

Clarke, Modet & C^o
COLOMBIA

ESCOBAR - URIBE ASOCIADOS
Intellectual Property

As. 3058/PCT.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

E. S. D.

Ref.: Expediente No. 07-050.827
Solicitud de Patente a nombre de
JANSSEN PHARMACEUTICA N.V.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-050827- -00002-0000

Fecha: 2008-06-06 10:06:39 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 7

Yo, **JIMENA ESCOBAR URIBE**, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **JANSSEN PHARMACEUTICA N.V.**, con domicilio en Beerse, Bélgica, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial los recibos Nrs. 08-41,057, 08-41,058, 08-41,094, 08-41,035, 08-41,124 y 08-41,125, todos los anteriores de 21 de mayo de 2008 por la suma de \$420.000.00, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de Usaquén
T.P. 68.228

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800174089-2

CERTIFICACION DE EXCEDENTE : 08 - 41,057
FECHA : MAYO 21 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-050827- -00002-0000

Fecha: 2008-06-06 10:06:39 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 7

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	693066	21/05/2008	27,730,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVICIOS ADMINISTRATIVOS	120,000.00
TOTAL :			\$ 120,000.00

SON: CIENTO VEINTE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA

216

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 41,058
FECHA : MAYO 21 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-050827- -00002-0000

Fecha: 2008-06-06 10:06:39 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 7

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CLARKE MODET Y CG. COLOMBIA	CONSIGNACION	BANCO DE BOGOTA	062754387	593066	21/05/2008	27,730,000.00

***** CONCEPTO *****

CANT.	RENTISTADO	CONCEPTO	TOTAL CONCEPTO
50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVICIOS ADMINISTRATIVOS	120,000.00
TOTAL :			120,000.00

SON: CIENTO VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

3050/P

277

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.76089-2

RECIBO OFICIAL DE CAJA : 06 - 41,094
FECHA : MAYO 21 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-050827- -00002-0000

Fecha: 2008-06-06 10:06:39 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 7

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	693066	21/05/2008	27,730,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-08	PRORROGA DE TERMINOS	31 PRORROGA DE TERMINOS	75,000.00
TOTAL :			\$ 75,000.00

SON: SETENTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

25515

278

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 41,035
FECHA : MAYO 21 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-050827- -00002-0000

Fecha: 2008-06-06 10:06:39 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 7

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MOJET Y CO. COLOMBIA	CONSIGNACION	BANCO DE BOGOTA	062754387	693066	21/05/2008	27,730,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LENAS COMERCIALES	103,000.00
		TOTAL :	\$ 103,000.00

SON: CIENTO TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

231

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-050827- -00002-0000

CERTIFICACION DE EXCEDENTE : 08 - 41,124
FECHA : MAYO 21 DE 2008

Fecha: 2008-06-06 10:06:39 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 7

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMBIA	CONSIGNACION	BANCO DE BOGOTA	062754387	693066	21/05/2008	27,730,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVICIOS ADMINISTRATIVOS	1,000.00
TOTAL :			\$ 1,000.00

SDN: MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

280

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 41,125
FECHA : MAYO 21 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-050827- -00002-0000

Fecha: 2008-06-06 10:06:39 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 7

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CLARKE MODET Y CO. COLOMBIA	CONSIGNACION	BANCO DE BOGOTA	062754387	693066	21/05/2008	27,730,000.00

***** CONCEPTO *****

CANT.	RENTISTADO	CONCEPTO	TOTAL CONCEPTO
50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVICIOS ADMINISTRATIVOS	1,000.00
TOTAL :			\$ 1,000.00

SON: MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

1054

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-50827

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **583** DE

FECHA **18 DE DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **14 DE MARZO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

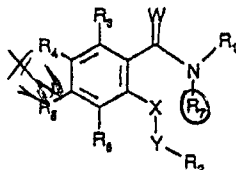
NO X



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 213/38, A61K 31/44, C07D 215/12, A61K 31/47, C07D 213/64, 233/54, A61K 31/415, C07D 213/89, 405/12, A61P 35/00	A1	(11) International Publication Number: WO 00/27820 (43) International Publication Date: 18 May 2000 (18.05.00)
(21) International Application Number: PCT/EP99/08545 (22) International Filing Date: 8 November 1999 (08.11.99) (30) Priority Data: 9824579.8 10 November 1998 (10.11.98) GB (71) Applicant (for all designated States except AT US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH). (71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT). (71) Applicant (for all designated States except US): SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstrasse 178, D-13342 Berlin (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): ALTMANN, Karl-Heinz [DE/CH]; Tannenweg 5, CH-4153 Reinach (CH). BOLD, Guido [CH/CH]; Bleumathöhe 16, CH-5073 Gipf-Oberfrick (CH). FURET, Pascal [FR/FR]; 24, rue du Riegelsbourg, F-68800 Thann (FR). MANLEY, Paul,		William [GB/CH]; Bruggweg 12, CH-4144 Arlesheim (CH). WOOD, Jeanette, Marjorie [NZ/CH]; In den Kleematten 18, CH-4105 Biel-Benken (CH). FERRARI, Stefano [IT/CH]; Baselstrasse 63, CH-4132 Muttensz (CH). HOFMANN, Francesco [CH/CH]; Fiechthagstrasse 8, CH-4103 Bottmingen (CH). MESTAN, Jürgen [DE/DE]; Simon-Veit-Gasse 4, D-79312 Emmendingen (DE). HUTH, Andreas [DE/DE]; Dammweg 113, D-12437 Berlin (DE). KRÜGER, Martin [DE/DE]; Heerruferweg 7A, D-13465 Berlin (DE). SEIDELMANN, Dieter [DE/DE]; Stierstrasse 14, D-12159 Berlin (DE). MENRAD, Andreas [DE/DE]; Allerstrasse 7, D-16515 Oranienburg (DE). HABEREY, Martin [DE/DE]; Steinstrasse 1, D-12169 Berlin (DE). THIERAUCH, Karl-Heinz [DE/DE]; Hochwildpfad 45, D-14169 Berlin (DE). (74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Dept., CH-4002 Basel (CH). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.

(54) Title: N-ARYL(THIO)ANTHRANILIC ACID AMIDE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS VEGF RECEPTOR TYROSINE KINASE INHIBITORS



(I)

(57) Abstract

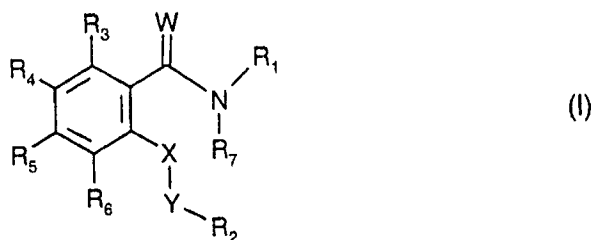
Described are compounds of formula (I), wherein W is O or S; X is NR₈; Y is CR₉R₁₀-(CH₂)_n wherein R₉ and R₁₀ are independently of each other hydrogen or lower alkyl, and n is an integer of from and including 0 to and including 3; or Y is SO₂; R₁ is aryl; R₂ is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms with the exception that R₂ cannot represent 2-phthalimidyl, and in case of Y = SO₂ cannot represent 2,1,3-benzothiadiazol-4-yl; any of R₃, R₄, R₅ and R₆, independently of the other, is H or a substituent other than hydrogen; and R₇ and R₈, independently of each other, are H or lower alkyl; or a N-oxide or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical product for the treatment of a neoplastic disease which responds to an inhibition of the VEGF receptor tyrosine kinase activity. The compounds of formula (I) can be used for the treatment e.g. of a neoplastic disease, such as a tumor disease, of retinopathy and age-related macular degeneration.

Surprisingly, it has now been found that benzamide derivatives of formula I, described below, are a new class of compounds that have advantageous pharmacological properties and inhibit, for example, the activity of the VEGF receptor tyrosine kinase, the growth of tumors and VEGF-dependent cell proliferation, or the treatment of especially inflammatory rheumatic or rheumatoid diseases, such as rheumatoid arthritis, and/or pain, or the other diseases mentioned above and below.

The compounds of formula I open up, for example, an unexpected new therapeutic approach, especially for diseases in the treatment of which, and also for the prevention of which, an inhibition of angiogenesis and/or of the VEGF receptor tyrosine kinase shows beneficial effects.

Full description of the invention

The invention relates the use of a compound of formula I,



wherein

W is O or S;

X is NR₈;

Y is CR₉R₁₀-(CH₂)_n wherein

R₉ and R₁₀ are independently of each other hydrogen or lower alkyl, and

n is an integer of from and including 0 to and including 3; or

Y is SO₂;

R₁ is any;

R₂ is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms with the exception that R₂ cannot represent 2-phthalimidyl, and in case of Y = SO₂ cannot represent 2,1,3-benzothiadiazol-4-yl;

any of R₃, R₄, R₅ and R₆, independently of the other, is H or a substituent other than hydrogen; and

(R₇) and R₈, independently of each other, are H or lower alkyl; or a N-oxide or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical product for the treatment of a neoplastic disease which responds to an inhibition of the VEGF receptor tyrosine kinase activity.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

The prefix "lower" denotes a radical having up to and including a maximum of 7, especially up to and including a maximum of 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching.

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

Any asymmetric carbon atoms (for example in compounds of formula I, wherein R₉ is lower alkyl) may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. The compounds may thus be present as mixtures of isomers or as pure isomers, preferably as enantiomer-pure diastereomers.

The invention relates also to possible tautomers of the compounds of formula I.

Lower alkyl is preferably alkyl with from and including 1 up to and including 7, preferably from and including 1 to and including 4, and is linear or branched; preferably, lower alkyl is butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl, propyl, such as n-propyl or isopropyl, ethyl or preferably methyl.

The index n is preferably 0 or 1, especially 0.

Y is preferably methylene (CH₂) or ethylene (CH₂-CH₂), most preferably methylene.

"Aryl" is an aromatic radical which is bound to the molecule via a bond located at an aromatic ring carbon atom of the radical. In a preferred embodiment, aryl is an aromatic radical having 6 to 14 carbon atoms, especially phenyl, naphthyl, tetrahydronaphthyl, fluorenyl or phenanthrenyl, and is unsubstituted or substituted by one or more, preferably up to three, especially one or two substituents, especially selected from amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, benzoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amidino, guanidino, ureido, mercapto, sulfo, lower alkylthio, phenyl, phenoxy, phenylthio, phenyl-lower alkylthio, alkylphenylthio, lower alkylsulfinyl, phenylsulfinyl, phenyl-lower alkylsulfinyl, alkylphenylsulfinyl, lower alkanesulfonyl, phenylsulfonyl, phenyl-lower alkylsulfonyl, alkylphenylsulfonyl, lower alkenyl, lower alkanoyl, halogen-lower alkylmercapto, halogen-lower alkylsulfonyl, such as especially trifluoromethane sulfonyl, dihydroxybora (-B(OH)₂), heterocyclyl, and lower alkylene dioxy bound at adjacent C-atoms of the ring, such as methylene dioxy; aryl is preferably phenyl or naphthyl, which in each case is either unsubstituted or independently substituted by one or two substituents selected from the group comprising halogen, especially fluorine, chlorine, or bromine; hydroxy; hydroxy, etherified by lower alkyl, e.g. methyl, or by halogen-lower alkyl, e.g. trifluoromethyl; esterified carboxy, especially lower alkoxy carbonyl, e.g. methoxy carbonyl, *n*-propoxy carbonyl or *iso*-propoxy carbonyl; N-mono-substituted carbamoyl, in particular carbamoyl monosubstituted by lower alkyl, e.g. methyl, *n*-propyl or *iso*-propyl; lower alkyl, especially methyl, ethyl or propyl; substituted alkyl, especially lower alkyl, e.g. methyl or ethyl, substituted by lower alkoxy carbonyl, e.g. methoxy carbonyl or ethoxy carbonyl; halogen-lower alkyl, especially trifluoromethyl; lower alkylsulfinyl, such as methylsulfinyl, and lower alkanesulfonyl, such as methane sulfonyl. Aryl is preferably 3- or 4-chlorophenyl, 3-bromophenyl, 4-phenoxyphenyl, 2, 3- or 4-methylphenyl, 4-methoxyphenyl, 3- or 4-tert-butylphenyl, 4-*n*-propylphenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 3-trifluoromethoxyphenyl, 3,4-(trifluoromethyl)phenyl, 3-fluoro-4-methylphenyl, 3-chloro-4-methylphenyl, 4-chloro-3-trifluoromethylphenyl, 3-chloro-5-trifluoromethylphenyl, 4-methylsulfinylphenyl, 4-methanesulfonylphenyl, 4-biphenyl, naphthyl, 2-naphthyl; tetrahydronaphthyl, in particular 5,6,7,8-tetrahydronaphthyl; hydroxynaphthyl, in particular 7-hydroxynaphthyl, 8-hydroxynaphthyl or 8-hydroxy-2-

naphthyl; methoxynaphthyl, in particular 4-methoxy-2-naphthyl; halonaphthyl, in particular 4-chloronaphthyl or 3-bromo-2-naphthyl.

Mono- or disubstituted amino is especially amino substituted by one or two radicals selected independently of one another from lower alkyl, such as methyl; hydroxy-lower alkyl, such as 2-hydroxyethyl; phenyl-lower alkyl; lower alkanoyl, such as acetyl; benzoyl; substituted benzoyl, wherein the phenyl radical is especially substituted by one or more, preferably one or two, substituents selected from nitro, amino, halogen, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl, and carbamoyl; and phenyl-lower alkoxycarbonyl, wherein the phenyl radical is unsubstituted or especially substituted by one or more, preferably one or two, substituents selected from nitro, amino, halogen, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl, and carbamoyl; and is preferably N-lower alkylamino, such as N-methylamino, hydroxy-lower alkylamino, such as 2-hydroxyethylamino, phenyl-lower alkylamino, such as benzylamino, N,N-di-lower alkylamino, N-phenyl-lower alkyl-N-lower alkylamino, N,N-di-lower alkylphenylamino, lower alkanoylamino, such as acetylamino, or a substituent selected from the group comprising benzoylamino and phenyl-lower alkoxycarbonylamino, wherein the phenyl radical in each case is unsubstituted or especially substituted by nitro or amino, or also by halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl, carbamoyl or aminocarbonylamino.

Halogen is especially fluorine, chlorine, bromine, or iodine, especially fluorine, chlorine, or bromine.

In the preferred embodiment, alkyl has up to a maximum of 12 carbon atoms and is especially lower alkyl, especially methyl, or also ethyl, n-propyl, isopropyl, or tert-butyl.

Substituted alkyl is alkyl as last defined, especially lower alkyl, preferably methyl; where one or more, especially up to three, substituents may be present, primarily from the group selected from halogen, especially fluorine, amino, N-lower alkylamino, N,N-di-lower alkylamino, N-lower alkanoylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, and phenyl-lower alkoxycarbonyl. Trifluoromethyl is especially preferred.

Etherified hydroxy is especially C₈-C₂₀alkyloxy, such as n-decyloxy, lower alkoxy (preferred), such as methoxy, ethoxy, isopropoxy, or n-pentyloxy, phenyl-lower alkoxy, such as benzyloxy, or also phenyloxy, or as an alternative or in addition to the previous group C₈-C₂₀alkyloxy, such as n-decyloxy, halogen-lower alkoxy, such as trifluoromethyloxy or 1,1,2,2-tetrafluoroethoxy.

Esterified hydroxy is especially lower alkanoyloxy, benzoyloxy, lower alkoxycarbonyloxy, such as tert-butoxycarbonyloxy, or phenyl-lower alkoxycarbonyloxy, such as benzyloxycarbonyloxy.

Esterified carboxy is especially lower alkoxycarbonyl, such as tert-butoxycarbonyl, isopropoxycarbonyl, methoxycarbonyl or ethoxycarbonyl, phenyl-lower alkoxycarbonyl, or phenyloxycarbonyl.

Alkanoyl is primarily alkylcarbonyl, especially lower alkanoyl, e.g. acetyl.

N-mono- or N,N-disubstituted carbamoyl is especially substituted by one or two substituents independently selected from lower alkyl, phenyl-lower alkyl, and hydroxy-lower alkyl, at the terminal nitrogen atom.

Alkylphenylthio is especially lower alkylphenylthio.

Alkylphenylsulfonyl is especially lower alkylphenylsulfonyl.

Alkylphenylsulfinyl is especially lower alkylphenylsulfinyl.

Heterocyclyl is especially a five or six-membered heterocyclic system with 1 or 2 heteroatoms selected from the group comprising nitrogen, oxygen, and sulfur, which may be unsaturated or wholly or partly saturated, and is unsubstituted or substituted especially by lower alkyl, such as methyl; a radical selected from 2-methylpyrimidin-4-yl, oxazol-5-yl, 2-methyl-1,3-dioxolan-2-yl, 1H-pyrazol-3-yl, and 1-methyl-pyrazol-3-yl is preferred.

Aryl in the form of phenyl which is substituted by lower alkylene dioxy bound to two adjacent C-atoms, such as methylenedioxy, is preferably 3,4-methylenedioxyphenyl.

Heteroaryl refers to a heterocyclic moiety that is unsaturated in the ring binding the heteroaryl radical to the rest of the molecule in formula I and is preferably mono-, bi- or tricyclic, preferably mono- or bicyclic; where at least in the binding ring, but optionally also in any annealed ring, one or more, preferably 1 to 4, most preferably 3 or 4, carbon atoms are replaced each by a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur; where the binding ring preferably has 5 to 12, more preferably 5 to 7 ring atoms; and may be unsubstituted or substituted by one or more, especially one or two, substituents selected from the group defined above as substituents for aryl, most preferably by lower alkyl, such as methyl; preferably heteroaryl is selected from thienyl, furyl, pyranlyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2H-pyrrolyl, pyrrolyl, lower-alkyl substituted imidazolyl, benzimidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indoliziny, isoindolyl, 3H-indolyl, indolyl, indazolyl, triazolyl, tetrazolyl, purinyl, 4H-quinoliziny, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, cinnoliny, pteridinyl, carbazolyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl and furazanyl; more preferably selected from the group consisting of triazolyl, especially 1,2,4-triazolyl, 1,2,3-triazolyl or 1,3,4-triazolyl, pyridyl, especially 2-, 3- or 4-pyridyl, indolyl, especially 3-indolyl, lower-alkylthiazolyl, especially 2-(4-methylthiazolyl), pyrrolyl, especially 1-pyrrolyl, lower alkylimidazolyl, especially 4-(1-methylimidazolyl), 4-(2-methylimidazolyl) or 4-(5-methylimidazolyl), benzimidazolyl, such as 1-benzimidazolyl, or tetrazolyl, such as 5-(1,2,3,4-tetrazolyl).

A mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms is preferably a heteroaryl group as defined above for heteroaryl, with the proviso that preferably at least one nitrogen is present as ring heteroatom in the binding ring (that is, the ring from which the bond starts that binds the heteroaryl moiety to the rest of the molecule) and with the exception that R₂ cannot represent 2-phthalimidyl, and in case of Y = SO₂ R₂ cannot represent 2,1,3-benzothiadiazol-4-yl. Preferred is imidazolyl, especially imidazol-4-yl, quinolyl, especially 3-, 4-, 5-quinolyl, naphthyridinyl, especially 3-(1,8-naphthyridinyl) or 4-(1,8-naphthyridinyl), or especially a moiety of the formula Ib or Ic