time [min] 1.675, $M+H^+$ [m/e] 363.82.

The examples below relate to pharmaceutical compositions:

Example A: Injection vials

A solution of 100 g of an active compound according to the invention and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of active compound.

Example B: Suppositories

A mixture of 20 g of an active compound according to the invention with 100 g of soya lecithin and 1400 g of cocoa butter is melted, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

A solution is prepared from 1 g of an active compound according to the invention, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active compound according to the invention are mixed with 99.5 g of Vaseline under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active compound according to the invention, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium

stearate is pressed in a conventional manner to give tablets in such a way that each tablet contains 10 mg of active compound.

Example F: Dragees

Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

Example G: Capsules

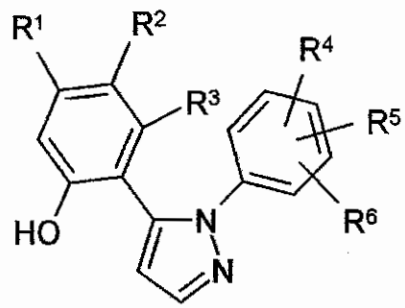
2 kg of active compound according to the invention are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of the active compound.

Example H: Ampoules

A solution of 1 kg of an active compound according to the invention in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of active compound.

Patent Claims

1. Compounds of the formula I



I

in which

R^1 denotes OH, OCH_3, OCF_3, $OCHF_2$, OBzl, OAc, p-methoxybenzyloxy, SH, $S(O)_mCH_3$, SO_2NH_2, Hal, CF_3 or CH_3,

R^2, R^3 each, independently of one another, denote H, Hal, CN, NO_2, A, Alk, $(CH_2)_nAr$, $(CH_2)_nHet$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, COOAr, COOHet, $CONH_2$, CONHA, CONAA', CONHAr, CONAAr, $CON(Ar)_2$, CONHHet, $CON(Het)_2$, NH_2, NHA, NHAr, NHHet, NAA', NHCOA, NACOA', NHCOAr, NHCOHet, NHCOOA, NHCOOAr, NHCOOHet, NHCONHA, NHCONHAr, NHCONHHet, OH, OA, OAr, OHet, SH, $S(O)_mA$, $S(O)_mAr$, $S(O)_mHet$, SO_2NH_2, SO_2NHA, SO_2NAA', SO_2NHAr, SO_2NAAr, SO_2NHHet, $SO_2N(Ar)_2$, $SO_2N(Het)_2$, $CONH(CH_2)_oHet$, $NH(CH_2)_oHet$, $O(CH_2)_oAr$, $S(O)_m(CH_2)_oHet$, $S(O)_m(CH_2)_oAr$, $(CH_2)_oCH(Ar)CH_3$, $CONAR^{12}$, $SO_2NA(CH_2CONAA')$, $SO_2NH(CH_2Ar)$, $SO_2NA[(CH_2)_oCN]$, $SO_2NA(CH_2Ar)$, $(CH_2)_oNHAr$, $(CH_2)_oNAAr$, $(CH_2)_oOAr$, $(CH_2)_oS(O)_mAr$, CH=CH-Ar, CHO, COA or R^{12},

R^4, R^5, R^6 each, independently of one another, denote H, Hal, CN, NO_2, A, Alk, $(CH_2)_nAr$, $(CH_2)_nHet$, COOH, COOA, COOAr, COOHet, $CONH_2$, CONHA, CONAA', CONHAr, CONAAr, $CON(Ar)_2$, CONHHet, $CON(Het)_2$, NH_2, NHA, NHAr, NHHet, NAA', NHCOA, NACOA', NHCOAr, NHCOHet, NHCOOA, NHCOOAr, NHCOOHet, NHCONHA, NHCONHAr, NHCONHHet, OH, OA, OAr, OHet, SH, $S(O)_mA$, $S(O)_mAr$, $S(O)_mHet$, SO_2NH_2, SO_2NHA, SO_2NAA', SO_2NHAr, SO_2NAAr, SO_2NHHet, $SO_2N(Ar)_2$, $SO_2N(Het)_2$, $CONH(CH_2)_oAr$, $NHCO(CH_2)_oAr$, $NHCO(CH_2)_oOA$ or $O(CH_2)_oHet$,

R^4 and R^5 together also denote OCH_2O or OCH_2CH_2O,

A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH, NR^8 and/or by -CH=CH- groups and/or, in addition, 1-5 H atoms may be replaced by F, Cl, Br and/or R^7,

Alk or cyclic alkyl having 3-7 C atoms,

A and A' together also denote an alkylene chain having 2, 3, 4, 5 or 6 C atoms, which may be substituted by CH_2OH, CH_2Br, CH_2NEt_2,
and/or in which a CH_2 group may be replaced by O, S, SO, SO_2, N, NH, NR^8, $NCOR^8$ or $NCOOR^8$,

Alk denotes alkenyl having 2-6 C atoms,

R^7 denotes $COOR^9$, $CONR^9R^{10}$, NR^9R^{10}, $NHCOR^9$, $NHCOOR^9$ or OR^9,

R^8 denotes cycloalkyl having 3-7 C atoms, cycloalkylalkylene having 4-10 C atoms, Alk or

unbranched or branched alkyl having 1-6 C atoms, in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl,

R^9, R^{10} each, independently of one another, denote H or alkyl having 1-5 C atoms, in which 1-3 CH_2 groups may be replaced by O, S, SO, SO_2, NH, NMe or NEt and/or, in addition, 1-5 H atoms may be replaced by F and/or Cl,

R^9 and R^{10} together also denote an alkylene chain having 2, 3, 4, 5 or 6 C atoms, in which a CH_2 group may be replaced by O, S, SO, SO_2, NH, NR^8, $NCOR^8$ or $NCOOR^8$,

Ar denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR^{11}, $N(R^{11})_2$, NO_2, CN, phenyl, $CON(R^{11})_2$, $NR^{11}COA$, $NR^{11}CON(R^{11})_2$, $NR^{11}SO_2A$, COR^{11}, $NR^{11}CO(CH_2)_oR^{11}$, $SO_2N(R^{11})_2$, $S(O)_mA$, $-[C(R^{11})_2]_n-COOR^{11}$ and/or $-O[C(R^{11})_2]_o-COOR^{11}$,

Het denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono-, di- or trisubstituted by Hal, A, OR^{11}, $N(R^{11})_2$, NO_2, CN, $COOR^{11}$, $CON(R^{11})_2$, $NR^{11}COA$, $NR^{11}SO_2A$, COR^{11}, SO_2NR^{11}, $S(O)_mA$, =S, $=NR^{11}$ and/or =O (carbonyl oxygen),

R^{11} denotes H or A,

R^{12} denotes cycloalkyl having 3-7 C atoms or cycloalkyl-alkylene having 4-12 C atoms,

Hal denotes F, Cl, Br or I,

m denotes 0, 1 or 2,

n denotes 0, 1, 2, 3 or 4,

o denotes 1, 2 or 3,

and pharmaceutically usable derivatives, salts, solvates and stereo-isomers thereof, including mixtures thereof in all ratios.

2. Compounds according to Claim 1 in which

R^1 denotes OH, OCH_3 or SH,

and pharmaceutically usable derivatives, salts, solvates and stereo-isomers thereof, including mixtures thereof in all ratios.

3. Compounds according to Claim 1 or 2 in which

R^2, R^3 each, independently of one another, denote H, Hal, A, $(CH_2)_nAr$, $(CH_2)_nHet$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, $CONH_2$, CONHA, CONAA', CONHAr, CONHHet, NH_2, NHA, NHAr, NHHet, NAA', $S(O)_mA$, $S(O)_mAr$, SO_2NH_2, SO_2NHA, SO_2NAA', SO_2NHAr, SO_2NAAr, SO_2NHHet, $CONH(CH_2)_oHet$, $NH(CH_2)_oHet$, $O(CH_2)_oAr$, $S(O)_m(CH_2)_oHet$, $S(O)_m(CH_2)_oAr$, $(CH_2)_oCH(Ar)CH_3$, $CONAR^{12}$, $SO_2NA(CH_2CONAA')$, $SO_2NH(CH_2Ar)$, $SO_2NA[(CH_2)_oCN]$, $SO_2NA(CH_2Ar)$, $(CH_2)_oNHAr$, $(CH_2)_oNAAr$, $(CH_2)_oOAr$, $(CH_2)_oS(O)_mAr$ or R^{12},

and pharmaceutically usable derivatives, salts, solvates and stereo-isomers thereof, including mixtures thereof in all ratios.

4. Compounds according to one or more of Claims 1-3 in which

R^4, R^5, R^6 each, independently of one another, denote H, Hal, CN, NO_2, A, $(CH_2)_nAr$, COOH, COOA, $CONH_2$, CONHA, CONAA', CONHAr, NH_2, NHA, NAA', NHCOA, NHCOAr, NHCOHet, OH, OA, SO_2NH_2, SO_2NHA, SO_2NAA', $CONH(CH_2)_oAr$, $NHCO(CH_2)_oAr$, $NHCO(CH_2)_oOA$ or $O(CH_2)_oHet$,

and pharmaceutically usable derivatives, salts, solvates and stereo-isomers thereof, including mixtures thereof in all ratios.

5. Compounds according to one or more of Claims 1-4 in which

A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH, NR^8 and/or by -CH=CH- groups and/or, in addition, 1-5 H atoms may be replaced by F, Cl, Br and/or R^7,

Alk or cyclic alkyl having 3-7 C atoms,

A and A' together also denote an alkylene chain having 2, 3, 4, 5 or 6 C atoms, which may be substituted by CH_2OH, CH_2Br or CH_2NEt_2,

and/or in which a CH_2 group may be replaced by O, N, NH or NR^8,

and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

6. Compounds according to one or more of Claims 1-5 in which

A, A' each, independently of one another, denote unbranched or branched alkyl having 1-6 C atoms, in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH and/or by -CH=CH- groups and/or, in addition, 1-5 H atoms may be replaced by F, Cl and/or Br,

Alk or cyclic alkyl having 3-7 C atoms,

and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

7. Compounds according to one or more of Claims 1-6 in which

R^7 denotes $COOR^9$, $CONR^9R^{10}$, NR^9R^{10}, $NHCOR^9$, $NHCOOR^9$ or OR^9,

and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

8. Compounds according to one or more of Claims 1-7 in which

R^8 denotes unbranched or branched alkyl having 1-6 C atoms,

and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

9. Compounds according to one or more of Claims 1-8 in which

R^9, R^{10} each, independently of one another, denote H or alkyl having 1-5 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl,

and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

10. Compounds according to one or more of Claims 1-9 in which

A, A' each, independently of one another, denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-5 H atoms may be replaced by F, Cl and/or Br,

or cyclic alkyl having 3-7 C atoms,

and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

11. Compounds according to one or more of Claims 1-10 in which

Ar denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR^{11}, $N(R^{11})_2$, $NR^{11}COA$, $NR^{11}CO(CH_2)_oR^{11}$, and/or $-[C(R^{11})_2]_n-COOR^{11}$,

and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

12. Compounds according to one or more of Claims 1-11 in which

Het denotes a mono- or bicyclic saturated or aromatic heterocycle having 1 to 2 N and/or O atoms, which may be mono- or disubstituted by A,

and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

13. Compounds according to one or more of Claims 1-12 in which

R^1 denotes OH, OCH_3 or SH,

R^2, R^3 each, independently of one another, denote H, Hal, A, $(CH_2)_nAr$, $(CH_2)_nHet$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, $CONH_2$, CONHA, CONAA', CONHAr, CONHHet, NH_2, NHA, NHAr, NHHet, NAA', $S(O)_mA$, $S(O)_mAr$, SO_2NH_2, SO_2NHA, SO_2NAA', SO_2NHAr, SO_2NAAr, SO_2NHHet, $CONH(CH_2)_oHet$, $NH(CH_2)_oHet$, $O(CH_2)_oAr$, $S(O)_m(CH_2)_oHet$, $S(O)_m(CH_2)_oAr$, $(CH_2)_oCH(Ar)CH_3$, $CONAR^{12}$, $SO_2NA(CH_2CONAA')$, $SO_2NH(CH_2Ar)$, $SO_2NA[(CH_2)_oCN]$, $SO_2NA(CH_2Ar)$, $(CH_2)_oNHAr$, $(CH_2)_oNAAr$, $(CH_2)_oOAr$, $(CH_2)_oS(O)_mAr$ or R^{12},

R^4, R^5, R^6 each, independently of one another, denote H, Hal, CN, NO_2, A, $(CH_2)_nAr$, COOH, COOA, $CONH_2$, CONHA, CONAA', CONHAr, NH_2, NHA, NAA', NHCOA, NHCOAr, NHCOHet, OH, OA, SO_2NH_2, SO_2NHA, SO_2NAA', $CONH(CH_2)_oAr$, $NHCO(CH_2)_oAr$, $NHCO(CH_2)_oOA$ or $O(CH_2)_oHet$,

R^4 and R^5 together also denote OCH_2O or OCH_2CH_2O,

A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH, NR^8 and/or by -CH=CH- groups and/or, in addition, 1-5 H atoms may be replaced by F, Cl, Br and/or R^7,

Alk or cyclic alkyl having 3-7 C atoms,

A and A' together also denote an alkylene chain having 2, 3, 4, 5 or 6 C atoms, which may be substituted by CH_2OH, CH_2Br or CH_2NEt_2, and/or in which a CH_2 group may be replaced by O, N, NH or NR^8,

R^7 denotes $COOR^9$, $CONR^9R^{10}$, NR^9R^{10}, $NHCOR^9$, $NHCOOR^9$ or OR^9,

R^8 denotes unbranched or branched alkyl having 1-6 C atoms,

R^9, R^{10} each, independently of one another, denote H or alkyl having 1-5 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl,

Ar denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR^{11}, $N(R^{11})_2$, $NR^{11}COA$, $NR^{11}CO(CH_2)_oR^{11}$, and/or $-[C(R^{11})_2]_n-COOR^{11}$,

Het denotes a mono- or bicyclic saturated or aromatic heterocycle having 1 to 2 N and/or O atoms, which may be mono- or disubstituted by A,

R^{11} denotes H or A,

R^{12} denotes cycloalkyl having 3-7 C atoms or cycloalkylalkylene having 4-12 C atoms,

Hal denotes F, Cl, Br or I,

m denotes 0, 1 or 2,

n denotes 0, 1, 2, 3 or 4,

o denotes 1, 2 or 3,

and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

14. Compounds according to Claim 1 selected from the group

5-(2-hydroxy-4-methoxyphenyl)-1-(3-nitrophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methyl-5-chlorophenyl)-1-phenyl-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(3,5-dichlorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(2-chloro-5-trifluoromethylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(2-ethylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(3-methoxyphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(3-cyanophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(3-trifluoromethylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(3-chlorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(3-fluorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-phenyl-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(4-trifluoromethylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(4-chlorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(4-aminosulfonylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(4-carboxyphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(4-cyanophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(3-chloro-4-methylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(4-methylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(4-bromophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(2-methoxyphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(2-fluorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-fluorophenyl)-1-(2,6-difluorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(3-nitrophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-nitrophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-aminophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(2-nitrophenyl)-1*H*-pyrazole

5-(2-hydroxy-4-methoxyphenyl)-1-(2-aminophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-aminophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(2-fluorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(2-fluorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(2,4-difluorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(3,5-dichlorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(3-chloro-2-cyanophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(2,6-dichlorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(2-chloro-5-trifluoromethylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(2-ethylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(3-methoxyphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(3-cyanophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(3-trifluoromethylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(3-chlorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(3-carboxyphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(3-fluorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-bromophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-phenyl-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-trifluoromethylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-chlorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-aminosulfonylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-carboxyphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-cyanophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-methoxyphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(3-chloro-4-methylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-methylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(2,6-difluorophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-cyano-2-nitrophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-trifluoromethyl-2-nitrophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(2-nitrophenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(4-ethoxycarbonylphenyl)-1*H*-pyrazole,

5-(2-hydroxy-4-methoxyphenyl)-1-(2-aminophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(2,4-difluorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(3,5-dichlorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(3-chloro-2-cyanophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(2,6-dichlorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(2-chloro-5-trifluoromethylphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(2-ethylphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(3-hydroxyphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(3-cyanophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(3-trifluoromethylphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(3-chlorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(3-carboxyphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(3-fluorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-bromophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-phenyl-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-trifluoromethylphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-chlorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-aminosulfonylphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-carboxyphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-cyanophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-hydroxyphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(3-chloro-4-methylphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-methylphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(2,6-difluorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-cyano-2-nitrophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-trifluoromethyl-2-nitrophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(2-nitrophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-ethoxycarbonylphenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(2-aminophenyl)-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-(4-nitrophenyl)-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-(4-aminophenyl)-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-(4-benzoylaminophenyl)-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-(4-acetylaminophenyl)-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-(4-propionylaminophenyl)-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-[4-(butyrylamino)phenyl]-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-[4-(pyridin-4-ylcarbonylamino)-phenyl]-1*H*-pyrazole,

5-(2,4-dimethoxyphenyl)-1-[4-(phenylacetylamino)phenyl]-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-benzoylaminophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-acetylaminophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-(4-propionylaminophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-[4-(butyrylamino)phenyl]-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-[4-(pyridin-4-ylcarbonylamino)-phenyl]-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-[4-(phenylacetylamino)phenyl]-1*H*-pyrazole,

5-(2,4-dibenzyloxyphenyl)-1-(4-carboxyphenyl)-1*H*-pyrazole,

5-(2,4-dibenzyloxyphenyl)-1-[4-(benzylaminocarbonyl)-phenyl]-1*H*-pyrazole,

5-(2,4-dibenzyloxyphenyl)-1-[4-(methylaminocarbonyl)-phenyl]-1*H*-pyrazole,

5-(2,4-dibenzyloxyphenyl)-1-[4-(ethylaminocarbonyl)phenyl]-1*H*-pyrazole,

5-(2,4-dibenzyloxyphenyl)-1-[4-(propylaminocarbonyl)-phenyl]-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-[4-(benzylaminocarbonyl)phenyl]-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-[4-(methylaminocarbonyl)phenyl]-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-[4-(ethylaminocarbonyl)phenyl]-1*H*-pyrazole,

5-(2,4-dihydroxyphenyl)-1-[4-(propylaminocarbonyl)phenyl]-1*H*-pyrazole,

and pharmaceutically usable derivatives, salts, solvates and stereo-isomers thereof, including mixtures thereof in all ratios.

15. Compounds according to Claim 1 selected from the group

5-(5-aminosulfonyl-2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-ethyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-*N'*-diethylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(piperidine-1-sulfonyl)-2,4-dihydroxyphenyl]-1-(2-chloro-phenyl)-1*H*-pyrazole,

5-[5-(*N*-phenylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-phenylaminosulfonyl)-2-hydroxy-4-methoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(2-fluorophenyl)aminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(3-fluorophenyl)aminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(4-fluorophenyl)aminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(pyridin-3-yl)aminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(3-hydroxymethylpiperidine-1-sulfonyl)-2,4-dihydroxy-phenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(3-bromomethylpiperidine-1-sulfonyl)-2,4-dihydroxy-phenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-benzyl-*N'*-methylaminosulfonyl)-2,4-dihydroxy-phenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-benzyl-*N'*-methylaminosulfonyl)-2-methoxy-4-hydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-*N'*-dimethylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-(2-bromoethyl)-*N'*-methylaminosulfonyl)-2,4-di-hydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-cyclohexyl-*N'*-methylaminosulfonyl)-2,4-dihydroxy-phenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-(2,3-dibromopropyl)-*N'*-methylaminosulfonyl)-2,4-di-hydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-butyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(2-cyanoethyl)-*N'*-methylaminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-isopropyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(dimethylaminocarbonylmethyl)-*N'*-methylaminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(2-hydroxymethylpiperidine-1-sulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(morpholine-4-sulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole and

5-{5-[*N*-(2-hydroxyethyl)-*N'*-(2-bromoethyl)aminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(2-hydroxyethyl)-*N'*-(2-bromoethyl)aminosulfonyl]-2-hydroxy-4-methoxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole;

5-{5-[2-(*N,N'*-diethylaminomethyl)piperidin-4-yl]sulfonyl}-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(1-methylpiperazin-4-yl)sulfonyl]-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-methylaminosulfonyl)-2,4-hydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[*N*-(pyridin-4-yl)aminosulfonyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-(*N*-phenylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(*N*-phenylaminosulfonyl)-2-hydroxy-4-methoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(*N*-benzylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(*N*-benzylaminosulfonyl)-2-hydroxy-4-methoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(*N,N'*-diethylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(*N,N'*-diethylaminosulfonyl)-2-hydroxy-4-methoxy-phenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(ethylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methyl-phenyl)-1*H*-pyrazole,

5-[5-(ethylaminosulfonyl)-2-hydroxy-4-methoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(aminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methyl-phenyl)-1*H*-pyrazole,

5-[5-(aminosulfonyl)-2-hydroxy-4-methoxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-iodo-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-iodo-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-carboxyethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-methoxycarbonylethyl-2,4-dihydroxyphenyl]-1-(2-fluoro-phenyl)-1*H*-pyrazole,

5-[5-(2-phenylethyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(2-phenylethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-(2-phenyl-2-methoxyethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-styryl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-{5-[2-(pyridin-4-yl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[2-(pyridin-4-yl)vinyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[2-(pyridin-2-yl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

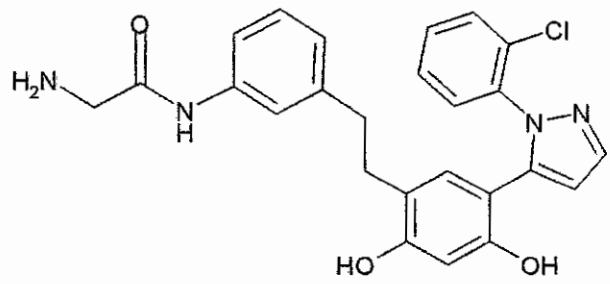
5-{5-[2-(4-fluorophenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[2-(3-fluorophenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[2-(2-fluorophenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[1-(4-fluorophenyl)ethyl]-2,4-dihydroxyphenyl}-1-phenyl-1*H*-pyrazole,

5-{5-[2-(3-(aminomethylcarbonylamino)phenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole



,

5-{5-[2-(3-carboxyphenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[2-(2-chlorophenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2,3-dihydrobenzo-1,4-dioxin-6-yl)-1*H*-pyrazole,

5-{5-propyl-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole

5-{5-cyclopropylmethyl-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-(2-methylbutyl)-2,4-dihydroxyphenyl}-1-(3-methylphenyl)-1*H*-pyrazole,

5-{5-(2-fluoropropyl)-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[2-(4-methylphenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2,3-dihydrobenzo-1,4-dioxin-6-yl)-1*H*-pyrazole,

5-{5-(2-phenylpropyl)-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-(2-phenylpropyl)-2,4-dihydroxyphenyl}-1-(2-aminophenyl)-1*H*-pyrazole,

5-[5-phenylaminomethyl-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-phenylaminomethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-phenoxymethyl-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-phenoxymethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-phenylthiomethyl-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-phenylthiomethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-(4-methoxyphenylthiomethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-phenylsulfinylmethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-(4-methoxyphenylsulfinylmethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-phenylsulfonylmethyl-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-(4-methoxyphenylsulfonylmethyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-phenylsulfanyl-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-phenylsulfanyl-2-hydroxy-4-methoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-phenylsulfonyl-2-hydroxy-4-methoxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-phenylsulfonyl-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(2-fluorobenzylamino)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(5-benzyloxy-2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(pyridin-4-ylmethylsulfanyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(5-phenylamino-2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(3-fluorophenylmethylsulfinyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(pyridin-2-ylmethylamino)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(4-fluorobenzyloxy)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(4-fluorophenylmethylsulfonyl)-2,4-dihydroxyphenyl]-1-phenyl-1*H*-pyrazole,

5-[5-(3-fluorophenylsulfonyl)-2,4-dihydroxyphenyl]-1-(3-ethylphenyl)-1*H*-pyrazole,

5-[5-phenylsulfanyl-2,4-dihydroxyphenyl]-1-(3-methylphenyl)-1*H*-pyrazole,

5-[5-(2-fluorophenylsulfanyl)-2-hydroxy-4-methoxyphenyl]-1-(4-nitrophenyl)-1*H*-pyrazole,

5-[5-(2-fluorophenylsulfanyl)-2-hydroxy-4-methoxyphenyl]-1-(4-aminophenyl)-1*H*-pyrazole,

5-[5-(*N,N*-diethylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(5-phenylaminocarbonyl-2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N,N*-dimethylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-ethylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-cyclopentyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-{*N*-[(benzo-1,3-dioxol-5-yl)methyl]aminocarbonyl}-2,4-dihydroxyphenyl}-1-(2-chloro-5-fluorophenyl)-1*H*-pyrazole,

5-[5-(*N*-ethyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-ethylphenyl)-1*H*-pyrazole,

5-[5-(*N*-butyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2,3-dichlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-{4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-1*H*-pyrazole,

5-(5-benzyl-2,4-dihydroxyphenyl)-1-(2-benzylphenyl)-1*H*-pyrazole,

5-(5-benzyl-2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(5-phenyl-2,4-dihydroxyphenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

16. Compounds according to Claim 1 selected from the group

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-methylphenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-fluorophenyl)-1*H*-pyrazole,

5-[5-(*N*-isopropyl-*N'*-methylaminosulfonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-{5-[2-(2-fluorophenyl)ethyl]-2,4-dihydroxyphenyl}-1-(2-chlorophenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxy-5-bromophenyl)-1-(2-chlorophenyl)-1*H*-pyrazole,

5-(2,4-dihydroxy-5-chlorophenyl)-1-(2-fluorophenyl)-1*H*-pyrazole,

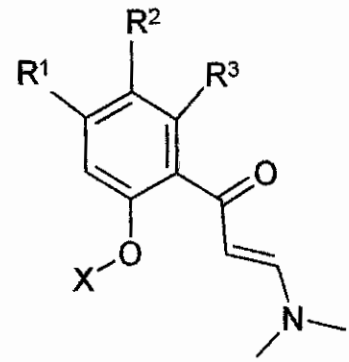
5-(2,4-dihydroxy-5-bromophenyl)-1-(2-ethylphenyl)-1*H*-pyrazole,

5-[5-(*N*-propyl-*N*-methylaminocarbonyl)-2,4-dihydroxyphenyl]-1-{4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-1*H*-pyrazole,

and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

17. Process for the preparation of compounds of the formula I according to Claims 1-16 and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, characterised in that

a) a compound of the formula II



II

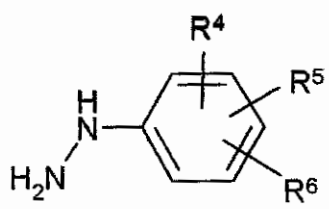
in which

R^1, R^2 and R^3 have the meanings indicated in Claim 1,

and X denotes H or methyl,

is reacted with

a compound of the formula III



III

in which

R^4, R^5 and R^6 have the meanings indicated in Claim 1,

the resultant compound in which X denotes methyl is subsequently, if desired, converted into a compound of the formula I in which X denotes H by ether cleavage,

and/or in that one or more radical(s) R^1,R^2, R^3, R^4 and/or R^5 in a compound of the formula I are converted into one or more radical(s) R^1,R^2, R^3, R^4 and/or R^5

by, for example,

i) reducing a nitro group to an amino group,

ii) hydrolysing an ester group to a carboxyl group,

iii) converting an amino group into an alkylated amine by reductive amination,

iv) converting a carboxyl group into a sulfonamidocarbonyl group,

v) converting an acid chloride into an amide,

and/or a base or acid of the formula I is converted into one of its salts.

18. Medicaments comprising at least one compound according to Claim 1-16 and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

19. Use of compounds according to Claim 1-16, and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment and/or prophylaxis of diseases in which the inhibition, regulation and/or modulation of HSP90 plays a role.

20. Use according to Claim 19 of compounds according to Claim 1-16, and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment or prevention of tumour diseases, viral diseases, for immune suppression in transplants, inflammation-induced diseases, cystic fibrosis, diseases associated with angiogenesis, infectious diseases, autoimmune diseases, ischaemia, fibrogenetic diseases,
for the promotion of nerve regeneration,
for inhibiting the growth of cancer, tumour cells and tumour metastases,
for the protection of normal cells against toxicity caused by chemotherapy,
for the treatment of diseases in which incorrect protein folding or aggregation is a principal causal factor.

21. Use according to Claim 20, where the tumour diseases are fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumour, leiosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, syringocarcinoma, sebaceous cell carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinomas, bone marrow car-

cinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonic carcinoma, Wilm's tumour, cervical cancer, testicular tumour, lung carcinoma, small-cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, haemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukaemia, lymphoma, multiple myeloma, Waldenström's macroglobulinaemia and heavy-chain disease.

22. Use according to Claim 20, where the viral pathogen of the viral diseases is selected from the group consisting of hepatitis type A, hepatitis type B, hepatitis type C, influenza, varicella, adenovirus, herpes simplex type I (HSV-I), herpes simplex type II (HSV-II), cattle plague, rhinovirus, echovirus, rotavirus, respiratory syncytial virus (RSV), papillomavirus, papovavirus, cytomegalovirus, echinovirus, arbovirus, huntavirus, Coxsackie virus, mumps virus, measles virus, rubella virus, polio virus, human immunodeficiency virus type I (HIV-I) and human immunodeficiency virus type II (HIV-II).

23. Use according to Claim 20, where the inflammation-induced diseases are rheumatoid arthritis, asthma, multiple sclerosis, type 1 diabetes, lupus erythematosus, psoriasis and inflammatory bowel disease.

24. Use according to Claim 20, where the diseases in connection with angiogenesis are diabetic retinopathy, haemangiomas, endometriosis and tumour angiogenesis.

25. Use according to Claim 20, where the fibrogenetic diseases are dermatosclerosis, polymyositis, systemic lupus, cirrhosis of the liver, keloid formation, interstitial nephritis and pulmonary fibrosis.

26. Use according to Claim 20, where the diseases in which incorrect protein folding or aggregation is a principal causal factor are scrapie, Creutzfeldt-Jakob disease, Huntington's or Alzheimer's.

27. Medicaments comprising at least one compound according to Claim 1-16 and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active compound.

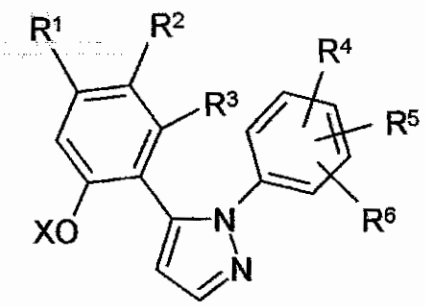
28. Set (kit) consisting of separate packs of

(a) an effective amount of a compound according to Claim 1-16 and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios,

and

(b) an effective amount of a further medicament active compound.

29. Intermediate compounds of the formula I-I



I-I

in which

R^1 denotes OCH_3, OBzl, OAc, p-methoxybenzyloxy or I,

R^2, R^3 denote H

R^4, R^5, R^6	each, independently of one another, denote H, Hal, CN, NO_2, A, COOH, COOA, NH_2, OH, OA or SO_2NH_2,
X	denotes CH_3, Bzl, Ac or p-methoxybenzyl,
A	denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl, or cyclic alkyl having 3-7 C atoms,

and salts thereof.