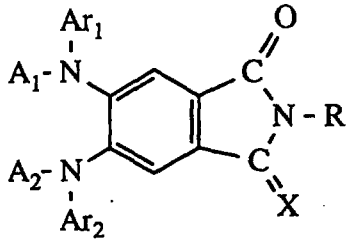
The invention relates to compounds of formula I



(I)

wherein

A_1 and A_2 are each independently of the other hydrogen, C_1-C_7alkyl, C_2-C_7alkenyl, C_2-C_7alkynyl, phenyl or naphthyl that is unsubstituted or substituted by one or more substituents from the group consisting of: C_1-C_7alkyl, C_2-C_7alkenyl, C_2-C_7alkynyl, C_3-C_4-alkylene (linked to two adjacent carbon atoms), C_3-C_8cycloalkyl, phenyl-C_1-C_7alkyl, phenyl; C_1-C_7alkyl substituted by hydroxy, C_1-C_7alkoxy, phenyl-C_1-C_7alkoxy, C_1-C_7-alkanoyloxy, halogen, amino, C_1-C_7alkylamino, di-C_1-C_7alkylamino, mercapto, C_1-C_7-alkylthio, C_1-C_7alkylsulfinyl, C_1-C_7alkylsulfonyl, carboxy, C_1-C_7alkoxycarbonyl, carbamoyl, N-C_1-C_7alkylcarbamoyl, N,N-di-C_1-C_7alkylcarbamoyl and/or by cyano; hydroxy, C_1-C_7alkoxy, halo-C_1-C_7alkoxy, phenyl-C_1-C_7alkoxy, phenoxy, C_2-C_7alkenyl-oxy, halo-C_2-C_7alkenyloxy, C_2-C_7alkynyloxy, C_2-C_7alkylenedioxy (linked to two adjacent carbon atoms), C_1-C_7alkanoyloxy, phenyl-C_1-C_7alkanoyloxy, phenylcarbonyloxy, mercapto, C_1-C_7alkylthio, phenyl-C_1-C_7alkylthio, phenylthio, C_1-C_7alkylsulfinyl, phenyl-C_1-C_7alkylsulfinyl, phenylsulfinyl, C_1-C_7alkylsulfonyl, phenyl-C_1-C_7alkylsulfonyl, phenylsulfonyl, halogen, nitro, amino, C_1-C_7alkylamino, C_3-C_8cycloalkylamino, phenyl-C_1-C_7alkylamino, phenylamino, di-C_1-C_7alkylamino, N-C_1-C_7alkyl-N-phenylamino, N-C_1-C_7alkyl-N-phenyl-C_1-C_7alkylamino, C_4-C_7alkyleneamino, C_4-C_7alkyleneamino interrupted by -O-, -S- or -NR"- (wherein R" is hydrogen, C_1-C_7alkyl or C_1-C_7alkanoyl), C_1-C_7alkanoylamino, phenyl-C_1-C_7alkanoylamino, phenylcarbonylamino, C_1-C_7alkanoyl, phenyl-C_1-C_7alkanoyl, phenylcarbonyl, carboxy, C_1-C_7alkoxycarbonyl, carbamoyl, C_1-C_7alkylcarbamoyl, N,N-di-C_1-C_7alkylcarbamoyl, N-hydroxycarbamoyl, N-phenyl-carbamoyl, cyano, sulfo, C_1-C_7alkoxysulfonyl, sulfamoyl, N-C_1-C_7alkylsulfamoyl, N,N-di-C_1-C_7alkylsulfamoyl and N-phenylsulfamoyl (phenyl groups occurring in the substituents being unsubstituted or substituted by C_1-C_7alkyl, C_1-C_7alkoxy, hydroxy, halogen and/or by trifluoromethyl); C_1-C_7alkanoyl, halo-C_1-C_7alkanoyl, phenyl- or naphthyl-C_1-C_7alkanoyl that in the phenyl or naphthyl radical is unsubstituted or substituted as above or phenyl- or naphthyl-carbonyl that in the phenyl or naphthyl radical is unsubsti-

tuted or substituted as above, C_1-C_7alkylsulfonyl or phenyl- or naphthyl-sulfonyl wherein phenyl or naphthyl is unsubstituted or substituted as above; or wherein
A_1 and A_2 together form unsubstituted or C_1-C_7alkyl- or hydroxy-substituted C_1-C_4alkylene;
Ar_1 and Ar_2 are each independently of the other phenyl or naphthyl that is unsubstituted or substituted as above; imidazolyl, triazolyl, pyridyl, pyrimidinyl or triazinyl that is unsubstituted or substituted by C_1-C_7alkyl, hydroxy, C_1-C_7alkoxy, halogen, cyano and/or by trifluoromethyl; or C_3-C_8cycloalkyl that is unsubstituted or substituted by C_1-C_7alkyl or by hydroxy;
the group -C(=X)- is -C(=O)-, -C(=S)-, -CH_2- or -C(=CR_1R_2)- wherein R_1 and R_2 are each independently of the other hydrogen or C_1-C_7alkyl; and
R is hydrogen, C_1-C_7alkyl, aryl-C_1-C_7alkyl or aryl wherein aryl is phenyl or naphthyl that is unsubstituted or substituted as above; amino, hydroxy or C_1-C_7alkoxy; with the proviso that R is other than phenyl when A_1 and A_2 are hydrogen, Ar_1 and Ar_2 are phenyl and the group -C(=X)- is -C(=O)-; and to salts thereof when salt-forming groups are present, to processes for the preparation of those compounds, to pharmaceutical compositions comprising those compounds, and to those compounds for use in a method for the therapeutic treatment of the human or animal body or to the use of those compounds for the preparation of pharmaceutical compositions.

The general terms used hereinbefore and hereinafter preferably have the following meanings within the scope of this Application:

The term "lower" denotes a radical having up to and including 7, especially up to and including 4, and more especially having 1 or 2, carbon atoms, unless defined to the contrary.

Lower alkyl is preferably n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl or n-heptyl, preferably ethyl and especially methyl.

Lower alkenyl has from 2 to 7, preferably from 2 to 4, carbon atoms and is, for example, allyl or crotyl.

Lower alkynyl has from 2 to 7, preferably from 2 to 4, carbon atoms and is, for example, propyn-1-yl or propyn-2-yl or 2-butyn-1-yl.

Lower alkyl substituted by halogen is, for example, trifluoromethyl.

Phenyl and naphthyl radicals can be unsubstituted or substituted, especially as indicated below for phenyl. Preferred is phenyl that is unsubstituted or substituted by one or more, especially one or two, substituents from the group consisting of: lower alkyl, lower alkenyl, lower alkynyl, lower alkylene (linked to two adjacent carbon atoms), cycloalkyl, phenyl-lower alkyl or phenyl; lower alkyl substituted by hydroxy, lower alkoxy, phenyl-lower alkoxy, lower alkanoyloxy, halogen, amino, lower alkylamino, di-lower alkylamino, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl and/or by cyano; hydroxy; lower alkoxy, halo-lower alkoxy, phenyl-lower alkoxy, phenoxy, lower alkenyloxy, halo-lower alkenyloxy, lower alkynyloxy or lower alkylenedioxy (linked to two adjacent carbon atoms); lower alkanoyloxy, phenyl-lower alkanoyloxy or phenylcarbonyloxy (≙ benzoyloxy); mercapto; lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkylsulfinyl [-S(=O)-lower alkyl], phenyl-lower alkylsulfinyl, phenylsulfinyl, lower alkylsulfonyl [-S(O_2)-lower alkyl], phenyl-lower alkylsulfonyl or phenylsulfonyl; halogen; nitro; amino; lower alkylamino, cycloalkylamino, phenyl-lower alkylamino or phenylamino; di-lower alkylamino, N-lower alkyl-N-phenylamino, N-lower alkyl-N-phenyl-lower alkylamino, lower alkyleneamino, or lower alkyleneamino interrupted by -O-, -S- or -NR" (wherein R" is hydrogen, lower alkyl or lower alkanoyl); lower alkanoylamino, phenyl-lower alkanoylamino or phenylcarbonylamino (≙ benzoylamino); phenyl-lower alkanoyl or phenylcarbonyl (= benzoyl); carboxy; lower alkoxycarbonyl; carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-hydroxycarbamoyl or N-phenylcarbamoyl; cyano; sulfo (SO_3H); lower alkoxysulfonyl; sulfamoyl (SO_2NH_2), N-lower alkylsulfamoyl, N,N-di-lower alkylsulfamoyl or N-phenylsulfamoyl; phenyl groups occurring in the substituents each being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl.

R is preferably selected from all the above-mentioned definitions except the unsubstituted or substituted phenyl or naphthyl radicals mentioned in the previous paragraph.

Of the radicals imidazolyl, triazolyl, pyridyl, pyrimidinyl and triazinyl, pyridyl is especially preferred. Those radicals may be unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen, cyano and/or by trifluoromethyl.

Pyridyl is, for example, 2-, 3- or 4-pyridyl.

Imidazolyl is, for example, 2- or 4(5)-imidazolyl.

Triazolyl is, for example, 1,2,4-triazol-3- or -4-yl or 1,2,3-triazol-4-yl.

Pyrimidinyl is, for example, 2-, 4- or 5-pyrimidinyl.

Triazinyl is, for example, 1,3,5-triazin-2-yl.

Lower alkylene, formed from A_1 and A_2 together, is unbranched and is a $(CH_2)_n$ group wherein n is from 1 to 4, preferably 2 or 3. It is preferably unsubstituted but may also be substituted by lower alkyl or hydroxy.

Lower alkylene, linked to two adjacent carbon atoms of a benzene ring, is C_3-C_4alkylene, for example 1,3-propylene or 1,4-butylene.

Lower alkylenedioxy, linked to two adjacent carbon atoms, is C_1-C_2alkylenedioxy, for example methylene- or 1,2-ethylene-dioxy.

Lower alkyleneamino is C_4-C_7- and especially C_4-C_5-alkyleneamino, for example piperidino. Lower alkyleneamino interrupted by -O-, -S- or -NR"- is C_4-C_7- and especially C_4-C_5-alkyleneamino in which a ring carbon atom has been replaced by the corresponding hetero group, and is especially morpholino, thiomorpholino, piperazino or 4-lower alkyl- or 4-lower alkanoyl-piperazino.

Lower alkanoyl, halo-lower alkanoyl, phenyl- or naphthyl-lower alkanoyl that in the phenyl or naphthyl radical are unsubstituted or substituted as above, or phenyl- or naphthyl-carbonyl that in the phenyl or naphthyl radical are unsubstituted or substituted as above, are acyl radicals. Lower alkanoyl is preferred.

Lower alkanoyl is preferably formyl, acetyl, propionyl, n-butyryl, pivaloyl or valeroyl, especially acetyl.

Phenyl-lower alkyl is especially benzyl.

Cycloalkyl is C_3-C_8- and especially C_5-C_7-cycloalkyl, which is intended to indicate that it contains from 3 to 8 and from 5 to 7 ring carbon atoms, respectively. It may, however, also be substituted, for example by lower alkyl or hydroxy.

Halogen is especially fluorine, chlorine and bromine, but may also be iodine.

Salts of compounds according to the invention having salt-forming groups are especially pharmaceutically acceptable, non-toxic salts. For example, compounds of formula I having basic groups may form acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulfuric acid or phosphoric acid, or with suitable organic carboxylic or sulfonic acids, for example acetic acid, fumaric acid or methanesulfonic acid, or with amino acids, such as arginine or lysine. Compounds of formula I having an acidic group, for example carboxy, form, for example, metal or ammonium salts, such as alkali metal and alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, and also ammonium salts with ammonia or suitable organic amines, such as lower alkylamines, for example triethylamine, hydroxy-lower alkylamines, for example 2-hydroxyethylamine, bis(2-hydroxyethyl)amine or tris(2-hydroxyethyl)amine, basic aliphatic esters of carboxylic acids, for example 4-aminobenzoic acid 2-diethylaminoethyl ester, lower alkyleneamines, for example 1-ethylpiperidine, cycloalkylamines, for example dicyclohexylamine, or benzylamines, for example N,N'-dibenzylethylene-diamine, dibenzylamine or benzyl-ß-phenethylamine. Compounds of formula I having an acidic group and a basic group can also be in the form of internal salts, that is to say in zwitterionic form.

The salts of compounds according to the invention also include complexes of compounds of formula I (A_1, A_2 = hydrogen) with transition metal ions, for example copper, cobalt or manganese.

For the purposes of isolation or purification it is also possible to use pharmaceutically un-acceptable salts, for example picrates or perchlorates. Only the pharmaceutically acceptable, non-toxic salts are used therapeutically and these are therefore preferred.

The compounds according to the invention have valuable, especially pharmacologically acceptable, properties. In particular they exhibit specific inhibitory activities that are of pharmacological interest. They act especially as tyrosine protein kinase inhibitors and exhibit, for example, a potent inhibition of the tyrosine kinase activity of the receptor for

the epidermal growth factor (EGF) and the c-erbB2 kinase. These receptor-specific enzyme activities play a key role in the signal transmission in a large number of mammal cells, including human cells, especially epithelial cells, cells of the immune system and cells of the central and peripheral nervous system. The EGF-induced activation of the receptor-associated tyrosine protein kinase (EGF-R-PTK) is in various cell types a pre-requisite for cell division and thus for the proliferation of a cell population. The addition of EGF-receptor-specific tyrosine kinase inhibitors therefore inhibits the reproduction of those cells.

The inhibition of EGF-receptor-specific tyrosine protein kinase (EGF-R-PTK) can be demonstrated, for example, using the method of C. House et al., Europ. J. Biochem. 140, 363-367 (1984). The compounds according to the invention inhibit the enzyme activity by 50 % (IC50) in concentrations of from 0.1 to 10 μM. Furthermore, in the micromolar range too, for example, they also exhibit an inhibition of the cell growth of an EGF-dependent cell line, for example the epidermoid mouse keratinocyte cell line. In order to measure this inhibition of cell growth, the EGF-stimulated cell proliferation of epidermal Balb/MK keratinocytes is used (description of the method in Meyer, T., et al., Int. J. Cancer 43, 851 (1989)). Those cells are to a high degree dependent upon the presence of EGF for proliferation (Weissmann, B. E., Aaronson, S. A., Cell 32, 599 (1983)). In order to carry out the test, Balb/MK cells (10 000/well) are transferred to 96-well microtitre plates and incubated overnight. The test substances (dissolved in DMSO) are added in various concentrations (in dilution series) so that the final concentration of DMSO is no greater than 1 %. After the addition, the plates are incubated for three days, during which time the control cultures without the test substance are able to undergo at least three cell division cycles. The growth of the MK cells is measured by means of methylene blue staining. The IC_{50} value is defined as that concentration of the test substance in question which results in a 50 % decrease in comparison with the control cultures without inhibitor.

In addition to inhibiting EGF-R-PTK, the compounds according to the invention also inhibit other tyrosine kinases that are involved in signal transmission mediated by trophic factors, for example the abl-kinase, kinases from the family of src-kinases and the c-erbB2 kinase (HER-2), and also serine/threonine kinases, for example protein kinase C, all of which have a role to play in growth regulation and transformation in the cells of mammals, including humans.

The inhibition of the c-erbB2 tyrosine kinase (HER-2) can be demonstrated, for example,

analogously to the method of C. House et al., Europ. J. Biochem. 140, 363-367 (1984) used for EGF-R-PTK. The c-erbB2 kinase can be isolated, and its activity determined, in accordance with known protocols, for example in accordance with T. Akiyama et al., Science 232, 1644 (1986).

The compounds according to the invention are therefore also suitable for the inhibition of processes mediated by these and related tyrosine kinases.

The compounds according to the invention are therefore useful, for example, in the treatment of benign or malignant tumours. They are able to bring about the regression of tumours and to prevent the formation of tumour metastases and the growth of micro-metastases. In particular, they can be used in epidermal hyperproliferation (psoriasis), in the treatment of neoplasias of epithelial character, for example mammary carcinoma, and in leukaemias. In addition, the compounds can be used in the treatment of diseases of the immune system and in the treatment of inflammation insofar as protein kinases are involved in those disorders. The compounds can also be used in the treatment of disorders of the central or peripheral nervous system insofar as signal transmission by protein kinases is involved.

The compounds according to the invention can be used both on their own and in combination with other pharmacologically active substances, for example together with (a) inhibitors of enzymes of polyamine synthesis, (b) inhibitors of protein kinase C, (c) inhibitors of other tyrosine kinases, (d) cytokines, (e) negative growth regulators, for example TGF-ß or IFN-ß, (f) aromatase inhibitors, (g) anti-oestrogens or (h) cytostatics.

The invention preferably relates to compounds of formula I wherein A_1 and A_2 are each independently of the other hydrogen, lower alkyl; lower alkenyl; phenyl or 1-naphthyl or 2-naphthyl, the three last-mentioned radicals being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; lower alkanoyl, lower alkylsulfonyl or phenylsulfonyl wherein the phenyl group is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; or wherein A_1 and A_2 together are lower alkylene; wherein Ar_1 and Ar_2 are each independently of the other phenyl or naphthyl, each of which is unsubstituted or substituted by one or more substituents from the group consisting of: lower alkyl, lower alkenyl, lower alkynyl, lower alkylene (linked to two adjacent carbon atoms), C_3-C_8cycloalkyl, phenyl-lower alkyl, phenyl; lower alkyl substituted by hydroxy, lower alkoxy, phenyl-lower alkoxy, lower

alkanoyloxy, halogen, amino, lower alkylamino, di-lower alkylamino, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl and/or by cyano; hydroxy, lower alkoxy, halo-lower alkoxy, phenyl-lower alkoxy, phenoxy, lower alkenyloxy, halo-lower alkenyloxy, lower alkynyloxy, lower alkylenedioxy (linked to two adjacent carbon atoms), lower alkanoyloxy, phenyl-lower alkanoyloxy, phenylcarbonyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkylsulfinyl, phenyl-lower alkylsulfinyl, phenylsulfinyl, lower alkylsulfonyl, phenyl-lower alkylsulfonyl, phenylsulfonyl, halogen, nitro, amino, lower alkylamino, C_3-C_8cycloalkylamino, phenyl-lower alkylamino, phenylamino, di-lower alkylamino, N-lower alkyl-N-phenylamino, N-lower alkyl-N-phenyl-lower alkylamino, lower alkyleneamino, lower alkyleneamino interrupted by -O-, -S- or -NR" (wherein R" is hydrogen, lower alkyl or lower alkanoyl), lower alkanoylamino, phenyl-lower alkanoylamino, phenylcarbonylamino, lower alkanoyl, phenyl-lower alkanoyl, phenylcarbonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-hydroxycarbamoyl, N-phenylcarbamoyl, cyano, sulfo, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl, N,N-di-lower alkylsulfamoyl and N-phenylsulfamoyl (phenyl groups occurring in the substituents each being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl); pyridyl or pyrimidinyl that is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen, cyano and/or by trifluoromethyl; or C_3-C_8cycloalkyl; the group -C(=X)- is -C(=O)-, -C(=S)-, -CH_2- or -C(=CR_1R_2)- wherein R_1 and R_2 are each independently of the other hydrogen or lower alkyl, and R is hydrogen, lower alkyl, phenyl-lower alkyl, phenyl, 1-naphthyl or 2-naphthyl, in the four last-mentioned radicals the phenyl or naphthyl group being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; or R is amino, hydroxy or lower alkoxy, with the proviso that R is other than phenyl when A_1 and A_2 are hydrogen, Ar_1 and Ar_2 are phenyl and the group -C(=X)- is -C(=O)-; and salts thereof when salt-forming groups are present.

Of those last-mentioned compounds of formula I, very special preference is given to those wherein R is as defined except for phenyl, and the other radicals are as defined, and salts thereof when salt-forming groups are present.

The invention relates more especially to compounds of formula I wherein A_1 and A_2 are each independently of the other hydrogen, lower alkyl; phenyl or 1-naphthyl or 2-naphthyl, the three last-mentioned radicals being unsubstituted or substituted by lower

alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; lower alkanoyl, lower alkylsulfonyl or phenylsulfonyl wherein the phenyl group is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; or wherein A_1 and A_2 together are lower alkylene; wherein Ar_1 and Ar_2 are each independently of the other phenyl or naphthyl, each of which is unsubstituted or substituted by one or more substituents from the group consisting of: lower alkyl, lower alkenyl, lower alkynyl, lower alkylene (linked to two adjacent carbon atoms), C_3-C_8cycloalkyl, phenyl-lower alkyl, phenyl; lower alkyl substituted by hydroxy, lower alkoxy, phenyl-lower alkoxy, lower alkanoyloxy, halogen, amino, lower alkylamino, di-lower alkylamino, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl and/or by cyano; hydroxy, lower alkoxy, halo-lower alkoxy, phenyl-lower alkoxy, phenoxy, lower alkenyloxy, halo-lower alkenyloxy, lower alkynyloxy, lower alkylenedioxy (linked to two adjacent carbon atoms), lower alkanoyloxy, phenyl-lower alkanoyloxy, phenylcarbonyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkylsulfinyl, phenyl-lower alkylsulfinyl, phenylsulfinyl, lower alkylsulfonyl, phenyl-lower alkylsulfonyl, phenylsulfonyl, halogen, nitro, amino, lower alkylamino, C_3-C_8cycloalkylamino, phenyl-lower alkylamino, phenylamino, di-lower alkylamino, N-lower alkyl-N-phenylamino, N-lower alkyl-N-phenyl-lower alkylamino, lower alkyleneamino, lower alkyleneamino interrupted by -O-, -S- or -NR" (wherein R" is hydrogen, lower alkyl or lower alkanoyl), lower alkanoylamino, phenyl-lower alkanoylamino, phenylcarbonylamino, lower alkanoyl, phenyl-lower alkanoyl, phenylcarbonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-hydroxycarbamoyl, N-phenylcarbamoyl, cyano, sulfo, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl, N,N-di-lower alkylsulfamoyl and N-phenylsulfamoyl (phenyl groups occurring in the substituents each being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl); pyridyl that is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen, cyano and/or by trifluoromethyl; or C_3-C_8cycloalkyl; the group -C(=X)- is -C(=O)-, -C(=S)-, $-CH_2-$ or $-C(=CR_1R_2)-$ wherein R_1 and R_2 are each independently of the other hydrogen or lower alkyl, and R is hydrogen, lower alkyl; phenyl-lower alkyl, phenyl, 1-naphthyl or 2-naphthyl, in the four last-mentioned radicals the phenyl or naphthyl group being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; or R is amino, hydroxy or lower alkoxy, with the proviso that R is other than phenyl when A_1 and A_2 are hydrogen, Ar_1 and Ar_2 are phenyl and the group -C(=X)- is -C(=O)-; and salts thereof when salt-forming groups are present.

The invention relates especially preferably to the compounds of formula I mentioned in the preceding paragraph wherein A_1 and A_2 are each independently of the other hydrogen or lower alkyl, the group -C(=X)- is -C(=O)-, -C(=S)- or -C(=CH_2)-, and R is hydrogen or lower alkyl, and salts thereof when salt-forming groups are present.

The invention relates more especially to compounds of formula I wherein A_1 and A_2 are each independently of the other hydrogen; lower alkyl; lower alkenyl; or lower alkanoyl; or wherein A_1 and A_2 together are lower alkylene; wherein Ar_1 and Ar_2 are each independently of the other phenyl or naphthyl, each of which is unsubstituted or substituted by one or more substituents from the group consisting of: lower alkyl, lower alkylene (linked to two adjacent carbon atoms), hydroxy, phenoxy, halogen, nitro, amino, lower alkylamino, di-lower alkylamino, lower alkanoylamino, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl and cyano; pyridyl; pyrimidinyl; or C_3-C_8cycloalkyl; the group -C(=X)- is -C(=O)- or -C(=S)-, and R is hydrogen, lower alkyl, phenyl-lower alkyl, amino or hydroxy; and salts thereof when salt-forming groups are present.

The invention relates even more especially to compounds of formula I wherein A_1 and A_2 are each independently of the other hydrogen or methyl; or wherein A_1 and A_2 together are -$(CH_2)_2$- or -$(CH_2)_3$-; Ar_1 and Ar_2 are each independently of the other phenyl or naphthyl, each of which is unsubstituted or substituted by one or more substituents from the group consisting of: lower alkyl, lower alkoxy, phenyl-lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, lower alkylamino, di-lower alkylamino, lower alkanoylamino, halogen, trifluoromethyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, cyano, lower alkanoyl, benzoyl, lower alkoxysulfonyl and sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl; cyclopentyl; cyclohexyl; or pyridyl; the group -C(=X)- is -C(=O)-, -C(=S)- or -C(=CH_2)-, and R is hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

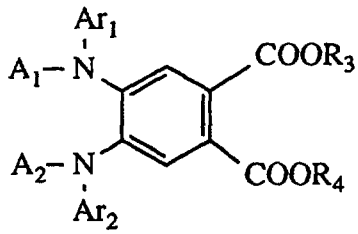
The invention relates most especially to compounds of formula I wherein A_1 and A_2 are hydrogen; Ar_1 and Ar_2 are each independently of the other phenyl that is unsubstituted or substituted by lower alkyl, trifluoromethyl, phenyl, hydroxy, lower alkoxy, benzyloxy, amino, di-lower alkylamino, lower alkanoylamino, halogen, carboxy, lower alkoxycarbonyl, carbamoyl, N,N-di-lower alkylcarbamoyl or by cyano; or cyclohexyl; the group -C(=X)- is -C(=O)-, -C(=S)- or -C(=CH_2)-, and R is hydrogen; and pharmaceutically

acceptable salts thereof.

The invention relates more especially to the specific compounds described in the Examples and pharmaceutically acceptable salts thereof.

The compounds of formula I can be prepared in a manner known per se, for example by

(a) reacting a compound of formula II



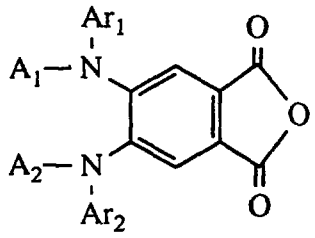
(II)

wherein Ar_1, Ar_2, A_1 and A_2 are as defined under formula I and R_3 and R_4 are each independently of the other aryl or lower alkyl, with a compound of formula III

$$H_2N\text{-}R \qquad \text{(III)}$$

wherein R is as defined under formula I, or

(b) reacting a compound of formula IV



(IV)

wherein Ar_1, Ar_2, A_1 and A_2 are as defined under formula I, with a compound of formula III

$$H_2N\text{-}R \qquad \text{(III)}$$

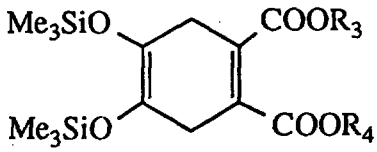
wherein R is as defined under formula I;

and, if desired, converting a resulting compound of formula I into a different compound of formula I, and/or converting a resulting salt into the free compound or into a different salt, and/or converting a resulting free compound of formula I into a salt and/or separating a resulting mixture of isomeric compounds of formula I into the individual isomers.

In the following, more detailed description of the processes, the symbols Ar_1, Ar_2, A_1, A_2, X, R, R_3 and R_4 are each as defined under formulae I and II unless indicated to the contrary.

Process (a): The reaction according to process (a) corresponds to the aminolysis, known per se, of phthalic acid diesters with ammonia or primary amines. The reaction with activated phthalic acid diesters, for example the di(p-nitrophenyl) ester, normally takes place at room temperature, but the reaction with di-lower alkyl esters generally takes place only at high temperatures. Preferably the dimethyl ester is used. Preferred is the reaction of di-lower alkyl esters in a solvent, especially in a high-boiling alcohol, for example a diol, such as ethylene glycol, at temperatures of from 100 to 150°C, for example approximately 120°C, or the reaction of the lower alkyl esters with ammonia or the respective amine of formula II at the same temperatures in the presence of a solvent, for example an alcohol, such as a lower alkanol, for example methanol or ethanol, or in the absence of a solvent, in an autoclave at elevated pressure.

The starting compounds of formula II are prepared, for example, by reacting a cyclohexadiene of formula V



(V)

wherein Me is methyl, with an aniline of formula VI

AHN-Ar (VI)

wherein A is especially hydrogen or lower alkyl, under acid catalysis [see Matlin, Stephen

A. and Barron, Kenneth, J. Chem. Res. Synop. 8, 246-247 (1990)].

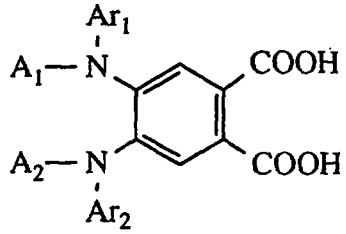
The preparation of the compounds of formula V is effected, for example, by means of a Diels-Alder reaction and is likewise described in the literature mentioned.

For the preparation of asymmetrical compounds of formula II, wherein A_1 and A_2 and/or Ar_1 and Ar_2 are different, for example compounds of formula V can be reacted - for example stepwise - with two different compounds of formula VI and the desired compounds of formula II can be isolated by chromatographic separation.

Furthermore, for example, compounds of formula II wherein $A_1 = A_2 = H$ can be reacted in a ratio of 1:1 with a lower alkyl-introducing agent, for example methyl iodide, yielding asymmetrical compounds of formula II wherein A_1 = lower alkyl and $A_2 = H$. If the lower alkyl-introducing agent is used in excess, for example 10:1, then symmetrical compounds of formula II wherein $A_1 = A_2$ = lower alkyl are obtained.

Process (b): The reaction according to process (b) corresponds to the aminolysis, known per se, of phthalic acid anhydrides, for example with ammonia or primary amines at relatively high temperatures or with hexamethyldisilazane and methanol at room temperature [Davis, Peter D. and Bit, Rino A., Tetrahedron Lett. 31, 5201-5204 (1990)].

The starting compounds of formula IV are prepared, for example, by reacting a compound of formula VII



(VII)

with an acid anhydride of formula VIII, $(R_5CO)(R_5'CO)O$, wherein R_5 and R_5' are each independently of the other hydrogen or lower alkyl, but are not both hydrogen.

The compounds of formula VII can be obtained, for example, by hydrolysis, for example in an acidic or alkaline medium, of a corresponding compound of formula II.

Compounds of formula I can be converted into different compounds of formula I in a manner known per se.

For example, a compound of formula I wherein the group -C(=X)- is -C(=O)- can be reacted with a suitable reagent in order to obtain a different compound of formula I wherein the group -C(=X)- is -C(=S)-, $-CH_2-$ or $-C(=CR_1R_2)-$. A suitable reagent for the conversion of -C(=O)- into -C(=S)- is, for example, the Lawesson reagent (= 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiaphosphetane), the reaction being carried out, for example, in a halogenated hydrocarbon, such as dichloromethane, at temperatures of from 30°C to the reflux temperature, especially at reflux temperature. Suitable systems for the conversion of -C(=O)- into $-CH_2-$ are, for example, $LiAlH_4$/tetrahydrofuran or zinc amalgam/HCl/ethanol. The conversion of -C(=O)- into $-C(=CR_1R_2)-$ is effected, for example, by reaction with a strong base, for example LDA (lithium diisopropylamide) and then with a Grignard reagent of the formula HCR_1R_2MgHal (Hal = halogen, for example iodine).

Furthermore, for example, compounds of formula I wherein R is hydrogen can be converted by alkylation, for example with lower alkyl or aryl-lower alkyl halides, after treatment with suitable bases, for example sodium hydride or potassium tert-butoxide, into different compounds of formula I wherein R is lower alkyl or aryl-lower alkyl, aryl here being in each case phenyl or naphthyl that is unsubstituted or substituted as above.

Moreover, for example, compounds of formula I wherein A_1 and/or A_2 are hydrogen can be converted by reaction with suitable reagents into different compounds of formula I wherein A_1 and/or A_2 have the above-mentioned meanings other than hydrogen.

A suitable method for the introduction of A_1 and/or A_2 = lower alkyl is, for example, treatment with the base LDA and subsequent reaction with a di-lower alkyl ether or a lower alkyl halide. Under those conditions a group -N(-R)- = -NH- which may be present in the molecule is alkylated only slightly or not at all.

For the introduction of A_1 and/or A_2 = acyl, lower alkylsulfonyl or phenyl- or naphthyl-sulfonyl that is unsubstituted or substituted as above, the starting compound can be reacted, for example, again first with LDA and then with an acylating agent, for example acetyl chloride, or with an agent that introduces the lower alkylsulfonyl or arylsulfonyl group, for example methylsulfonyl chloride or p-toluenesulfonyl chloride.

Compounds of formula I wherein Ar_1 and/or Ar_2 are phenyl or naphthyl substituted by halogen, preferably by bromine, can be converted into the corresponding derivatives in which one or all of the halogen atoms present in the said radicals Ar_1 and/or Ar_2 have been replaced by cyano, for example by reaction with a cyanide salt of a transition metal, especially CuCN, at temperatures of from 50 to 150°C, preferably from 60 to 140°C, in an inert polar solvent, such as an N,N-di-lower alkyl-lower alkanecarboxylic acid amide, for example dimethylformamide, with or without the subsequent addition of a catalyst, for example a transition metal halide, such as iron(III) chloride, in aqueous solution (see also Rosenmund et al., Ber. 52, 1749 (1916); von Braun et al., Ann. 488, 111 (1931)).

In compounds of formula I, the radicals Ar_1 and/or Ar_2 that are phenyl or naphthyl unsubstituted or substituted as defined above can be nitrated independently of one another, with the introduction of one or more nitro groups, for example under conditions customary for the introduction of a nitro group into aromatic compounds, for example with concentrated or 100 % nitric acid at temperatures of from 0 to 100°C, preferably from 10 to 40°C, in an inert solvent, for example an organic acid anhydride, such as acetic anhydride. If the nitration results in several different products in which the number of nitro groups and their position(s) are different, they can be separated according to customary methods, for example by column chromatography.

Nitro substituents in radicals Ar_1 and/or Ar_2 can be reduced to amino groups, for example by hydrogenation under customary conditions, for example hydrogenation in the presence of a hydrogenation catalyst suitable for the selective reduction of nitro groups, such as Raney nickel, in an inert solvent, for example a cyclic or acyclic ether, such as tetrahydrofuran, under normal pressure or under elevated pressure of up to 5 bar.

Compounds of the formula I with etherified hydroxy groups, for example with lower alkoxy radicals as substituents within Ar_1 and/or Ar_2, can be converted into the corresponding hydroxy-substituted compounds of formula I by ether cleavage. The ether cleavage takes place under conditions known per se, for example in the presence of hydrohalic acids, such as hydrobromic or hydroiodic acid, in the presence or absence of solvents, such as carboxylic acids, for example, lower alkanecarboxylic acids, such as acetic acid, at temperatures between 20°C and the reflux temperature of the reaction mixture, or preferably under mild conditions with boron halides, especially boron tribromide, in an inert solvent, for example a chlorinated hydrocarbon, such as methylene

chloride or chloroform, at temperatures between -80 and 0°C, preferably between -50 and -20°C.

Free compounds of formula I obtainable in accordance with the process having salt-forming properties can be converted into their salts in a manner known per se; compounds having basic properties can be converted into their salts, for example, by treatment with acids or suitable derivatives thereof, and compounds having acidic properties can be converted into their salts, for example, by treatment with bases or suitable derivatives thereof.

Mixtures of isomers obtainable in accordance with the invention can be separated into the individual isomers in a manner known per se; racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the diastereoisomeric mixture so obtainable, for example by fractional crystallisation.

The above-mentioned reactions can be carried out under reaction conditions known per se, in the absence or, usually, in the presence of solvents or diluents, preferably those solvents or diluents which are inert towards the reagents used and are solvents therefor, in the absence or presence of catalysts, condensation agents or neutralising agents, and, depending upon the nature of the reaction and/or the reactants, at reduced, normal or elevated temperature, for example in a temperature range of from approximately -80°C to approximately 200°C, preferably from approximately -20°C to approximately 150°C, for example at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under a nitrogen atmosphere.

As a result of the close relationship between the compounds of formula I in free form and in the form of their salts, hereinbefore and hereinafter any reference to the free compounds or their salts should be understood, where appropriate, as meaning also the corresponding salts or free compounds, respectively, when the compounds contain salt-forming groups, for example basic groups, such as amino or imino groups, and also those groups which contain no more than one unsaturated carbon atom, such as the groups $-NA_1Ar_1$ and/or $-NA_2Ar_2$ at the carbon atom of the central phenyl ring, wherein Ar_1 and A_1 and/or Ar_2 and A_2 are not bonded via an unsaturated carbon atom, and/or acidic groups, such as carboxy or sulfo (SO_3H).

The compounds, including their salts, can also be obtained in the form of hydrates, or their crystals may include, for example, the solvent used for crystallisation.

In the processes of this invention it is preferable to use those starting materials which result in the compounds described at the beginning as being especially valuable.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example a salt, thereof.

The present invention relates also to pharmaceutical compositions that comprise one of the compounds of formula I as active ingredient. Compositions for enteral, especially oral, and for parenteral administration are especially preferred. The compositions comprise the active ingredient on its own or, preferably, together with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends upon the disease to be treated and upon the species, its age, weight and individual condition, and also upon the mode of administration.

Preferred is a pharmaceutical composition suitable for administration to a warm-blooded animal, especially a human, suffering from a disease responsive to the inhibition of a protein kinase, for example psoriasis or a tumour, comprising a compound of formula I, or a salt thereof when salt-forming groups are present, in an amount effective for the inhibition of the protein kinase, together with at least one pharmaceutically acceptable carrier.

The pharmaceutical compositions comprise from approximately 5 % to approximately 95 % active ingredient, dosage forms in single dose form preferably comprising from approximately 20 % to approximately 90 % active ingredient and dosage forms that are not in single dose form preferably comprising from approximately 5 % to approximately 20 % active ingredient. Unit dose forms, such as dragées, tablets or capsules, comprise from approximately 0.05 g to approximately 1.0 g of active ingredient.

The pharmaceutical compositions of this invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical compositions for oral use can be

obtained by combining the active ingredient with one or more solid carriers, optionally granulating a resulting mixture, and, if desired, processing the mixture or granules, if necessary with the addition of additional excipients, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tri-calcium phosphate or calcium hydrogen phosphate, also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, cross-linked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or poly-ethylene glycol, or derivatives thereof.

Dragée cores can be provided with suitable, optionally enteric, coatings, there being used inter alia concentrated sugar solutions which may contain gum arabic, talc, polyvinyl-pyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the production of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Orally administrable pharmaceutical compositions also include dry-filled capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also be added.

Other oral dosage forms are, for example, syrups prepared in customary manner which comprise the active ingredient, for example, in suspended form and in a concentration of about 5 % to 20 %, preferably about 10 %, or in a similar concentration that provides a

suitable single dose, for example, when administered in measures of 5 or 10 ml. Also suitable are, for example, powdered or liquid concentrates for the preparation of shakes, for example in milk. Such concentrates may also be packaged in single dose quantities.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

For parenteral administration there are especially suitable aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilisers. The active ingredient, optionally together with excipients, can also be in the form of a lyophilisate and can be made into a solution prior to parenteral administration by the addition of suitable solvents.

Solutions such as are used, for example, for parenteral administration can also be used as infusion solutions.

Compounds of formula I can be used in methods of treating the above-mentioned pathological conditions, especially those conditions responsive to the inhibition of protein kinases. The compounds of this invention can be administered prophylactically or therapeutically, preferably in an amount effective against the said diseases, to a warm-blooded animal, for example a human, requiring such treatment, the compounds preferably being used in the form of pharmaceutical compositions. In the case of an individual having a body weight of about 70 kg the daily dose administered is from approximately 0.1 g to approximately 5 g, preferably from approximately 0.5 g to approximately 2 g, of a compound of this invention.

The following Examples illustrate the present invention; temperatures are given in degrees Celsius. The following abbreviations are used: ether ≙ diethyl ether; THF = tetrahydrofuran; DMF = N,N-dimethylformamide; MS ≙ mass spectrum; FAB ≙ Fast Atom Bombardment.

Example 1: 4,5-Bis(anilino)phthalimide

A suspension of 230 mg (0.7 mmol) of 4,5-bis(anilino)phthalic acid dimethyl ester in 23 ml of ethylene glycol is heated at 120°; ammonia gas is passed through the suspension, with stirring, for 24 hours. The reaction mixture is cooled and extracted with ethyl acetate. The ethyl acetate phases are washed in succession three times with water and once with saturated sodium chloride solution, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with dichloromethane/methanol 40:1 and the product fractions are combined and concentrated by evaporation, yielding the title compound in the form of yellow crystals, m.p. 215-217°, FAB-MS: 330 [M^++H].

a) 4,5-Bis(trimethylsilyloxy)cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester

Under argon, a solution of 7.1 g (50 mmol) of acetylenedicarboxylic acid dimethyl ester in 30 ml of toluene is added dropwise to 12.5 g (50 mmol) of 2,3-bis(trimethylsilyloxy)-1,3-butadiene (95 %) and then boiled under reflux for 19 hours. The reaction mixture is cooled, the solvent is evaporated off and the residue is distilled under a high vacuum (0.1 mbar, 124-127°), yielding the title compound in the form of a yellow, highly viscous oil, ^{1}H-NMR ($CDCl_3$): δ = 0.18 (s, 18H), 3.09 (s, 4H), 3.78 (s, 6H).

b) 4,5-Bis(anilino)phthalic acid dimethyl ester

A solution of 5.6 g (15 mmol) of 4,5-bis(trimethylsilyloxy)cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester and 5.5 ml (60 mmol) of aniline in 60 ml of glacial acetic acid is boiled under reflux for 4 hours. The reaction mixture is cooled, the solvent is evaporated off and the dark-brown residue is dissolved in dichloromethane and the solution is washed in succession with 20 ml of 1N HCl, 50 ml of saturated $NaHCO_3$ and twice with 20 ml of water, dried with sodium sulfate and concentrated by evaporation. The crude product is recrystallised from ethanol, yielding the title compound in the form of yellow crystals, m.p. 178°, FAB-MS: 377 [M^++H].

Example 2: 5,8-Diphenyl-5,8-diaza-5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylic acid imide

Analogously to Example 1, 40 mg (0.1 mmol) of 5,8-diphenyl-5,8-diaza-5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylic acid dimethyl ester in 4 ml of ethylene glycol are heated at 120°, ammonia gas being passed through the mixture, with stirring, for 24 hours. The reaction mixture is cooled and extracted with ethyl acetate. The ethyl acetate phases are washed in succession three times with water and once with saturated sodium chloride solution, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with dichloromethane/methanol 20:1 and the product fractions are combined and concentrated by evaporation, yielding the title compound in the form of yellow crystals, FAB-MS: 356 [M^++H].

a) 5,8-Diphenyl-5,8-diaza-5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylic acid dimethyl ester

A solution of 2.24 g (6 mmol) of 4,5-bis(trimethylsilyloxy)cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester (Example 1a) and 5.1 g (24 mmol) of N,N'-diphenylethylenediamine in 24 ml of glacial acetic acid is boiled under reflux for 2 hours. The reaction mixture is cooled, the solvent is evaporated off and the dark-brown residue is dissolved in dichloromethane and the solution is washed in succession with 20 ml of 1N HCl, 50 ml of saturated $NaHCO_3$ and twice with 20 ml of water, dried with sodium sulfate and concentrated by evaporation. The crude product is chromatographed on silica gel with hexane/ethyl acetate 3:1 and the product fractions are concentrated by evaporation and the residue is recrystallised from ethanol, yielding the title compound in the form of orange crystals, FAB-MS: 402 [M^+], 403 [M^++H].

Example 3: 4,5-Bis(4-fluoroanilino)phthalimide

Analogously to Example 1, 290 mg (0.7 mmol) of 4,5-bis(4-fluoroanilino)phthalic acid dimethyl ester in 22 ml of ethylene glycol are heated at 120° and, with stirring, ammonia gas is passed through the mixture for 18 hours. The reaction mixture is cooled and extracted with ethyl acetate. The ethyl acetate phases are washed in succession three times with water and once with saturated sodium chloride solution, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with hexane/ethyl acetate 1:1 and the product fractions are combined and

concentrated by evaporation, yielding the title compound in the form of orange crystals, m.p. > 220°C, FAB-MS: 366 [M^++H].

a) 4,5-Bis(4-fluoroanilino)phthalic acid dimethyl ester

A solution of 2.4 g (6 mmol) of 4,5-bis(trimethylsilyloxy)cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester (Example 1a) and 2.3 ml (24 mmol) of 4-fluoroaniline in 60 ml of glacial acetic acid is boiled under reflux for 2 hours. The reaction mixture is cooled, the solvent is evaporated off and the dark-brown residue is dissolved in dichloromethane and the solution is washed in succession with 20 ml of 1N HCl, 50 ml of saturated $NaHCO_3$ and twice with 20 ml of water, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with ethyl acetate/hexane 2:1 and the product fractions are concentrated by evaporation and recrystallised from ethyl acetate/hexane, yielding the title compound in the form of yellow crystals, ^{1}H-NMR ($CDCl_3$): δ = 7.40 (s, 2H), 7.10-6.80 (m, 8H), 5.70 (br s, 2H), 3.83 (s, 6H).

Example 4: 4,5-Bis(4-benzyloxy-anilino)phthalimide

Analogously to Example 1, 294.4 mg (0.5 mmol) of 4,5-bis(4-benzyloxy-anilino)phthalic acid dimethyl ester in 22 ml of ethylene glycol are heated at 120°, ammonia gas being passed through the mixture, with stirring, for 16 hours. The reaction mixture is cooled and extracted with ethyl acetate. The ethyl acetate phases are washed in succession three times with water and once with saturated sodium chloride solution, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with dichloromethane/methanol 50:1 and the product fractions are combined and concentrated by evaporation, yielding the title compound in the form of red crystals, m.p.187-189°C, FAB-MS: 542 [M^++H].

a) 4,5-Bis(4-benzyloxy-anilino)phthalic acid dimethyl ester

A solution of 2.4 g (6 mmol) of 4,5-bis(trimethylsilyloxy)cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester (Example 1a) and 4.8 g (24 mmol) of 4-benzyloxyaniline in 24 ml of glacial acetic acid is boiled under reflux for 2 hours. The reaction mixture is cooled, the solvent is evaporated off and the dark-brown residue is dissolved in dichloromethane and the solution is washed in succession with 20 ml of 1N HCl, 50 ml of

saturated $NaHCO_3$ and twice with 20 ml of water, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is dissolved while hot in ethyl acetate and filtered, then allowed to crystallise at 0°. The crystalline residue is chromatographed on silica gel with ethyl acetate/hexane 3:2 and the product fractions are concentrated by evaporation and recrystallised from ethyl acetate/hexane, yielding the title compound in the form of beige crystals, FAB-MS: 589 [M^++H].

Example 5: 4,5-Bis[4-(N,N-diethylamino)-anilino]phthalimide bishydrochloride

Analogously to Example 1, 294.4 mg (0.5 mmol) of 4,5-bis[4-(N,N-diethylamino)-anilino]phthalic acid dimethyl ester in 22 ml of ethylene glycol are heated at 120°, ammonia gas being passed through the mixture, with stirring, for 22 hours. The reaction mixture is cooled and extracted with ethyl acetate. The ethyl acetate phases are washed in succession three times with water and once with saturated sodium chloride solution, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with dichloromethane/methanol 30:1 and the product fractions are combined and concentrated by evaporation. The red crystalline evaporation residue is dissolved in dichloromethane, and 4.1N HCl (g) in ether is added thereto. The crystalline precipitate is filtered off and dried, yielding the title compound in the form of yellow crystals, m.p. 228-230°C, FAB-MS: 472 [M^++H].

a) 4,5-Bis[4-(N,N-diethylamino)-anilino]phthalic acid dimethyl ester

A solution of 2.4 g (6 mmol) of 4,5-bis(trimethylsilyloxy)cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester (Example 1a) and 3.94 g (24 mmol) of 4-(N,N-diethylamino)-aniline in 24 ml of glacial acetic acid is boiled under reflux for 2 hours. The reaction mixture is cooled, the solvent is evaporated off and the dark-brown residue is dissolved in dichloromethane and the solution is washed in succession with 50 ml of saturated $NaHCO_3$ and twice with 20 ml of water, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with dichloromethane/methanol 400:15 and the product fractions are concentrated by evaporation and again chromatographed on silica gel with ethyl acetate/hexane 1:1. The product fractions are concentrated by evaporation, yielding the title compound in the form of green crystals, FAB-MS: 518 [M^+], 519 [M^++H].

Example 6: 4,5-Bis(cyclohexylamino)phthalimide

Analogously to Example 1, 194 mg (0.5 mmol) of 4,5-bis(cyclohexylamino)phthalic acid dimethyl ester in 15 ml of ethylene glycol are heated at 120°, ammonia gas being passed through the mixture, with stirring, for 12 hours. The reaction mixture is cooled, saturated with sodium chloride and extracted with ethyl acetate. The ethyl acetate phases are washed in succession three times with water and once with saturated sodium chloride solution, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with hexane/ethyl acetate 3:1 and the product fractions are combined and concentrated by evaporation, yielding the title compound in the form of orange crystals, m.p. 170-175°C, FAB-MS: 342 [M^++H].

a) 4,5-Bis(cyclohexylamino)phthalic acid dimethyl ester

A solution of 2.4 g (6 mmol) of 4,5-bis(trimethylsilyloxy)cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester (Example 1a) in 21.5 ml (188 mmol) of cyclohexylamine and 4.5 ml of glacial acetic acid is boiled under reflux for 3.5 hours. The reaction mixture is cooled, the solvent is evaporated off and the dark-brown residue is dissolved in dichloromethane and the solution is washed in succession with 100 ml of 2N HCl, 50 ml of saturated $NaHCO_3$ and twice with 20 ml of water, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with ethyl acetate/hexane 5:12 and the product fractions are concentrated by evaporation and again chromatographed with ethyl acetate/hexane 1:4, yielding the title compound in the form of a yellow oil, FAB-MS: 388 [M^+].

4-Cyclohexylaminophthalic acid dimethyl ester is obtained as a secondary product and is converted into 4-cyclohexylaminophthalimide analogously to Example 6, yielding a colourless powder, FAB-MS: 245 [M^+], m.p. 217-219°C.

Example 7: 4,5-Bis(4-methoxyanilino)phthalimide

Analogously to Example 1, 393 mg (0.9 mmol) of 4,5-bis(4-methoxyanilino)phthalic acid dimethyl ester in 25 ml of ethylene glycol are heated at 120°, ammonia gas being passed through the mixture, with stirring, for 18 hours. The reaction mixture is cooled, saturated with sodium chloride and extracted with ethyl acetate. The ethyl acetate phases are washed in succession three times with water and once with saturated sodium chloride

solution, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with ethyl acetate/hexane 1:1 and the product fractions are combined and concentrated by evaporation, yielding the title compound in the form of yellow crystals, m.p. 191-193°C, FAB-MS: 390 [M^++H].

a) 4,5-Bis(4-methoxyanilino)phthalic acid dimethyl ester

A solution of 2.4 g (6 mmol) of 4,5-bis(trimethylsilyloxy)cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester (Example 1a) and 3.0 g (24 mmol) of 4-anisidine in 24 ml of glacial acetic acid is boiled under reflux for 2 hours. The reaction mixture is cooled, the solvent is evaporated off and the dark-brown residue is dissolved in dichloromethane and the solution is washed in succession with 20 ml of 1N HCl, 50 ml of saturated $NaHCO_3$ and twice with 20 ml of water, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with ethyl acetate/-hexane 1:1 and the product fractions are concentrated by evaporation, yielding the title compound in the form of a yellow foam, FAB-MS: 437 [M^++H].

Example 8: 4,5-Bis(2-iodoanilino)phthalimide

Analogously to Example 1, 1.48 g (2.36 mmol) of 4,5-bis(2-iodoanilino)phthalic acid dimethyl ester in 25 ml of ethylene glycol are heated at 120° and, with stirring, ammonia gas is passed through the mixture for 19 hours. The reaction mixture is cooled, diluted with brine and extracted with ethyl acetate. The ethyl acetate phases are washed in succession three times with water and once with saturated sodium chloride solution, dried with sodium sulfate and concentrated by evaporation. The residue obtained after concentration by evaporation is filtered through silica gel with dichloromethane and the product fractions are combined and concentrated by evaporation. The residue obtained after concentration by evaporation is crystallised from boiling dichloromethane, yielding the title compound in the form of yellow crystals, m.p. 108-110°C, FAB-MS: 582 [M^++H].

a) 4,5-Bis(2-iodoanilino)phthalic acid dimethyl ester

A solution of 2.4 g (6 mmol) of 4,5-bis(trimethylsilyloxy)cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester (Example 1a) and 5.3 g (24 mmol) of 2-iodoaniline in 24 ml of glacial acetic acid is boiled under reflux for 2 hours. The reaction mixture is cooled, the solvent is evaporated off and the dark-brown residue is dissolved in dichloro-

methane and the solution is washed in succession with 20 ml of 1N HCl, 50 ml of saturated $NaHCO_3$ and twice with 20 ml of water, dried with sodium sulfate and concentrated by evaporation. The residue obtained after concentration by evaporation is chromatographed on silica gel with ethyl acetate/hexane 2:1 and the product fractions are concentrated by evaporation, yielding the title compound in the form of a yellow foam: ^{1}H-NMR (DMSO-d_6): δ = 7.91 (dxd, J_1=8, J_2=1, 2H), 7.39 (dxdxd, J_1=10, J_2=8, J_3=1, 2H), 7.32 (br s, 2H), 7.22-7.05 (m, 2H), 7.01 (s, 2H), 6.88 (txd, J_t=8, J_d=1, 2H), 3.73 (s, 6H).

Example 9: 4,5-Bis(2-cyanoanilino)phthalimide

A solution of 581 mg (1 mmol) of 4,5-bis(2-iodoanilino)phthalimide and 197 mg (2.2 mmol) of copper(I) cyanide in DMF is stirred for 6 hours at 130-140°C, the dark-brown solution changing into a dark-yellow suspension. The reaction mixture is cooled to 80°C and diluted with 8 ml of ethyl acetate. After further cooling to 60-70°C, a solution of 467 mg (2.88 mmol) of iron(III) chloride in 1.6 ml of water and 300 µl of concentrated hydrochloric acid is added dropwise and the mixture is stirred for 30 minutes. 2 ml of water and Hyflo Super Cel® (kieselguhr from Fluka, Buchs, Switzerland) are added to the reaction mixture which is then filtered through Hyflo Super Cel® and the phases are separated. The aqueous phase is extracted once with ethyl acetate and the combined organic phases are washed twice with water, once with saturated sodium hydrogen carbonate solution and twice more with water, dried over magnesium sulfate and concentrated by evaporation. The resulting oily brown crystal mixture is chromatographed on silica gel with ethyl acetate/hexane 2:3. The product fractions are concentrated by evaporation and crystallised from boiling dichloromethane, yielding the title compound in the form of pale-yellow crystals: FAB-MS: 380 (M^++H), m.p.: 279-280°C.

5-Anilino-4-(2-cyanoanilino)phthalimide is obtained as a secondary product in the form of yellow crystals: FAB-MS: 355 (M^++H), m.p.: 115-117°C.

Example 10: 4,5-Bis(2-nitroanilino)phthalimide, 4-(4-nitroanilino)-5-(2,4-dinitroanilino)-phthalimide and 4,5-bis(4-nitroanilino)phthalimide

990 mg (3 mmol) of 4,5-bis(anilino)phthalimide are added to a mixture of 12 mmol of acetic anhydride and 24 mmol of glacial acetic acid and 7.5 mmol of nitric acid (100 %) at temperatures of less than 20°C. After stirring for 20 minutes, the reaction mixture is poured onto ice and extracted with ethyl acetate. The organic phases are washed once

with saturated $NaHCO_3$ solution and once with water, dried over sodium sulfate and filtered. Chromatography twice on silica gel using a gradient of dichloromethane/ethyl acetate 1:1 to 3:1 yields the following amorphous compounds: 4,5-bis(2-nitroanilino)-phthalimide in the form of a reddish-black powder: m.p. 87-90°C; 4-(4-nitroanilino)-5-(2,4-dinitroanilino)phthalimide in the form of a reddish-black powder: m.p. 176-178°C, ^{1}H-NMR (DMSO-d_6): 9.25 (br s, 2H), 8.85 (d, J=2.5, 1H), 8.16 (dxd, J_1=8, J_2=2.5, 1H), 8.13 (d, j=9, 2H), 7.88 (s, 1H), 7.75 (s, 1H), 7.17 (d, J=9, 2H), 6.96 (d, J=9.5, 1H); 4,5-bis(4-nitroanilino)phthalimide in the form of a red, lustrous powder: m.p. > 250°C, decomposition from ~105°C, ^{1}H-NMR (DMSO-d_6): 9.22 (br s, 2H), 8.12 (d, J=9.1, 4H), 7.71 (s, 2H), 7.13 (d, J=9.1, 4H); ^{13}C-NMR (DMSO-d_6): 168.9 s, 149.8 s, 139.6 s, 138.2 s, 128.2 s, 125.9 d, 116.2 d, 115.6 d.

Example 11: 4,5-Bis(4-aminoanilino)phthalimide

A solution of 38 mg (0.09 mmol) of 4,5-bis(4-nitroanilino)phthalimide in 15 ml of THF is hydrogenated with 10 % Raney nickel as catalyst for three hours at normal pressure and room temperature. The catalyst is filtered off and the reaction mixture is concentrated by evaporation, yielding the title compound in the form of a slightly yellowish powder: m.p. 154-157°C, FAB-MS: 360 (M^++H).

Example 12: Analogously to the Example given in parentheses after each compound there are prepared:

(a) 4,5-Bis(4-iodoanilino)phthalimide, FAB-MS: 582 (M^++H), m.p.: 246-247°C (analogously to Example 8)
(b) 4,5-Bis(3-iodoanilino)phthalimide, FAB-MS: 582 (M^++H), m.p.: 244-245°C (analogously to Example 8)
(c) 4,5-Bis(2,6-dibromoanilino)phthalimide, FAB-MS: 642 (M^++H), m.p.: 235-237°C (analogously to Example 8)
(d) 4,5-Bis(3-methoxyanilino)phthalimide, FAB-MS: 390 (M^++H), m.p.: 169-171°C (analogously to Example 7)
(e) 4,5-Bis(2-methoxyanilino)phthalimide, FAB-MS: 390 (M^++H), m.p.: 227-228°C (analogously to Example 7)
(f) 4,5-Bis(4-trifluoromethylanilino)phthalimide, FAB-MS: 512 (M^++H), ^{1}H-NMR (CD_3OD): 7.7 (s, 2H), 7.5 (d, 4H), 7.2 (d, 4H) (analogously to Example 1),
(g) 4-Cyanoanilino-5-trifluoromethylanilino-phthalimide, FAB-MS: 423 (M^++H),

^{1}H-NMR ($CDCl_3$): 7.7 (d, 2H), 7.6 (d, 4H), 7.1 (d, 2H), 7.0 (d, 2H), 6.2 (s, 1H), 6.1 (s, 1H) (analogously to Example 1)

(h) 4,5-Bis(4-biphenylamino)phthalimide, FAB-MS: 482 (M^++H), m.p.: 230-231°C (analogously to Example 1)

(i) 4,5-Bis(4-cyanoanilino)phthalimide, FAB-MS: 380 (M^++H), m.p.: > 250°C, ^{1}H-NMR (DMSO-d_6): 7.1 (d, 4H), 7.6 (d, 4H), 7.7 (s, 2H) (analogously to Example 9)

(j) 4,5-Bis(3-cyanoanilino)phthalimide, FAB-MS: 380 (M^++H), m.p.: 255-257°C (analogously to Example 9)

(k) 4,5-Bis(4-pyridineamino)phthalimide (analogously to Example 1).

(l) 4,5-Bis(3-pyridineamino)phthalimide (analogously to Example 1)

(m) 4,5-Bis(2-pyridineamino)phthalimide (analogously to Example 1)

(n) 4,5-Bis(2-pyrimidineamino)phthalimide (analogously to Example 1)

(o) 4,5-Bis(3-pyrimidineamino)phthalimide (analogously to Example 1)

(p) 4,5-Bis(4-pyrimidineamino)phthalimide (analogously to Example 1)

(q) 4,5-Bis(2-triazineamino)phthalimide (analogously to Example 1)

(r) 4,5-Bis(3-fluoroanilino)phthalimide (analogously to Example 3)

(s) 4,5-Bis(2-fluoroanilino)phthalimide (analogously to Example 3)

(t) 4,5-Bis(pentafluoroanilino)phthalimide (analogously to Example 3)

(u) 4,5-Bis(4-hydroxyanilino)phthalimide (analogously to Example 1)

(v) 4,5-Bis(3-hydroxyanilino)phthalimide (analogously to Example 1)

(w) 4,5-Bis(2-hydroxyanilino)phthalimide (analogously to Example 1)

(x) 4,5-Bis(4-ethylanilino)phthalimide (analogously to Example 1)

(y) 4,5-Bis(3-ethylanilino)phthalimide (analogously to Example 1)

(z) 4,5-Bis(2-ethylanilino)phthalimide (analogously to Example 1)

(aa) 4,5-Bis(4-methylanilino)phthalimide (analogously to Example 1)

(ab) 4,5-Bis(3-methylanilino)phthalimide (analogously to Example 1)

(ac) 4,5-Bis(2-methylanilino)phthalimide (analogously to Example 1)

(ad) 4,5-Bis(3-trifluoromethylanilino)phthalimide (analogously to Example 1)

(ae) 4,5-Bis(2-trifluoromethylanilino)phthalimide (analogously to Example 1)

(af) 4,5-Bis[4-(N,N-dimethylamino)-anilino]phthalimide (analogously to Example 5)

(ag) 4,5-Bis[4-(N-acetylamino)-anilino]phthalimide (analogously to Example 1)

(ah) 4,5-Bis(3-biphenylylamino)phthalimide (analogously to Example 1)

(ai) 4,5-Bis(2-biphenylylamino)phthalimide (analogously to Example 1)

(aj) 4,5-Bis(1-naphthylamino)phthalimide (analogously to Example 1)

(ak) 4,5-Bis(2-naphthylamino)phthalimide (analogously to Example 1)

(al) 4,5-Bis(5-tetralinylamino)phthalimide (analogously to Example 1)

(am) 4,5-Bis(4-carboxyanilino)phthalimide (analogously to Example 1)
(an) 4,5-Bis(3-carboxyanilino)phthalimide (analogously to Example 1)
(ao) 4,5-Bis(2-carboxyanilino)phthalimide (analogously to Example 1)
(ap) 4,5-Bis(4-methoxycarbonyl-anilino)phthalimide (analogously to Example 1)
(aq) 4,5-Bis(3-methoxycarbonyl-anilino)phthalimide (analogously to Example 1)
(ar) 4,5-Bis(2-methoxycarbonyl-anilino)phthalimide (analogously to Example 1)
(as) 4,5-Bis(4-ethoxycarbonyl-anilino)phthalimide (analogously to Example 1)
(at) 4,5-Bis(3-ethoxycarbonyl-anilino)phthalimide (analogously to Example 1)
(au) 4,5-Bis(2-ethoxycarbonyl-anilino)phthalimide (analogously to Example 1)
(av) 4,5-Bis(4-isopropyloxycarbonyl-anilino)phthalimide (analogously to Example 1)
(aw) 4,5-Bis(4-tert-butyloxycarbonyl-anilino)phthalimide (analogously to Example 1)
(ax) 4,5-Bis(4-carbamoyl-anilino)phthalimide (analogously to Example 1)
(ay) 4,5-Bis(4-N,N-dimethylcarbamoyl-anilino)phthalimide (analogously to Example 1)
(az) 4,5-Bis(4-hydroxy-3-methylanilino)phthalimide (analogously to Example 1)
(ba) 4,5-Bis(2-hydroxy-5-methylanilino)phthalimide (analogously to Example 1).

Example 13: 4,5-Bis(N-methyl-N-phenylamino)phthalimide

Analogously to Example 1, 66 mg (0.16 mmol) of 4,5-bis(N-methyl-N-phenylamino)-phthalic acid dimethyl ester (Example 14 A) in 5 ml of ethylene glycol are heated at 120° and, with stirring, ammonia gas is passed through the mixture for 18 hours. The reaction mixture is cooled, and extracted with ethyl acetate. The ethyl acetate phases are washed in succession three times with water and once with saturated sodium chloride solution, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with hexane/ethyl acetate 1:1 and the product fractions are combined and concentrated by evaporation, yielding the title compound in the form of slightly yellow crystals, FAB-MS: 358 [M^++H], ^{1}H-NMR ($CDCl_3$): 3.05 (s, 6H).

Example 14: 4-(N-Methyl-N-phenylamino)-5-anilino-phthalimide

Analogously to Example 1, 160 mg (0.41 mmol) of 4-(N-methyl-N-phenylamino)-5-anilinophthalic acid dimethyl ester in 12 ml of ethylene glycol are heated at 120° and, with stirring, ammonia gas is passed through the mixture for 18 hours. The reaction mixture is cooled and extracted with ethyl acetate. The ethyl acetate phases are washed in succession three times with water and once with saturated sodium chloride solution, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is

chromatographed on silica gel with hexane/ethyl acetate 1:1 and the product fractions are combined and concentrated by evaporation, yielding the title compound in the form of slightly yellow crystals, FAB-MS: 344 [M^++H], ^{1}H-NMR ($CDCl_3$): 3.28 (s, 3H).

a) 4,5-Bis(N-methyl-N-phenylamino)phthalic acid dimethyl ester (A) and 4-(N-methyl-N-phenylamino)-5-anilino-phthalic acid dimethyl ester (B)

A solution of 564 mg (1.5 mmol) of 4,5-bis(anilino)phthalic acid dimethyl ester (Example 1b) in 5 ml of acetonitrile is heated at 80°C for 16 hours with 0.93 ml (15 mmol) of methyl iodide and 442 mg (3.2 mmol) of anhydrous potassium carbonate in a bomb tube. The reaction mixture is concentrated to dryness by evaporation, the residue is twice digested in dichloromethane and filtered, and the filtrate is concentrated by evaporation. Repeated chromatography on silica gel with hexane/ethyl acetate yields the title compounds in the form of slightly yellowish powders. (A): FAB-MS: 405 [M^++H]; (B): FAB-MS: 391 [M^++H].

Example 15: 4,5-Bis(anilino)-N-methyl-phthalimide

Analogously to Example 1, 376 mg (1 mmol) of 4,5-bis(anilino)phthalic acid dimethyl ester in 33 ml of ethylene glycol are heated at 120° and, with stirring, methylamine is passed through the mixture for 18 hours. The reaction mixture is cooled and extracted with ethyl acetate. The ethyl acetate phases are washed in succession three times with water and once with saturated sodium chloride solution, dried with sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with hexane/ethyl acetate 1:1 and the product fractions are combined and concentrated by evaporation, yielding the title compound in the form of slightly yellow crystals, FAB-MS: 344 [M^++H], m.p. 195-196°C.

Example 16: 4,5-Bis(anilino)-thiophthalimide [= 5,6-bis(anilino)-isoindol-1-one-3-thione]

138 mg (0.36 mmol) of Lawesson reagent [= 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiaphosphetane] are added to a solution of 100 mg (0.3 mmol) of 4,5-bis-(anilino)phthalimide (Example 1) in 15 ml of dichloromethane and the mixture is boiled under reflux for 4 hours. The reaction mixture is concentrated by evaporation and chromatographed directly on silica gel with hexane/ethyl acetate 2:1. The product fractions are concentrated by evaporation, yielding the title compound in the form of

yellow crystals, FAB-MS: 346 [M^++H].

Example 17: 4,5-Bis(anilino)-N^4,N^5-propane-1,3-diylphthalimide

In an autoclave, 457 mg (1 mmol) of 4,5-bis(anilino)-N^4,N^5-propane-1,3-diyl-phthalic acid dimethyl ester are dissolved in 5 ml of methanol, and 15 ml of ammonia are used for the purpose of amide formation. The autoclave is closed and then heated at 120°C for 24 hours, then cooled and opened, and the ammonia is driven off with nitrogen. The residue is rinsed out with ethyl acetate and filtered, and the filtrate is chromatographed on silica gel with hexane/ethyl acetate 3:1. The product fractions are concentrated by evaporation and crystallised from hexane/ethyl acetate, yielding the title compound in the form of yellow crystals, FAB-MS: 370 [M^++H].

a) 4,5-Bis(anilino)-N^4,N^5-propanediyl-phthalic acid dimethyl ester and 4,5-bis(N-allyl-anilino)phthalic acid dimethyl ester

0.6 g (15.4 mmol) of sodium amide is added at room temperature under argon to a solution of 3.76 g (10 mmol) of 4,5-bis(anilino)phthalic acid dimethyl ester (Example 1b) in 15 ml of HMPT (hexamethylphosphoric acid triamide) or DMPU, and the mixture is heated at 60°C for 30 minutes. The deep red solution is cooled to room temperature and evacuated for 5 minutes (1 torr), then a solution of 1.5 ml (15.2 mmol) of 1-bromo-3-chloropropane in 2 ml of THF is added dropwise and the reaction mixture is stirred for 18 hours at room temperature. The reaction mixture is poured onto ice-water, extracted with ethyl acetate and the organic phases are combined and washed with generous amounts of water, dried over sodium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with hexane/ethyl acetate 5:1, yielding the title compounds: 4,5-bis(anilino)-N^4,N^5-propanediyl-phthalic acid dimethyl ester in the form of colourless crystals, FAB-MS: 417 [M^++H]; and 4,5-bis(N-allylanilino)phthalic acid dimethyl ester in the form of a colourless oil, FAB-MS: 457 [M^++H].

Example 18: Analogously to Examples 13-17 there are prepared:

(a) 4-(N-Acetyl-N-phenyl)amino-5-anilino-phthalimide, FAB-MS: 372 [M^++H], ^{1}H-NMR (DMSO-d_6): 2.05 (s, 3H) (analogously to Example 14)
(b) 4,5-Bis(anilino)-N-benzyl-phthalimide (analogously to Example 15)
(c) 4,5-Bis(anilino)-N-amino-phthalimide (analogously to Example 15)

(d) 4,5-Bis(anilino)-N-hydroxy-phthalimide (analogously to Example 15)
(e) 4,5-Bis(N-allylanilino)phthalimide, FAB-MS: 410 (analogously to Example 17).

Example 19: 5000 capsules are prepared, each comprising 0.25 g of active ingredient, for example one of the compounds prepared in Examples 1 to 16:

Composition	
active ingredient	1250 g
talc	180 g
wheat starch	120 g
magnesium stearate	80 g
lactose	20 g

Method: The pulverulent substances are forced through a sieve having a mesh size of 0.6 mm and mixed together. 0.33 g portions of the mixture are filled into gelatin capsules using a capsule-filling machine.

Example 20: 4-Anilino-5-(4-hydroxy-anilino)-phthalimide

To a solution of 359.4 mg (1 mmol) of 4-anilino-5-(4-methoxy-anilino)-phthalimide in 5 ml of chloroform, a solution of 186 µl (2 mmol) of boron tribromide in 5 ml of chloroform is added dropwise at -40°C to -30°C. The reaction mixture is stirred for 5 hours at -30°C and is then quenched with 5 ml of water at -30°C. The reaction mixture is warmed up to room temperature, and the phases are separated. The organic phase is washed twice with water, dried over magnesium sulfate and concentrated by evaporation. Excluding light, the evaporation residue is chromatographed with ethyl acetate/hexane 1:1 on a silica gel column that is cooled with ice-water (double jacket), and the product fractions are combined and concentrated by evaporation. The title compound is obtained in the form of yellow crystals, FAB-MS: 346 [M^++H].

a) 4-Anilino-5-(4-methoxy-anilino)phthalimide

Analogously to Example 1, 0.7 g (1.7 mmol) of 4-anilino-5-(4-methoxy-anilino)-phthalic acid dimethyl ester in 20 ml of ethylene glycol is heated at 120°, ammonia gas being passed through the mixture, with stirring, for 18 hours. The reaction mixture is cooled and extracted with ethyl acetate. The ethyl acetate phases are washed in succession twice with

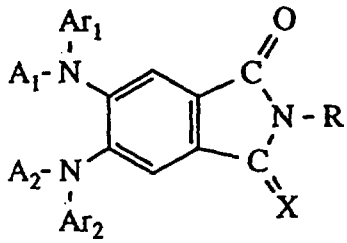
water and once with saturated sodium chloride solution, dried with magnesium sulfate and concentrated by evaporation. The evaporation residue is chromatorgaphed on silica gel with ethyl acetate/hexane 1:1 and the product fractions are combined and concentrated by evaporation, yielding the title compound in the form of yellow crystals, m.p. 266-267°C, FAB-MS: 360 [M^++H].

b) 4-Anilino-5-(4-methoxy-anilino)-phthalic acid dimethyl ester and 4,5-bis(4-methoxy-anilino)phthalic acid dimethyl ester

A solution of 4.8 g (12 mmol) of 4,5-bis(trimethylsilyloxy)-cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester (Example 1a), 2.6 g (24 mmol) of p-anisidine and 2.2 ml (24 mmol) of aniline in 48 ml of glacial acetic acid is boiled under reflux for 2 hours. The reaction mixture is cooled, the solvent is evaporated and the dark-brown residue is dissolved in ethyl acetate and the solution is washed in succession with 40 ml of 1N HCl, 100 ml of saturated $NaHCO_3$ and twice with 100 ml of water, dried with magnesium sulfate and concentrated by evaporation. The evaporation residue is chromatographed on silica gel with ethyl acetate/hexane 1:3 and the product fractions are concentrated by evaporation. In this way, 4,5-bis(4-methoxy-anilino)phthalic acid dimethyl ester is obtained from the first product fractions in the form of a yellow foam: FAB-MS: 437 [M^++H]. The evaporation residue of the product fractions following thereafter is recrystallised from ethyl acetate/hexane, and 4-anilino-5-(4-methoxy-anilino)-phthalic acid dimethyl ester is obtained in the form of yellow crystals, m.p. 122-124°C, FAB-MS: 407 [M^++H].

Patent claims for the Contracting States: AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, PT, SE.

1. A compound of formula I



(I)

wherein

A_1 and A_2 are each independently of the other hydrogen, C_1-C_7alkyl, C_2-C_7alkenyl, C_2-C_7alkynyl, phenyl or naphthyl that is unsubstituted or substituted by one or more substituents from the group consisting of: C_1-C_7alkyl, C_2-C_7alkenyl, C_2-C_7alkynyl, C_3-C_4-alkylene (linked to two adjacent carbon atoms), C_3-C_8cycloalkyl, phenyl-C_1-C_7alkyl, phenyl; C_1-C_7alkyl substituted by hydroxy, C_1-C_7alkoxy, phenyl-C_1-C_7alkoxy, C_1-C_7-alkanoyloxy, halogen, amino, C_1-C_7alkylamino, di-C_1-C_7alkylamino, mercapto, C_1-C_7-alkylthio, C_1-C_7alkylsulfinyl, C_1-C_7alkylsulfonyl, carboxy, C_1-C_7alkoxycarbonyl, carbamoyl, N-C_1-C_7alkylcarbamoyl, N,N-di-C_1-C_7alkylcarbamoyl and/or by cyano; hydroxy, C_1-C_7alkoxy, halo-C_1-C_7alkoxy, phenyl-C_1-C_7alkoxy, phenoxy, C_2-C_7alkenyl-oxy, halo-C_2-C_7alkenyloxy, C_2-C_7alkynyloxy, C_1-C_2alkylenedioxy (linked to two adjacent carbon atoms), C_1-C_7alkanoyloxy, phenyl-C_1-C_7alkanoyloxy, phenylcarbonyloxy, mercapto, C_1-C_7alkylthio, phenyl-C_1-C_7alkylthio, phenylthio, C_1-C_7alkylsulfinyl, phenyl-C_1-C_7alkylsulfinyl, phenylsulfinyl, C_1-C_7alkylsulfonyl, phenyl-C_1-C_7alkylsulfonyl, phenylsulfonyl, halogen, nitro, amino, C_1-C_7alkylamino, C_3-C_8cycloalkylamino, phenyl-C_1-C_7alkylamino, phenylamino, di-C_1-C_7alkylamino, N-C_1-C_7alkyl-N-phenylamino, N-C_1-C_7alkyl-N-phenyl-C_1-C_7alkylamino, C_4-C_7alkyleneamino, C_4-C_7alkyleneamino interrupted by -O-, -S- or -NR"- (wherein R" is hydrogen, C_1-C_7alkyl or C_1-C_7alkanoyl), C_1-C_7alkanoylamino, phenyl-C_1-C_7alkanoylamino, phenylcarbonylamino, C_1-C_7alkanoyl, phenyl-C_1-C_7alkanoyl, phenylcarbonyl, carboxy, C_1-C_7alkoxycarbonyl, carbamoyl, C_1-C_7alkylcarbamoyl, N,N-di-C_1-C_7alkylcarbamoyl, N-hydroxycarbamoyl, N-phenyl-carbamoyl, cyano, sulfo, C_1-C_7alkoxysulfonyl, sulfamoyl, N-C_1-C_7alkylsulfamoyl, N,N-di-C_1-C_7alkylsulfamoyl and N-phenylsulfamoyl (phenyl groups occurring in the substi-

tuents each being unsubstituted or substituted by C_1-C_7alkyl, C_1-C_7alkoxy, hydroxy, halogen and/or by trifluoromethyl); C_1-C_7alkanoyl, halo-C_1-C_7alkanoyl, phenyl- or naphthyl-C_1-C_7alkanoyl that in the phenyl or naphthyl radical is unsubstituted or substituted as above or phenyl- or naphthyl-carbonyl that in the phenyl or naphthyl radical is unsubstituted or substituted as above, C_1-C_7alkylsulfonyl or phenyl- or naphthyl-sulfonyl wherein phenyl or naphthyl is unsubstituted or substituted as above; or wherein
A_1 and A_2 together form unsubstituted or C_1-C_7alkyl- or hydroxy-substituted C_1-C_4-alkylene;
Ar_1 and Ar_2 are each independently of the other phenyl or naphthyl that is unsubstituted or substituted as above; imidazolyl, triazolyl, pyridyl, pyrimidinyl or triazinyl that is unsubstituted or substituted by C_1-C_7alkyl, hydroxy, C_1-C_7alkoxy, halogen, cyano and/or by trifluoromethyl; or C_3-C_8cycloalkyl that is unsubstituted or substituted by C_1-C_7alkyl or by hydroxy;
the group -C(=X)- is -C(=O)-, -C(=S)-, -CH_2- or -C(=CR_1R_2)- wherein R_1 and R_2 are each independently of the other hydrogen or C_1-C_7alkyl; and
R is hydrogen, C_1-C_7alkyl, aryl-C_1-C_7alkyl or aryl wherein aryl is phenyl or naphthyl that is unsubstituted or substituted as above; amino, hydroxy or C_1-C_7alkoxy; with the proviso that R is other than phenyl when A_1 and A_2 are hydrogen, Ar_1 and Ar_2 are phenyl and the group -C(=X)- is -C(=O)-; or a salt thereof when salt-forming groups are present.

2. A compound of formula I according to claim 1 wherein
A_1 and A_2 are each independently of the other hydrogen, lower alkyl; C_2-C_7alkenyl; phenyl or 1-naphthyl or 2-naphthyl, the three last-mentioned radicals being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; lower alkanoyl, lower alkylsulfonyl or phenylsulfonyl wherein the phenyl group is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; or wherein
A_1 and A_2 together are C_1-C_4alkylene; wherein
Ar_1 and Ar_2 are each independently of the other phenyl or naphthyl, each of which is unsubstituted or substituted by one or more substituents from the group consisting of: lower alkyl, C_2-C_7alkenyl, C_2-C_7alkynyl, C_3-C_4alkylene (linked to two adjacent carbon atoms), C_3-C_8cycloalkyl, phenyl-lower alkyl, phenyl; lower alkyl substituted by hydroxy, lower alkoxy, phenyl-lower alkoxy, lower alkanoyloxy, halogen, amino, lower alkylamino, di-lower alkylamino, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl and/or by cyano; hydroxy, lower alkoxy, halo-lower alkoxy, phenyl-lower

alkoxy, phenoxy, C_2-C_7alkenyloxy, halo-C_2-C_7alkenyloxy, C_2-C_7alkynyloxy, C_1-C_2-alkylenedioxy (linked to two adjacent carbon atoms), lower alkanoyloxy, phenyl-lower alkanoyloxy, phenylcarbonyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkylsulfinyl, phenyl-lower alkylsulfinyl, phenylsulfinyl, lower alkylsulfonyl, phenyl-lower alkylsulfonyl, phenylsulfonyl, halogen, nitro, amino, lower alkylamino, C_3-C_8cycloalkylamino, phenyl-lower alkylamino, phenylamino, di-lower alkylamino, N-lower alkyl-N-phenylamino, N-lower alkyl-N-phenyl-lower alkylamino, C_4-C_7-alkyleneamino, C_4-C_7alkyleneamino interrupted by -O-, -S- or -NR"- (wherein R" is hydrogen, lower alkyl or lower alkanoyl), lower alkanoylamino, phenyl-lower alkanoylamino, phenylcarbonylamino, lower alkanoyl, phenyl-lower alkanoyl, phenylcarbonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-hydroxycarbamoyl, N-phenylcarbamoyl, cyano, sulfo, lower alkoxysulfonyl, sulfamoyl, N-lower alkylsulfamoyl, N,N-di-lower alkylsulfamoyl and N-phenylsulfamoyl (phenyl groups occurring in the substituents each being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl); pyridyl or pyrimidinyl that is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen, cyano and/or by trifluoromethyl; or C_3-C_8cycloalkyl;
the group -C(=X)- is -C(=O)-, -C(=S)-, $-CH_2-$ or $-C(=CR_1R_2)-$ wherein R_1 and R_2 are each independently of the other hydrogen or lower alkyl, and
R is hydrogen, lower alkyl; phenyl-lower alkyl, phenyl, 1-naphthyl or 2-naphthyl, in the four last-mentioned radicals the phenyl or naphthyl group being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; or R is amino, hydroxy or lower alkoxy; with the proviso that R is other than phenyl when A_1 and A_2 are hydrogen, Ar_1 and Ar_2 are phenyl and the group -C(=X)- is -C(=O)-; or a salt thereof when salt-forming groups are present; in the above-mentioned radicals "lower" representing "C_1-C_7-" and "-lower" representing "-C_1-C_7-".

3. A compound of formula I according to claim 2 wherein R is as defined except for phenyl, and the other radicals are as defined, or a salt thereof when salt-forming groups are present.

4. A compound of formula I according to claim 1 wherein
A_1 and A_2 are each independently of the other hydrogen, lower alkyl; phenyl or 1-naphthyl or 2-naphthyl, the three last-mentioned radicals being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; lower alkanoyl, lower alkylsulfonyl or phenylsulfonyl wherein the phenyl group is unsubstituted

or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; or wherein

A_1 and A_2 together are C_1-C_4alkylene; wherein

Ar_1 and Ar_2 are each independently of the other phenyl or naphthyl, each of which is unsubstituted or substituted by one or more substituents from the group consisting of: lower alkyl, C_2-C_7alkenyl, C_2-C_7alkynyl, C_3-C_4alkylene (linked to two adjacent carbon atoms), C_3-C_8cycloalkyl, phenyl-lower alkyl, phenyl; lower alkyl substituted by hydroxy, lower alkoxy, phenyl-lower alkoxy, lower alkanoyloxy, halogen, amino, lower alkylamino, di-lower alkylamino, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl and/or by cyano; hydroxy, lower alkoxy, halo-lower alkoxy, phenyl-lower alkoxy, phenoxy, C_2-C_7alkenyloxy, halo-C_2-C_7alkenyloxy, C_2-C_7alkynyloxy, C_1-C_2alkylenedioxy (linked to two adjacent carbon atoms), lower alkanoyloxy, phenyl-lower alkanoyloxy, phenylcarbonyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkylsulfinyl, phenyl-lower alkylsulfinyl, phenylsulfinyl, lower alkylsulfonyl, phenyl-lower alkylsulfonyl, phenylsulfonyl, halogen, nitro, amino, lower alkylamino, C_3-C_8cycloalkylamino, phenyl-lower alkylamino, phenylamino, di-lower alkylamino, N-lower alkyl-N-phenylamino, N-lower alkyl-N-phenyl-lower alkylamino, C_4-C_7alkyleneamino, C_4-C_7alkyleneamino interrupted by -O-, -S- or -NR"- (wherein R" is hydrogen, lower alkyl or lower alkanoyl), lower alkanoylamino, phenyl-lower alkanoylamino, phenylcarbonylamino, lower alkanoyl, phenyl-lower alkanoyl, phenylcarbonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-hydroxycarbamoyl, N-phenylcarbamoyl, cyano, sulfo, lower alkoxysulfonyl, sulfamoyl, N-lower alkylsulfamoyl, N,N-di-lower alkylsulfamoyl and N-phenylsulfamoyl (phenyl groups occurring in the substituents each being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl); pyridyl that is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen, cyano and/or by trifluoromethyl; or C_3-C_8cycloalkyl;

the group -C(=X)- is -C(=O)-, -C(=S)-, $-CH_2-$ or $-C(=CR_1R_2)-$ wherein R_1 and R_2 are each independently of the other hydrogen or lower alkyl, and

R is hydrogen, lower alkyl; phenyl-lower alkyl, phenyl, 1-naphthyl or 2-naphthyl, in the four last-mentioned radicals the phenyl or naphthyl group being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; or R is amino, hydroxy or lower alkoxy; with the proviso that R is other than phenyl when A_1 and A_2 are hydrogen, Ar_1 and Ar_2 are phenyl and the group -C(=X)- is -C(=O)-; or a salt thereof when salt-forming groups are present; in the above-mentioned radicals "lower"

representing "C_1-C_7-" and "-lower" representing "-C_1-C_7-".

5. A compound of formula I according to claim 2 wherein A_1 and A_2 are each independently of the other hydrogen or lower alkyl, the group -C(=X)- is -C(=O)-, -C(=S)- or -C(=CH_2)-, and R is hydrogen or lower alkyl; or a salt thereof when salt-forming groups are present; in the above-mentioned radicals "lower" representing "C_1-C_7-".

6. A compound of formula I according to claim 1 wherein A_1 and A_2 are each independently of the other hydrogen; lower alkyl; C_2-C_7alkenyl; or lower alkanoyl; or wherein A_1 and A_2 together are C_1-C_4alkylene; wherein Ar_1 and Ar_2 are each independently of the other phenyl or naphthyl, each of which is unsubstituted or substituted by one or more substituents from the group consisting of: lower alkyl, C_3-C_4alkylene (linked to two adjacent carbon atoms), hydroxy, phenoxy, halogen, nitro, amino, lower alkylamino, di-lower alkylamino, lower alkanoylamino, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl and cyano; pyridyl; pyrimidinyl; or C_3-C_8cycloalkyl; the group -C(=X)- is -C(=O)- or -C(=S)-; and R is hydrogen, lower alkyl, phenyl-lower alkyl, amino or hydroxy; or a salt thereof when salt-forming groups are present; in the above-mentioned radicals "lower" representing "C_1-C_7-" and "-lower" representing "-C_1-C_7-".

7. A compound of formula I according to claim 1 wherein A_1 and A_2 are each independently of the other hydrogen or methyl; or wherein A_1 and A_2 together are -$(CH_2)_2$- or -$(CH_2)_3$-; Ar_1 and Ar_2 are each independently of the other phenyl or naphthyl, each of which is unsubstituted or substituted by one or more substituents from the group consisting of: lower alkyl, lower alkoxy, phenyl-lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, lower alkylamino, di-lower alkylamino, lower alkanoylamino, halogen, trifluoromethyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, cyano, lower alkanoyl, benzoyl, lower alkoxysulfonyl and sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl; or cyclopentyl; cyclohexyl; or pyridyl; the group -C(=X)- is -C(=O)-, -C(=S)- or -C(=CH_2)-, and R is hydrogen or lower alkyl; or a pharmaceutically acceptable salt thereof; in the above-mentioned radicals "lower" representing "C_1-C_7-" and "-lower" representing "-C_1-C_7-".

8. A compound of formula I according to claim 1 wherein A_1 and A_2 are hydrogen; Ar_1 and Ar_2 are each independently of the other phenyl that is unsubstituted or substituted by lower alkyl, trifluoromethyl, phenyl, hydroxy, lower alkoxy, benzyloxy, amino, di-lower

alkylamino, lower alkanoylamino, halogen, carboxy, lower alkoxycarbonyl, carbamoyl, N,N-di-lower alkylcarbamoyl or by cyano; or cyclohexyl; the group -C(=X)- is -C(=O)-, -C(=S)- or -C(=CH_2)-, and R is hydrogen; or a pharmaceutically acceptable salt thereof; in the above-mentioned radicals "lower" representing "C_1-C_7-" and "-lower" representing "-C_1-C_7-".

9. 4,5-Bis(anilino)phthalimide according to claim 1.

10. 4,5-Bis(4-fluoroanilino)phthalimide according to claim 1.

11. 4,5-Bis(cyclohexylamino)phthalimide according to claim 1 or a pharmaceutically acceptable salt thereof.

12. 5,8-Diphenyl-5,8-diaza-5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylic acid amide according to claim 1.

13. 4,5-Bis(2-nitroanilino)phthalimide according to claim 1.

14. 4,5-Bis(4-aminoanilino)phthalimide according to claim 1 or a pharmaceutically acceptable salt thereof.

15. 4,5-Bis(2-pyridineamino)phthalimide according to claim 1 or a pharmaceutically acceptable salt thereof.

16. 4,5-Bis(2-pyrimidineamino)phthalimide according to claim 1 or a pharmaceutically acceptable salt thereof.

17. 4-(N-Methyl-N-phenylamino)-5-anilinophthalimide according to claim 1.

18. 4,5-Bis(anilino)-N^4,N^5-propane-1,3-diyl-phthalimide according to claim 1.

19. 4,5-Bis(N-allylanilino)phthalimide according to claim 1.

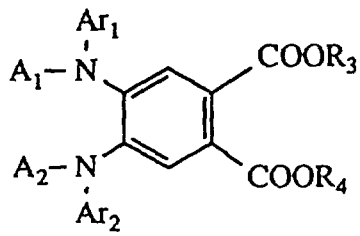
20. A pharmaceutical composition comprising a compound of formula I according to any one of claims 1 to 19 and at least one pharmaceutically acceptable carrier.

21. A compound of formula I according to any one of claims 1 to 19 for use in a method for the therapeutic treatment of the animal or human body.

22. The use of a compound according to any one of claims 1 to 19 for the preparation of a pharmaceutical composition for the treatment of diseases responsive to the inhibition of tyrosine protein kinases or serine/threonine kinases.

23. A process for the preparation of a compound of formula I according to claim 1, which process comprises

(a) reacting a compound of formula II



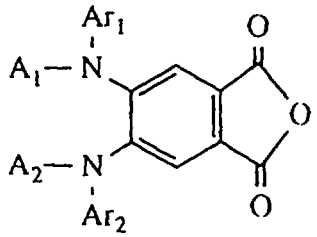
(II)

wherein Ar_1, Ar_2, A_1 and A_2 are as defined under formula I and R_3 and R_4 are each independently of the other aryl or C_1-C_7alkyl, with a compound of formula III

$$H_2N\text{-}R \qquad \text{(III)}$$

wherein R is as defined under formula I, or

(b) reacting a compound of formula IV



(IV)

wherein Ar_1, Ar_2, A_1 and A_2 are as defined under formula I, with a compound of formula III

H_2N-R (III)

wherein R is as defined under formula I;

and, if desired, converting a resulting compound of formula I into a different compound of formula I, and/or converting a resulting salt into the free compound or into a different salt, and/or converting a resulting free compound of formula I into a salt and/or separating a resulting mixture of isomeric compounds of formula I into the individual isomers.