TRIAZOLE COMPOUNDS AND THEIR USE AS DOPAMINE D_3 LIGANDS

The present invention relates to triazole compounds and to the use of such compounds. The compounds mentioned have valuable therapeutic properties and can be used for treating diseases which respond to dopamine D_3 receptor ligands.

Compounds of this type having physiological activity have been disclosed. US-A 4,338,453; 4,408,049 and 4,577,020 describe triazole compounds which have antiallergic or antipsychotic activity. DE-A 44 25 144 and WO 97/25324 describe triazole compounds which respond to dopamine D_3 receptor ligands. Compounds of the same structural type but containing other heterocycles instead of the triazole ring are described in DE-A-44 25 146, DE-A-44 25 143 and DE-A-44 25 145.

Neurons obtain their information by way of G protein-coupled receptors, inter alia. A large number of substances exert their effect by way of these receptors. One of these substances is dopamine.

It is known with certainty that dopamine is present and that it has a physiological function as a neurotransmitter. Cells responding to dopamine are connected with the etiology of schizophrenia and Parkinson's disease. These and other diseases are treated with drugs which interact with the dopamine receptors.

Prior to 1990, two dopamine receptor subtypes were clearly defined pharmacologically, ie. the D1 and D_2 receptors.

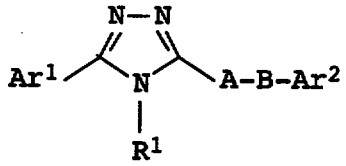
More recently, a third subtype has been found, ie. the D_3 receptor, which appears to mediate some of the effects of the antipsychotic drugs. (J.C. Schwartz et al., The Dopamine D_3 Receptor as a Target for Antipsychotics, in Novel Antipsychotic Drugs, H.Y. Meltzer, Ed. Raven Press, New York 1992, pages 135-144)

D_3 receptors are principally expressed in the limbic system. It is therefore assumed that a selective D_3 antagonist would probably have the antipsychotic properties of the D_2 antagonists but would not have their neurological side effects. (P. Solokoff et al., Localization and Function of the D_3 Dopamine Receptor, Arzneim. Forsch./Drug Res. 42(1), 224 (1992); P. Solokoff et al. Molecular

Cloning and Characterization of a Novel Dopamine Receptor (D_3) as a Target for Neuroleptics, Nature, 347, 146 (1990)).

Surprisingly, it has now been found that certain triazole compounds exhibit a high affinity for the dopamine D_3 receptor and a low affinity for the D_2 receptor. These compounds are therefore selective D_3 ligands.

The present invention relates, therefore, to compounds of the formula I:



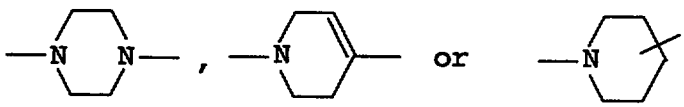
(I)

where

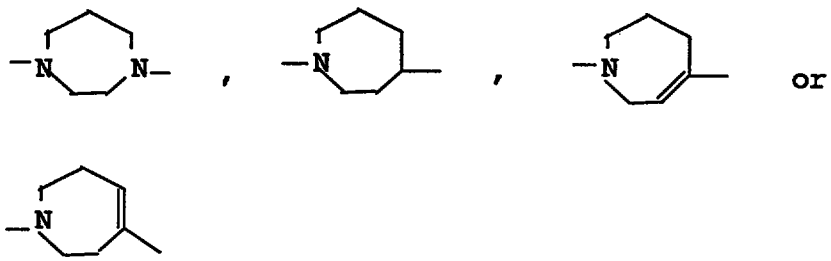
Ar^1 is phenyl, naphthyl or a 5- or 6-membered heterocyclic aromatic ring having 1, 2, 3 or 4 heteroatoms which are selected, independently from one another, from O, S and N, where Ar^1 may have 1, 2, 3 or 4 substituents which are selected, independently of each other, from C_1-C_6-alkyl, which may be substituted by OH, OC_1-C_6-alkyl, halogen or phenyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_6-cycloalkyl, halogen, CN, $COOR^2$, NR^2R^2, NO_2, SO_2R^2, $SO_2NR^2R^2$ or phenyl, which may be substituted by C_1-C_6-alkyl, OC_1-C_6-alkyl, NR^2R^2, CN, CF_3, CHF_2, or halogen, and where the heterocyclic, aromatic ring mentioned may be fused to a phenyl ring;

A is straight-chain or branched C_4-C_{10}-alkylene or straight-chain or branched C_3-C_{10}-alkylene which comprises at least one Z group which is selected from O, S, NR^2, $CONR^2$, COO, CO, or a double or triple bond,

B is a radical of the formula:



or if Ar^1 is the 5- or 6-membered heterocyclic aromatic ring which can be substituted as above, B is also a radical of the formulae



Ar^2 is phenyl, pyridyl, pyrimidinyl or triazinyl, where Ar^2 may have from 1 to 4 substituents which are selected, independently of each other, from OR^2, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-C_1-C_6-alkyl, halogen-C_1-C_6-alkoxy, halogen, CN, NO_2, SO_2R^2, NR^2R^2, $SO_2NR^2R^2$, a 5- or 6-membered carbocyclic, aromatic or non-aromatic ring and a 5- or 6-membered, heterocyclic aromatic or non-aromatic ring having 1 or 2 heteroatoms which are selected from O, S and N, where the carbocyclic or heterocyclic ring may be substituted by C_1-C_6-alkyl, phenyl, phenoxy, halogen, OC_1-C_6-alkyl, OH, NO_2 or CF_3 and/or fused to a phenyl ring and where Ar^2 may be fused to a carbocyclic or heterocyclic ring of the above-defined nature,

R^1 is H, C_3-C_6-cycloalkyl or C_1-C_6-alkyl which may be substituted by OH, OC_1-C_6-alkyl or phenyl;

the radicals R^2, which can be identical or different, are H or C_1-C_6-alkyl, which may be substituted by OH, OC_1-C_6-alkyl or phenyl;

and their salts with physiologically tolerated acids.

The novel compounds are selective dopamine D_3 receptor ligands which act in a regioselective manner in a limbic system and which, due to their low affinity for the D_2 receptor, have fewer side effects than the classic neuroleptics, which are D_2 receptor antagonists. The compounds can therefore be used for treating diseases which respond to dopamine D_3 receptor antagonists or dopamine D_3 receptor agonists, eg. for treating diseases of the central nervous system, in particular schizophrenia, depressions, neuroses, psychoses, Parkinson's disease and anxiety states.

Within the context of the present invention, the following expressions have the meanings given in conjunction with them:

Alkyl (also in radicals such as alkoxy, alkylamino, etc.) is a straight-chain or branched alkyl group having from 1 to 6 carbon atoms and, in particular, from 1 to 4 carbon atoms. The alkyl group can have one or more substituents which are selected, independently of each other, from OH, OC_1-C_6-alkyl, halogen or phenyl.

Examples of an alkyl group are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, etc.

Cycloalkyl is, in particular, C_3-C_6-cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Alkylene radicals are straight-chain or branched. If A does not have any group Z, A then comprises from 4 to 10 carbon atoms, preferably from 4 to 8 carbon atoms. The chain between the triazole nucleus and group B then has at least 4 carbon atoms. If A has at least one of said Z groups, A then comprises from 3 to 10 carbon atoms, preferably from 3 to 8 carbon atoms.

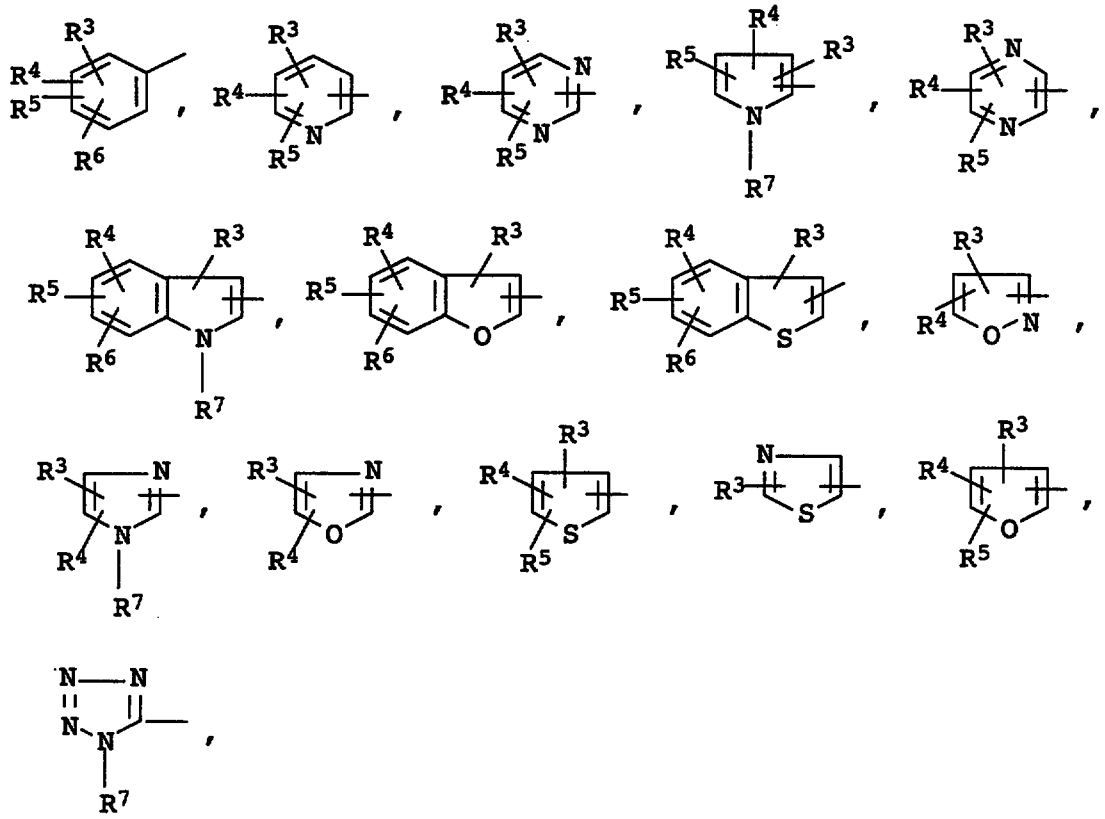
If the alkylene groups comprise at least one of the Z groups, these groups can either be arranged in the alkylene chain at an arbitrary site or in position 1 or 2 of group A (seen from the Ar^1 radical). The radicals $CONR^2$ and COO are preferably arranged in such a way that in each case the carbonyl group faces the triazole ring. Particular preference is given to compounds of the formula I in which A is -Z-C_3-C_6-alkylene, in particular -Z-$CH_2CH_2CH_2$-, -Z-$CH_2CH_2CH_2CH_2$-, -Z-CH_2CH=$CHCH_2$-, -Z-$CH_2C(CH_3)$=$CHCH_2$-, -Z-$CH_2C(=CH_2)CH_2$-, -Z-$CH_2CH(CH_3)CH_2$- or a linear -Z-C_7-C_{10}-alkylene radical, with z being bonded to the triazole ring. Z is preferably CH_2, O and, in particular, S. Furthermore, A is preferably -$(CH_2)_4$-, -$(CH_2)_5$-, -CH_2CH_2CH=$CHCH_2$-, -$CH_2CH_2C(CH_3)$=$CHCH_2$-, -$CH_2C(=CH_2)CH_2$-, or -$CH_2CH_2CH(CH_3)CH_2$-.

Halogen is F, Cl, Br or I.

Haloalkyl can comprise one or more, in particular 1, 2, 3 or 4 , halogen atoms which can be located on one or more C atoms, preferably in the α- or ω-position. CF_3, CHF_2, CF_2Cl or CH_2F are particularly preferred.

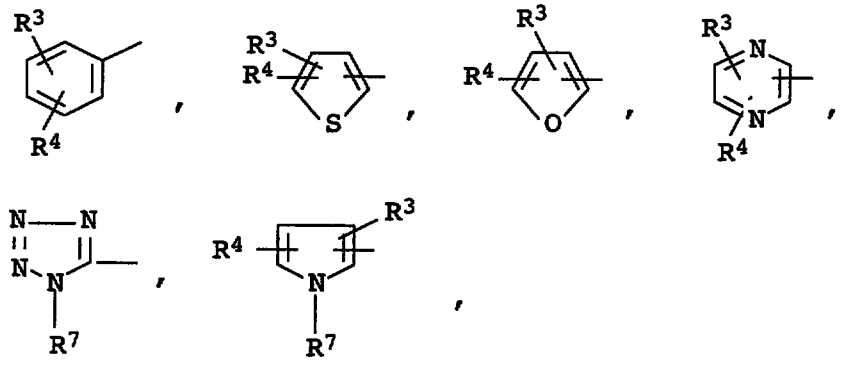
Acyl is preferably HCO or C_1-C_6-alkyl-CO, in particular acetyl. When Ar^1 is substituted, the substituent can also be located on the nitrogen heteroatom.

Preferably, Ar^1 is



where
R^3 to R^6 are H or the abovementioned substituents of the radical Ar^1,
R^7 is H, C_1-C_6-alkyl or phenyl, and
X is N or CH. If the phenyl radical is substituted, the substituents are preferably in the m position or the p position.

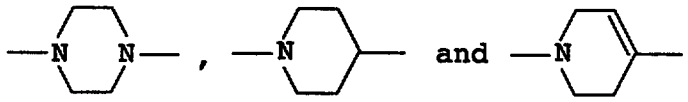
Particularly preferably, Ar^1 is



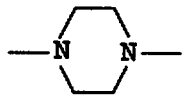
where R^3, R^4 and R^7 have the abovementioned meanings. The phenyl, pyrazinyl and pyrrole radicals which are indicated are particularly preferred.

The radicals R^3 to R^6 are preferably H, C_1-C_6-alkyl, OR^2, CN, phenyl which may be substituted by C_1-C_6-alkyl, C_1-C_6-alkoxy or halogen, CF_3 and halogen and, in particular, H, C_1-C_6-alkyl, OR^2 and halogen. In this context, R^2 has the abovementioned meanings.

The radical B is preferably



and, in particular,



The radical Ar^2 may have one, two, three or four substituents, preferably one or two substituents, which are located, in particular, in the m position and/or the p position. They are preferably selected, independently of each other, from C_1-C_6-alkyl, haloalkyl, NO_2, halogen, in particular chlorine, phenyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, cyclopentyl and cyclohexyl. When one of the substituents is C_1-C_6-alkyl, a branched group and, in particular, isopropyl or t-butyl is preferred.

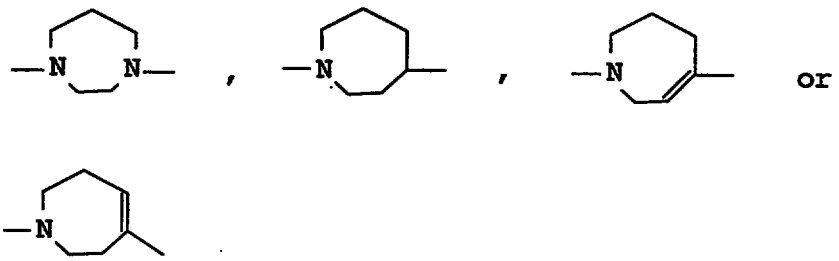
Ar^2 is preferably unsubstituted or substituted phenyl, 2-, 3- or 4-pyridinyl or 2-, 4(6)- or 5-pyrimidinyl.

When one of the substituents of the radical Ar^2 is a 5- or 6-membered heterocyclic ring, the ring is then, for example, a pyrrolidine, piperidine, morpholine, pyridine, pyrimidine, triazine, pyrrole, thiophene or pyrazole radical, with a pyrrole, pyrrolidine, pyrazole or thienyl radical being preferred.

When one of the substituents of the Ar^2 radical is a carbocyclic radical, this latter radical is then, in particular, a phenyl, cyclopentyl or cyclohexyl radical.

When Ar^2 is fused to a carbocyclic radical, this latter radical is, in particular, a naphthalene or dihydro- or tetrahydro-naphthalene radical.

According to one embodiment, the invention relates to compounds of the formula I, in which Ar^1 is a heterocyclic aromatic ring as defined above, B is



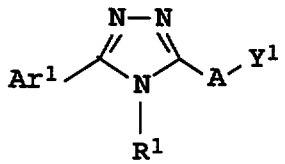
and A and Ar^2 are as defined above.

The invention also encompasses the acid addition salts of the compounds of the formula I with physiologically tolerated acids. Examples of suitable physiologically tolerated organic and inorganic acids are hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, oxalic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, adipic acid or benzoic acid. Other useful acids are described in Fortschritte der Arzneimittelforschung [Advances in drug research], Volume 10, pages 224 ff., Birkhäuser Verlag, Basle and Stuttgart, 1966.

The compounds of formula I can have one or more centers of asymmetry. The invention therefore also includes the relevant enantiomers and diastereomers in addition to the racemates. The respective tautomeric forms are also included in the invention.

The process for preparing the compound (I) consists in

a) reacting a compound of the formula (II)



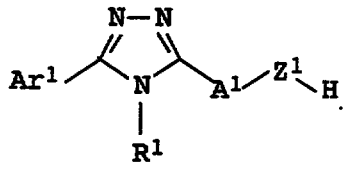
(II)

where Y^1 is a customary leaving group such as Hal, alkanesulfonyloxy, arylsulfonyloxy, etc., with a compound of the formula (III)

$$HB\text{-}Ar^2 \qquad \text{(III)};$$

or

b) reacting a compound of the formula (IV)



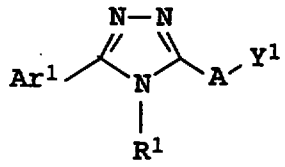
(IV)

where Z^1 is O, NR^2, or S and A^1 is C_1-C_{10}-alkylene or a bond, with a compound of the formula (V)

$$Y^1 - A^2 - B - Ar^2 \qquad (V)$$

where Y^1 has the abovementioned meaning and A^2 is C_2-C_{10}-alkylene, where A^1 and A^2 together have from 3 to 10 C atoms and A^1 and/or A^2 may or may not comprise at least one Z group; or

c) reacting a compound of the formula (VI)



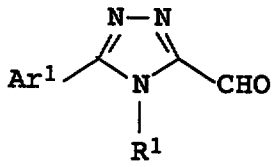
(VI)

where Y^1 and A^1 have the abovementioned meanings, with a compound of the formula (VII)

$$H - Z^1 - A - B - Ar^2 \qquad (VII)$$

where Z^1 has the abovementioned meanings;
or

d) reversing the polarity of a compound of the formula (VIII)



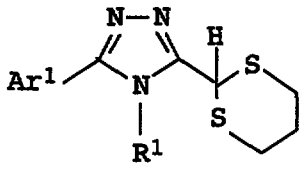
(VIII)

using reagents which are known from the literature, such as 1,3-propanedithiol, KCN/water, TMSCN or KCN/morpholine, as described, for example, in

Albright *Tetrahedron*, **1983**, 39, 3207 or
D. Seebach *Synthesis* **1969**, 17 and **1979**, 19 or
H. Stetter *Angew. Chem. Int. Ed.* **1976**, 15, 639 or
van Niel et al. *Tetrahedron* **1989**, 45, 7643

Martin et al. *Synthesis* **1979**, 633,

to give the products (VIIIa) (using 1,3-propanedithiol by way of example)



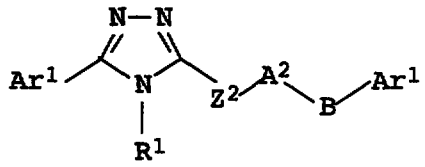
(VIIIa)

and then chain-elongating with compounds of the formula (IX)

$$Y^1 - A^3 - B - Ar^2 \qquad (IX)$$

where Y^1 has the abovementioned meanings and A^3 is C_3-C_9-alkylene, which may comprise a Z group

to give, after deprotecting and reducing, compounds of the formula (Ia)



(Ia)

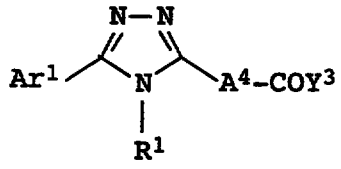
where Z^2 is CO, or a methylene group, and Z^2 and A^2 together have from 4 to 10 C atoms;
or

e) reacting a compound of the formula (VIII) with a compound of the formula X

$$Y^2 - A - B - Ar^2 \qquad (X)$$

where Y^2 is a phosphorane or a phosphonic acid ester, by a method similar to customary methods, as described, for example, in Houben Weyl "Handbuch der Organischen Chemie" [Handbook of organic chemistry], 4th edition, Thieme Verlag Stuttgart, Volume 5/1b p. 383 ff. or Volume 5/1c p. 575 ff.

The process for preparing a compound of the formula I where A comprises the group COO or $CONR^2$ consists in reacting a compound of the formula (XI)



(XI)

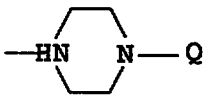
where Y^3 is OH, OC_1-C_4, Cl or, together with CO, is an activated carboxyl group, and A^4 is C_0-C_9-alkylene, with a compound of the formula (XII)

$$Z^3 - A - B - Ar^2 \qquad (XII)$$

where Z^3 is OH and NHR^2.

The compounds of the formula (III) are starting compounds for preparing compounds of the formulae (V), (VII) and (XII), and are prepared by standard methods as described, for example, in J.A. Kiristy et al., *J. Med. Chem.* **1978**, *21*, 1303 or C.B. Pollard, *J. Am. Chem. Soc.* **1934**, *56*, 2199, or by

a) reacting, in a known manner, a compound of the formula (XIII)



(XIII)

where Q is H or a customary amino protecting group, with a compound of the formula (XIV)

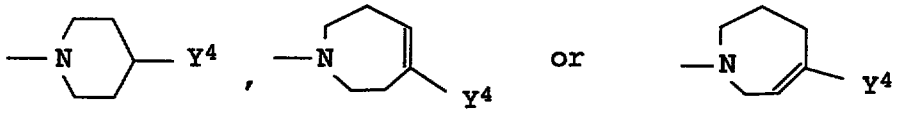
$$Y^4 - Ar^2 \qquad (XIV)$$

where Y^4 is $B(OH)_2$, $-SnR_3$ (R^3 = butyl or phenyl) trifluoromethanesulfonyloxy, or has the meanings given for Y^1, and R is C_1-C_4-alkyl;
or

b) reacting a compound of the formula (XV)

$$Q - B^1 \qquad (XV)$$

where B^1 is



Q is H or a customary amino protecting group, eg. butyloxycarbonyl, benzyl or methyl, and Y^4 is a leaving group, eg. OTf, $SnBu_3$, $B(OH)_2$ or halogen, with a compound of the formula (XIVa)

$$Y^5 - Ar^2 \qquad \text{(XIVa)}$$

where Y^5 is boron derivatives, such as $B(OH)_2$, or a metal-containing leaving group, for example SnR_3 (R_3 = butyl or phenyl) or zinc halide, if Y^4 is halogen or trifluoromethylsulfonyloxy, or Y^5 is halogen or trifluoromethylsulfonyloxy if Y^4 is boron derivatives, such as $B(OH)_2$, or a metal-containing leaving group, for example SnR_3 or zinc halide, using known methods, as described in

S. Buchwald et al. *Angew. Chem.* **1995**, *107*, 1456 or J.F. Hartwig et al. *J.Am. Chem. Soc* **1996**, *118*, 7217 or S. Buchwald *J.Org. Chem.* **1997**, *62*, 1264 or F. Kerrigan et al., *Tetrah. Lett.* **1998**, *39*, 2219 and the literature cited in that document, or
J.K. Stille, *Angew. Chem.* **1986**, *98*, 504 or
J.K.Stille et al. *J.Org.Chem.***1990**, *55*, 3014 or
M. Pereyre et al. "Tin in Organic Synthesis", Butterworth 1987; or

c) reacting a compound of the formula (XVI)



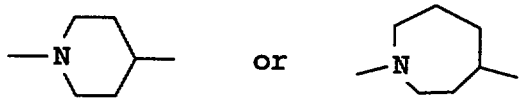
(XVI)

where Q has the abovementioned meanings, with a compound $M-Ar^2$, where M is a metal such as Li, or MgY^6 , and Y^6 is Br, Cl or I. $M-Ar^2$ can be obtained from compounds of the formula (XIV) using methods which are known from the literature, or

d) a compound of the formula (XVII)

$$Q\text{-}B^2\text{-}Ar^2 \qquad \text{(XVII)}$$

where B^2 is



and Q has the abovementioned meaning, by reducing, for example hydrogenating, compounds of the formula $Q-B^3-Ar^2$ (IIIa), where B^3 is one of the abovementioned unsaturated radicals, using methods which are known from the literature.

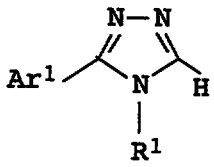
Compounds of Type B are either known or can be prepared by a method similar to known methods, such as, for example, 1,4-diazacycloalkanes: L. Borjeson et al., Acta Chem. Scand. 1991, 45, 621; Majahrzahl et al Acta Pol. Pharm., 1975, 32, 145, 1-azacycloheptanones: A. Yokoo et al., Bull Chem. Soc. Jpn. 1956, 29, 631 and WO 97/25324.

In the above formulae, Ar^1, R^1, A, B, Z and Ar^2 have the abovementioned meanings.

Compounds of the Ar^1-triazole, Ar^2, Ar^1 type are either known or can be prepared using known methods, as described, for example, in S. Kubota et al. *Chem. Pharm. Bull* 1975, *23*, 955 or A.R. Katritzky, C.W. Rees(ed.) "Comprehensive Heterocyclic Chemistry", Pergamon Press, or "The Chemistry of Heterocyclic Compounds"' J. Wiley&Sons Inc. NY and the literature cited in that document.

The compounds of the formula VIII are novel and are likewise part of the subject-matter of the present invention.

Compounds of the (VIII) and (XI) type, where A is C_0-alkylene, can be prepared by metallating the 3-aryl-5-H-1,2,4(4H)-triazoles



and by a method similar to methods described in T. Kauffman et al. Angew. Chem. Int. Ed. Engl. **1972**, *11*, 846 or by A.R. Katritzky, C.W. Rees(ed.) "Comprehensive Heterocyclic Chemistry", Pergamon Press Vol. 5, p 753.

The novel compounds and the starting materials and intermediates can also be prepared by a method similar to the methods described in the patent publications which were cited initially.

The above-described reactions generally take place in a solvent at between room temperature and the boiling temperature of the solvent employed. Examples of solvents which can be used are esters, such as ethyl acetate, ethers, such as diethyl ether or tetrahydrofuran, dimethylformamide, dimethyl sulfoxide,

dimethoxyethane, toluene, xylene, ketones, such as acetone or methyl ethyl ketone, or alcohols, such as ethanol or butanol.

If desired, the reaction can be carried out in the presence of an acid binder. Suitable acid binders are inorganic bases, such as sodium or potassium carbonate, sodium or potassium hydrogen carbonate, sodium methoxide or sodium hydride, or organometallic compounds, such butyllithium, or alkylmagnesium compounds, or organic bases, such as triethylamine or pyridine. The latter can simultaneously serve as solvents.

The reactions may be carried out using a catalyst, such as transition metals and their complexes, eg. $Pd(PPh_3)_4$, $Pd(OAc)_2$ or $Pd(P(oTol)_3)_4$, or using a phase transfer catalyst, eg. tetrabutylammonium chloride or tetrapropylammonium bromide.

The crude product is isolated in a customary manner, for example by filtering, by distilling off the solvent or by extracting from the reaction mixture, etc. The resulting compounds can be purified in a customary manner, for example by recrystallization from a solvent, by chromatography or by conversion into an acid addition compound.

The acid addition salts are prepared, in a customary manner, by mixing the free base with the appropriate acid, where appropriate in solution in an organic solvent, for example a lower alcohol, such as methanol, ethanol or propanol, an ether, such as methyl t-butyl ether, a ketone, such as acetone or methyl ethyl ketone, or an ester, such as ethyl acetate.

When used for treating the abovementioned diseases, the novel compounds are administered orally or parenterally (subcutaneously, intravenously, intramuscularly, or intraperitoneally) in a customary manner. They can also be administered through the nose/throat region using vapors or sprays.

The dose depends on the age, condition and weight of the patient and on the mode of administration. As a rule, the daily dose of active compound is from about 10 to 1000 mg per patient and day in the case of oral administration and from about 1 to 500 mg per patient and day in the case of parenteral administration.

The invention also relates to pharmaceuticals which comprise the novel compounds. These pharmaceuticals are present, in the customary pharmacological administration forms, in solid or liquid form, for example as tablets, film tablets, capsules,

powders, granules, coated tablets, suppositories, solutions or sprays. In this context, the active compounds can be worked up together with the customary pharmacological auxiliary substances, such as tablet binders, fillers, preservatives, tablet disintegrants, flowance agents, emollients, wetting agents, dispersants, emulsifiers, solubilizers, retarding agents, antioxidants and/or propellant gases (cf. H. Sucker et al., Pharmazeutische Technologie [Pharmaceutical Technology], Thieme-Verlag, Stuttgart, 1978). The resulting administration forms normally comprise the active compound in a quantity of from 1 to 99 % by weight.

The following examples serve to explain the invention without limiting it.

EXAMPLE 1

3-{3-[4-(2-t-Butyl-6-trifluoromethylpyrimidin-4-yl-)piperazin-1-yl]propylmercapto}-4-methyl-5-phenyl-1,2,4-(4H)-triazole

A. Preparation of the starting compounds:

A.1 2-t-Butyl-4-[4-(3-chloropropyl)piperazin-1-yl)-6-trifluoromethylpyrimidine and 2,2-dimethylpropanimidamide were reacted, in a known manner, with ethyl trifluoroacetate to give 2-(2,2-dimethylethyl)-4-hydroxy-6-trifluoromethylpyrimidine. Heterocyclic Compounds (John Wiley & Sons, 1994, Vol. 52, D.J. Brown (Ed.)).

$C_9H_{11}F_3N_2O$ m.p. 187-188° C.

A.2 After chlorinating with thionyl chloride, the crude product was treated with an excess of anhydrous piperazine, with 2-t-butyl-4-piperazin-1-yl-6-trifluoromethylpyrimidine being obtained.

$C_{13}H_{19}F_3N_4$ m.p. 78-80° C.

A.3 Alkylating the resulting compound with 1-bromo-3-chloropropane in tetrahydrofuran resulted in 2-t-butyl-4-[4-(2-chloropropyl)piperazin-1-yl]-6-trifluoromethylpyrimidine.

$C_{16}H_{24}ClF_3N_4$ m p. 83-84° C.

The triazoles employed were prepared, unless otherwise indicated, in accordance with the method of S. Kubota et al., Chem. Pharm. Bull. **1975**, *23*, 955, by reacting the corresponding carbonyl chlorides with alkylthiosemicarbazides in pyridine and then cyclizing in an aqueous solution of sodium hydrogen carbonate, or by the addition of the corresponding carbonyl hydrazides with alkyl isothiocyanates in a suitable solvent.

A.4 4-Methyl-3-mercapto-5-(thiophen-3-yl)1,2,4-(4H)-triazole
The sodium salt was isolated.
1H-NMR (DMSO-d_6): 3.7 (3H); 7.5 (m, 2H); 7.8 (m,1H).
m.p.: 146°C
$C_7H_6N_3S_2Na$ (219)

A.5 4-Methyl-3-mercapto-5-(2,5-dimethylfuran-3-yl)-1,2,4-(4H)-triazole
1H-NMR (DMSO-d_6): δ = 2.3 (s, 3H); 2.5 (s,3H); 3.7 (s, 3H); 6.1 (s, 1H).
28710/30

A.6 4-Methyl-3-mercapto-5-(2,6-dichlorophenyl)-1,2,4-(4H)-triazole
The sodium salt was isolated.
1H-NMR (DMSO-d_6): δ = 3.7 (s, 3H); 7.4 (dd,1H); 7.6 (d, 1H); 8.2 (d, 1H).
m.p.: 220-225°C

A.7 4-Methyl-3-mercapto-5-(4-methylsulfonylphenyl)-1,2,4-(4H)-triazole
1H-NMR (DMSO-d_6): δ = 3.7 (s, 3H); 7.4 (dd,1H); 7.6 (d, 1H); 8.2 (d, 1H).
m.p.: 238-239°C

A.8 4-Methyl-3-mercapto-5-(3-bromopyridyl-5)-1,2,4-(4H)-triazole
The sodium salt was isolated.
1H-NMR (DMSO-d_6): δ = 3.7 (s, 3H); 8.2(m,1H); 8.9 (m,2H).

A.9 4-Methyl-3-mercapto-5-(pyrrol-2-yl)-1,2,4-(4H)-triazole
1H-NMR (DMSO-d_6): δ = 3.7 (s, 3H); 6.2(m,1H); 6.8 (1,2H); 7.0 (m,1H); 11.8 (s,1H); 14.0 (s,1H).
m.p.: 200-201°C

A.10 4-Methyl-3-mercapto-5-(3-benzthienyl)-1,2,4-(4H)-triazole

The sodium salt was isolated.
1H-NMR (DMSO-d_6): 3.8 (s, 3H); 7.5(m,2H); 8.0 (m,3H).

A.11 4-Methyl-3-mercapto-5-(4-methylthiazol-5-yl)-1,2,4-(4H)-triazole
1H-NMR (DMSO-d_6): 2.4 (s,3H); 3.4 (s, 3H),9.2 (s,1H); 14.1 (s, 1H).

A.12 4-Methyl-3-mercapto-5-(6-chlorobiphenyl-2)-1,2,4-(4H)-triazole
1H-NMR (DMSO-d_6): 3.8 (s, 3H), 7.6 (m,1H), 7.9 (m,1H);8.1 (m,3H); 8.4 (s,1H).

A.13 4-Methyl-3-mercapto-5-(2,4-dinitrophenyl-)-1,2,4-(4H)-triazole
m.p.: 250-251°C
MS: m/z= 281[M^+]

A.14 4-Methyl-3-mercapto-5-(4-CF_3-phenyl)-1,2,4-(4H)-triazole
MS: m/z= 259[M^+]

A.15 4-Propyl-3-mercapto-5-(2-methyloxazol-4-yl)-1,2,4-(4H)-triazole
The potassium salt was isolated.

6.22 g (95 mmol) of potassium carbonate and 2.4 ml (23 mmol) of propyl isothiocyanate were added, one after the other, to a solution of 4.9 g (22.5 mmol) of 2-methyloxazole-4-carbonyl hydrazide bishydrochloride (prepared by hydrazinolysing the corresponding methyl ester in methanolic solution) in 60 ml of ethanol and the mixture was heated to boiling for 4 h.

The resulting suspension was filtered and concentrated and the residue (6.5 g) was purified by column chromatography. (Silica gel, methylene chloride/methanol 96:4).
Yield: 2.3 g (39% of theory)

1H-NMR ($CDCl_3$): δ= 1.0 (t, 3H): 1.7 (m,2H); 2.6 (s,3H); 4.2 (sm,2H); 8.1 (s,1H); 12.6 (s,1H).

A.16 4-Propyl-3-mercapto-5-(2-aminothiazol-4-yl) 1,2,4-(4H)-triazole
The potassium salt was isolated.
1H-NMR (DMSO-d_6): 0.8 (t,3H); 1.6 (m,2H); 3.4 (s, 2H); 4.3 (m,2H); 7.4 (s,1H); 13.8.

A.17 4-Methyl-3-mercapto-5-(5-methylimidazol-4-yl) 1,2,4-(4H)-triazole
The potassium salt was isolated.
1H-NMR (DMSO-d_6): 2.3 (s,3H); 3.4 (s,3H); 7.5 (s,1H).

A.18 4-Methyl-3-mercapto-5-(carboxamido)-1,2,4-(4H)-triazole
1H-NMR (DMSO-d_6): 3.7 (s,3H); 7.95 (s,1H); 8.25 (s,1H); 14.2 (s,1H).
MS: m/z= 158[M^+]

A.19 4-Methyl-3-mercapto-5-(N-methylpyrrol-2-yl)-1,2,4-(4H)-triazole

10.6 g (101.1 mmol) of 4-methyl-3-thiosemicarbazide and catalytic quantities of dimethylaminopyridine were added to 10.2 g (45.1 mmol) 2-trichloroacetoxy-N-methylpyrrole (prepared in accordance with Rappoport et al., J. Org. Chem. **1972**, *37*, 3618) in DMF and the mixture was heated at 90°C for 18 h. 77 ml of water were added at room temperature, after which the mixture was acidified with 10% HCl and stirred for 1 h at 0 °C; the undissolved material was filtered off and the original solution was extracted with ethyl acetate. The organic phases were dried and evaporated and the resulting crude product was heated to boiling together with 427 ml of a 1M solution of sodium hydrogen carbonate. After the reaction had come to an end, the undissolved material was filtered off and the original solution was acidified with conc. HCl, while cooling, and the precipitated solid was isolated.
Yield: 2.3 g (27% of theory)
MS: m/z= 194 [M+]
1H-NMR (DMSO-d_6): δ = 3.6 (s,3H); 3.9 (s,3H); 6.2 (m,1H); 6.6 (m,1H); 7.1 (m,1H); 14.0 (1H).

B: Preparation of the end product:

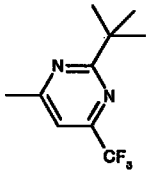
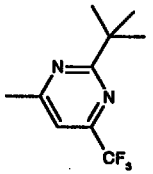
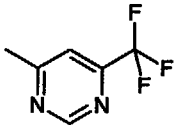
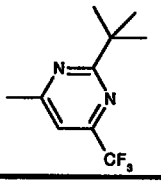
576 mg (3 mmol) of 4-mercapto-3-methyl-5-phenyl-1,2,4-(4H)-triazole (prepared in accordance with the method of S. Kubota and M. Uda, Chem. Pharm. Bull. (1975), 23, 955-966 by reacting benzoyl chloride with N-methylthiosemicarbazide and subsequently cyclizing) and 1.1 g (3 mmol) of the chloropropyl compound described above under A.3 were heated, at 100°C for 6 h, together with 7.2 mg (3 mmol) of lithium hydroxide in 10 ml of dry DMF while stirring. After the mixture had cooled down, 50 ml of water were added and the whole was extracted 3 times with t-butyl methyl ether. The organic phase was dried with sodium sulfate and concentrated

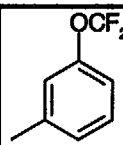
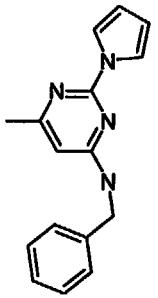
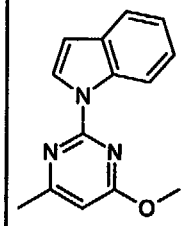
by evaporation; the residue was purified by column chromatography (silica gel). The resulting pure substance (920 mg = 59 %) was subsequently converted into its hydrochloride using ethereal hydrochloric acid.

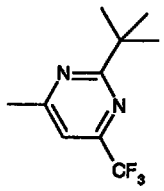
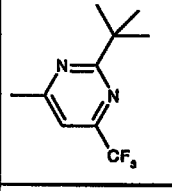
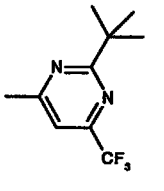
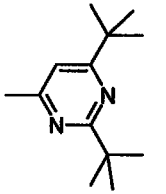
$C_{25}H_{33}ClF_3N_7S$ (556) m.p. 191-193°C.

The substances of the formula (I) which are listed in the following table were obtained in analogous manner.

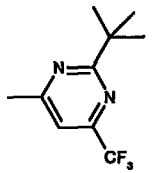
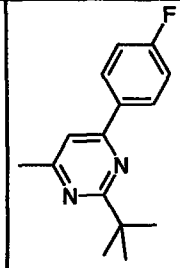
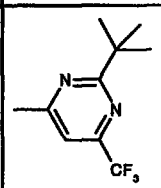
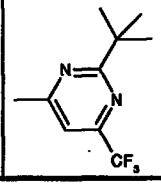
Table 1

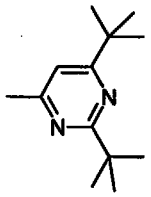
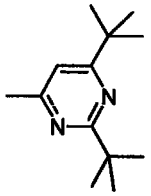
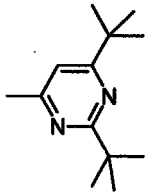
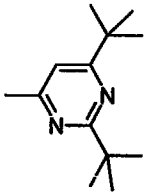
Ex.	Ar^1	R1	A	B	Ar^2	Analysis
1	Phenyl	Me	$-S(CH_2)_3-$	Piperazinyl		Hydrochloride Fp:191-193°C
2	2,4-Dime-thoxy-phenyl-	Me	$-S(CH_2)_3-$	Piperazinyl		Hydrochloride m.p.: 154-157°C
3	Phenyl	Me	$-S(CH_2)_3-$	Piperazinyl		m.p.: 91-93°C; 1H NMR (DMSO-d_6; ppm) 1.9 (q, 2H); 2.45 (m, 6H); 3.25 (t,2H); 3.6 (s,3H); 3.75 (m,4H); 7.25 (s, 1H); 7.5 (m, 3H); 7.8 (m, 2H); 8.6 (s, 1H).
4	4-CN-Phenyl	Me	$-S(CH_2)_3-$	Piperazinyl		Hydrochloride m.p.:82°C

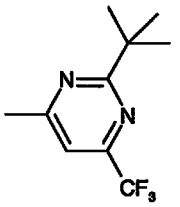
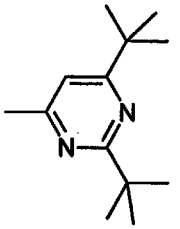
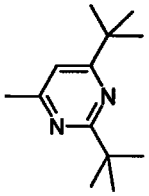
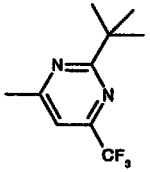
5	Phenyl	Me	-S-CH_2-C(=CH_2)-CH_2-	Piperazinyl		1H NMR ($CDCl_3$; ppm) 2.55 (t, 4H); 3.18 (s, 2H); 3.2 (t, 4H); 4.0 (s, 2H); 5.1 (s, 1H); 5.2 (s, 1H); 5.85 (t, 1H); 6.7 (m, 2H); 6.8 (d, 1H); 7.2 (d, 1H); 7.5 (m, 3H); 7.7 (m, 2H);
6	Phenyl	Me	-S(CH_2)$_3$-	Piperazinyl		1H NMR ($CDCl_3$; ppm) 2.1 (m, 2H); 2.5 (m, 6H); 3.3 (t, 2H); 3.8 (m, 7H); 4.5 (d, 2H); 5.0 (t, 1H); 5.2 (s, 1H);6.2 (m,2H); 7.3-7.4 (m, 5H); 7.5 (m, 3H); 7.6-7.7 (m, 4H).
7	Phenyl	Me	-S(CH_2)$_3$-	Piperazinyl		1H NMR ($CDCl_3$; ppm) 2.1 (m, 2H); 2.5 (m, 6H); 3.4 (t, 2H); 3.6 (s,3H); 3.7 (m, 4H); 4.1 (s, 3H); 5.7 (s,1H); 6.6 (d, 1H); 7.3 (m, 2H); 7.5 (m, 3H); 7.7 (m, 3H); 8.2 (d, 1H); 8.7 (d, 1H).

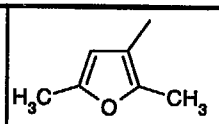
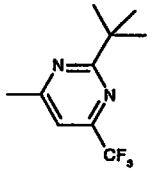
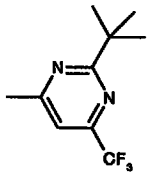
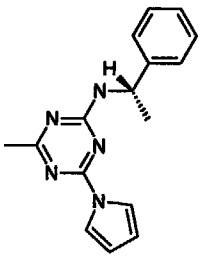
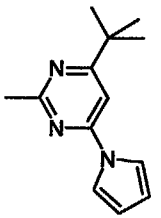
8	2-iodophenyl	Me	-S-CH_2-C(=CH_2)-CH_2-	Piperazinyl		1H NMR ($CDCl_3$; ppm) 1.3 (s, 9H); 2.6 (m, 4H); 3.1 (s, 2H); 3.3 (s, 3H); 3.7 (m, 6H); 4.9 (s, 1H); 5.1 (s, 1H); 6.6 (s, 1H); 7.2 (t, 1H); 7.4 (m, 1H); 7.6 (t, 1H); 8.0 (d, 1H).
9	4-Me-Phenyl	Me	-S$(CH_2)_3$-	Piperazinyl		1H NMR ($CDCl_3$; ppm) 1.3 (s, 9H); 2.0 (q, 2H); 2.5 (m, 6H); 3.3 (t, 2H); 3.6 (s, 3H); 3.7 (m, 4H); 6.6 (s,1H); 7.3 (d, 2H); 7.6 (d, 2H);
10	3-I-Phenyl	Me	-S$(CH_2)_3$-	Piperazinyl		1H NMR ($CDCl_3$; ppm) 1.3 (s, 9H); 2.0 (q, 2H); 2.4 (s, 3H); 2.6 (m, 6H); 3.4 (t, 2H); 3.6 (s, 3H); 3.8 (m, 4H); 6.6 (s, 1H); 7.2 (t, 1H); 7.6 (d, 1H); 7.85 (d, 1H); 8.0ss, 1H);.
11	2-Methoxy-phenyl	Me	-S$(CH_2)_3$-	Piperazinyl		Fumarate m.p.: 77-80°C

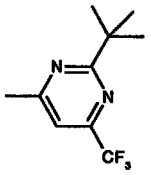
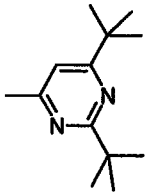
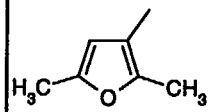
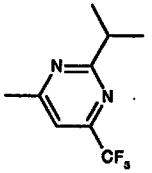
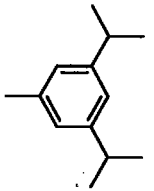
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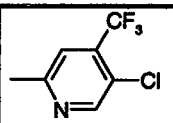
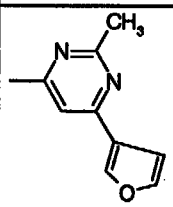
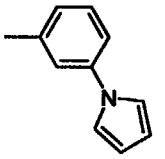
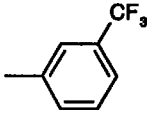
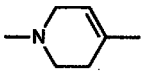
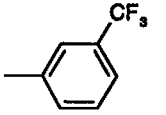
12	2-Methoxy-phenyl	Me	$-S(CH_2)_3-$	Piperazinyl		Fumarate m.p.: 87-90°C
13	Phenyl	Me	$-S(CH_2)_3-$	Piperazinyl		1H NMR ($CDCl_3$; ppm) 1.4 (s, 9H); 2.1 (m, 2H); 2.6 (mbr, 6H); 3.4 (t, 2H); 3.6 (s, 3H); 3.7 (mbr, 4H); 6.7 (s, 1H); 7.1 (d, 2H); 7.5 (m, 3H); 7.6 (m,2H); 8.0 (m, 2H);
14	4-tert.Butyl-phenyl	3-Me-thoxy-prop-1-yl	$-S(CH_2)_3-$	Piperazinyl		Hydrochloride m.p.:102°C
15	4-tert.Butyl-phenyl	Me	$-S(CH_2)_3-$	Piperazinyl		Hydrochloride m.p.: 155°C

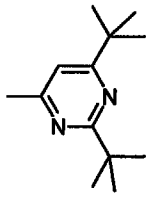
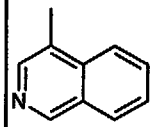
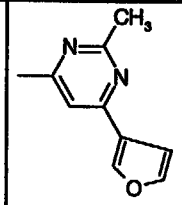
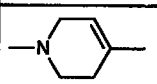
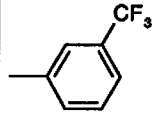
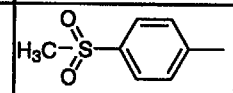
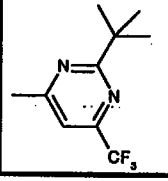
16	2-I-Phenyl	Me	$-S(CH_2)_3-$	Piperazinyl		1H NMR ($CDCl_3$; ppm) 1,3 (s,9H); 1.4 (s,9H); 2.1 (q, 2H); 2.6 (m, 6H); 3.4 (m, 5H); 3.7 (m, 4H); 6.3 (s, 1H); 7.2 (t, 1H); 7.4 (d, 1H); 7.5 (t, 1H); 7.9 (d, 1H).
17	4-Methyl-phenyl	Me	$-S(CH_2)_3-$	Piperazinyl		Hydrochloride m.p.: 156-160°C
18	4-Biphenyl	Me	$-S(CH_2)_3-$	Piperazinyl		m.p.:164-165°C
19	3-I-Phenyl	Me	$-S(CH_2)_3-$	Piperazinyl		Hydrochloride m.p.:164-167°C

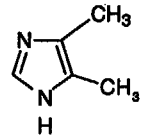
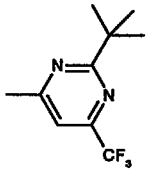
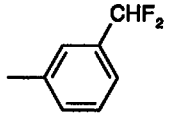
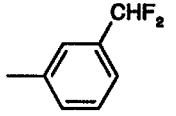
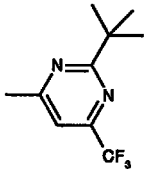
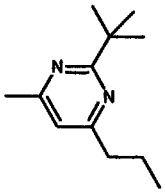
20	Phenyl	Me	-O-$(CH_2)_3$-	Piperazinyl		1H NMR ($CDCl_3$; ppm) 1.3 (s, 9H); 2.1 (m, 2H); 2.6-2.8 (m, 6H); 3.5 (s, 3H); 3.8 (mbr, 4H); 4.6 (t, 2H); 6.5 (s, 1H); 7.6 (m, 3H); 7.8 (m, 2H);
21	Phenyl	Me	-CH=CH-CH_2-CH_2-	Piperazinyl		m.p. 156-161°C 1H-NMR ($CDCl_3$; ppm) 1.3 (s, 9H); 1.4 (s, 9H); 2.6 (m, 8H); 3.7 (m, 7H); 6.2 (s, 1H); 6.4 (d, 1H); 7.0 (td, 1H); 7.5 (m,3H); 7.7 (m, 2H).
22	Phenyl	Me	- $(CH_2)_4$-	Piperazinyl		m.p.:144-145°C
23	Phenyl	Me	-$(CH_2)_4$-	Piperazinyl		1H NMR ($CDCl_3$; ppm) 1.3 (s, 9H); 1.7 (m, 2H); 1.9 (q, 2H); 2.4 (t, 2H); 2.5 (t, 4H); 2.8 (t, 2H); 3.6 (s, 3H); 3.75 (m, 4H); 6.6 (s, 1H); 7.4 (m, 3H); 7.6 (m, 2H);.

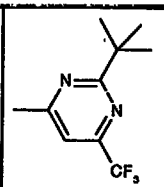
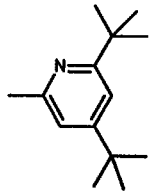
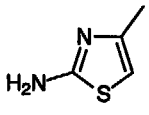
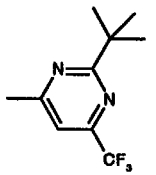
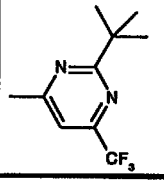
24		Me	-S(CH$_2$)$_3$-	Piperazinyl		m.p.:190-192°C
25	Pyrazinyl-phenyl	Me	-S(CH$_2$)$_3$-	Piperazinyl		Hydrochloride m.p.: 164°C
26	Phenyl	Me	-S(CH$_2$)$_3$-	Piperazinyl		1H NMR ($CDCl_3$; ppm) 1.5 (d, 3H); 2.0(m, 2H); 2.4-2.6 (m, 6H); 3.3 (t, 2H); 3.6 (m, 7H); 5.0-5.2 (m, 2H); 5.8 (s,1H); 6.3 (m, 2H); 7.2-7.4 (m, 8H); 7.5 (m, 3H); 7.6 (m, 2H);
27	Phenyl	Me	-S(CH$_2$)$_3$-	Piperazinyl		1H NMR ($CDCl_3$) 1.3 (s, 9H); 2.1 (m, 2H); 2.5 (m,6H); 3.4 (t,2H); 3.6 (s,3H). 3.9 (t,4H); 6.3 (m,2H); 6.5 (s,1H); 7.5(m,5H); 7.6(m,2H).

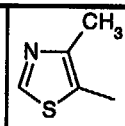
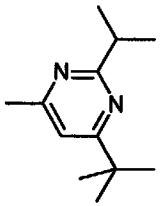
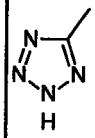
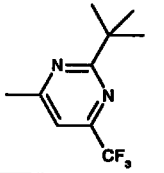
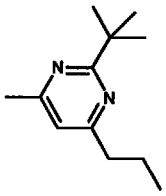
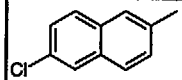
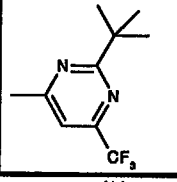
28	3-Thienyl-	Me	-S(CH_2)$_3$-	Piperazinyl		1H NMR ($CDCl_3$; ppm) 1.3 (s, 9H); 2.0(q, 2H); 2.5 (m,6H); 3.3 (t, 2H); 3.7 (s, 3H); 3.75 (m, 4H); 6.5 (s, 1H); 7.5 (m, 2H); 7.8 (m, 1H);.
29	3-Thienyl-	Me	-S-CH_2-C(=CH_2)-CH_2-	Piperazinyl		1H NMR ($CDCl_3$; ppm) 1.3 (s, 9H);1.4 (s, 9H); 2.6 (m, 4H); 3.1 (s, 2H); 3.3 (s, 3H); 3.7 (m, 6H); 4.9 (s, 1H); 5.1 (s, 1H); 6.3 (s, 1H); 7.5 (m, 2H); 7.75 (m, 1H);
30		Me	-S-CH_2-C(=CH_2)-CH_2-	Piperazinyl		1H NMR ($CDCl_3$) 1.2 (s, 6H);2.2 (s, 3H); 2.4 (s, 3H); 2.6 (m,4H);2.9 (m, 1H); 3.2 (m, 2H); 3.5 (br, 5H); 3.7 (m, 4H); 3.9 (s, 3H); 5.0 (s,1H); 5.15 (s, 1H); 6.0 (s,1H); 6.5(s,1H).
31	Phenyl	Me	-S(CH_2)$_3$-	Piperazinyl		Fumarate m.p.: 146°C

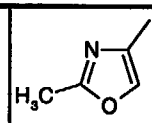
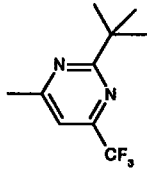
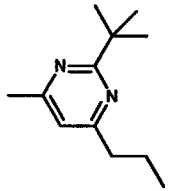
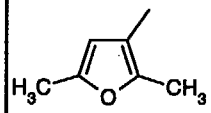
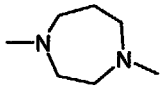
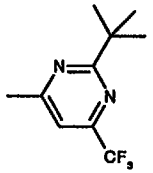
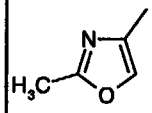
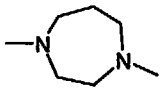
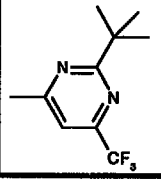
34	4-Methyl-phenyl	cProp	-S(CH_2)$_3$-	Piperazinyl		1H-NMR ($CDCl_3$):1.0 (m, 4H); 2.0 (q, 2H); 2.4 (s, 3H); 2,5 (m, 6H); 2.8 (m,1H); 3.7 (mbr, 6H); 6.6 (s, 1H); 6.7 (s, 1H) 7.3 (d, 2H); 7.6 (d, 2H).
32	Phenyl	Me	-S(CH_2)$_3$-	Piperazinyl		1H-NMR (DMSO-d_6) Fumarat: 2.0 (m, 2H); 2.3 (s, 3H); 2.7 (m, 4H); 2.8 (m, 2H); 3.2 (t, 2H); 3.6 (s, 3H);3,7 (m,4H); 6.6 (s, 1H); 6.7 (m, 1H); 7.15 (d, 1H); 7.5 (m, 3H); 7.7 (m, 2H); 7.9 (m, 1H).
33	Phenyl	Me	-S-CH_2-C(=CH_2)-CH_2-	Piperazinyl		1H-NMR ($CDCl_3$): 2.5 (m,4H); 3.1 (s, 2H); 3.3 (m, 4H); 3.7 (s, 2H); 5.1 (s,1H); 5.2 (s, 1H); 6.3 (m,2H); 6.7-6.9 (m, 3H); 7.1 (m,2H); 7.4-7.7 (m, 6H).
35	Phenyl	iProp	-S(CH_2)$_3$-			1H-NMR (DMSO-d_6) 1.5-2.0 (m, 13H); 2.5 (m, 4H), 2.7 (m, 2H); 3.4 (m, 2H); 3.9 (m, 1H); 7.5-7.7 (m, 9H.
36	Phenyl	Me	-S(CH_2)$_3$-			1H-NMR ($CDCl_3$) 2.0 (q, 2H); 2.5-2.7 (m, 6H); 3.2 (m, 2H); 3.5 (t, 25H); 6-1 (m, 1H); 7.3 (m, 3H); 7.4-7.7 (m, 6H).

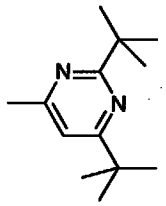
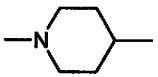
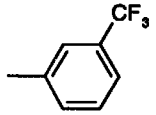
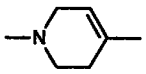
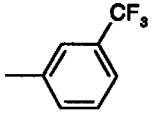
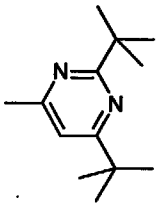
37	Phenyl	nProp	-CONH-$(CH_2)_4$-	Piperazinyl		1H-NMR ($CDCl_3$) 1.0 (t, 3H); 1.3 (s, 9H); 1.4 (s, 9H); 1.6-1.8 (m, 6H); 2.6 (m, 2H); 2.7 (m, 6H); 3.6 (t, 2H); 3.8 (m,4H); 6.3 (s, 1H); 7.5 (m, 3H); 7.7 (m, 2H).
38	Phenyl	Me	-$S(CH_2)_3$-	Piperazinyl		1H-NMR ($CDCl_3$) 2.05 (q, 2H); 2.6 (t, 2H); 2,7 (m, 4H); 3.2 (m, 4H); 3.4 (t, 2H); 3.6 (s, 3H); 7.4-7.7 (m,7H); 7.9 (d, 1H); 8.1 (d, 1H); 8.2 8s, 1H); 9.0 (s, 1H).
39	N-methyl-2-pyrrolyl	Et	-$S(CH_2)_3$-	Piperazinyl		1H-NMR (DMSO-D_6) 1.8-2.0 (m,5H); 2.4 (s,3H); 2.5-2.7 (m,6H); 3.3 (m,2H); 3.7-3.8 (m,7H); 4,0 (m,2H); 6.2 (s,1H); 6.4 (m,1H); 6.6 (m,3H); 6.9 (m,2H); 7.2 (s,1H); 7.9 (s,1H);
40	3,4-Dichloro-phenyl	Me	-$S(CH_2)_3$-			MS: m/z=473[M^+]
41		Me	-$S(CH_2)_3$-	Piperazinyl		m.p.. 154°C

42		Propyl	-S(CH_2)$_3$-	Piperazi-nyl-		1H-NMR ($CDCl_3$) 0.9 (t,3H); 1.3 (s,9H); 1.7 (m,2H);1.9 (m,2H); 2.3 (s,3H); 2.5 (m,6H); 3.3 (m,2H); 3.7 (m,1H); 3.8 (m,4H); 4.3 (t,2H); 6.7 (s,1H); 7.6 (s,1H).
43	Phenyl	Me	-S(CH_2)$_8$-	Piperazi-nyl-		Hydrochloride m.p.. 146°C
44	Phenyl	Me	-S(CH_2)$_6$-	Piperazi-nyl-		Hydrochloride m.p.. 253°C
45	3-Bromopyri-din-5-yl	Me	-S(CH_2)$_3$-	Piperazinyl		1H-NMR ($CDCl_3$) 1.3 (s,9H; 2.1 (m,2H); 2.6 (m,6H); 3.3 (m,3H); 3.7 (s,1H); 3.8 (m,4H); 6.6 (s,1H); 8.2 (s,1H); 8.9 (m,2H).
46	3-Thienyl	Me	-S(CH_2)$_3$-	Piperazinyl		1H-NMR ($CDCl_3$) 1.0 (t,3H); 1.3 (s,9H); 1.7 (m,2H), 1.9 (m,2H); 2.6 (m,8H); 3.4 (t,2H); 3.7 (m,7H); 6.2 (s,1H); 7.5 (m,2H); 7.7 (s,1H).

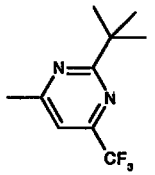
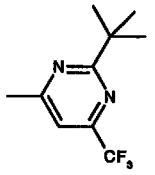
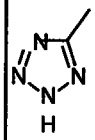
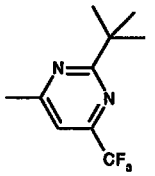
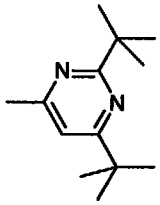
47	4-tert.-Butyl-phenyl-	Me	-S-CH_2-$C(CH_3)$=CH_2-	Piperazinyl		1H-NMR ($CDCl_3$) 1.4 (2s,18H); 1.9 (s,3H); 2.5 (t,4H); 3.0 (d,2H); 3.7 (m,7H); 3.9 (s,2H); 5.5 (t,1H); 6.5 (s,1H); 7.5 (d,2H); 7.6 (d,2H):
48	Phenyl	Propyl	-S$(CH_2)_3$-	Piperazinyl		1H-NMR ($CDCl_3$) 1.3 (s,9H); 1.4 (s,9H); 2.0 (m,2H); 2.6 (m,6H); 3.3 (t,3H); 3.6 (m,7H); 6.4 (s,1H); 6.7 (s,1H); 7.4 (m,3H); 7.7 (m,2H);
49		Propyl	-S$(CH_2)_3$-	Piperazinyl		1H-NMR ($CDCl_3$) 0.9 (t,3H); 1.3 (s,9H); 1.7 (m,2H); 2.0 (q,2H); 2.5 (m,6H); 3.3 (t,3H); 3.7 (mbr,2H); 4.3 (t,2H); 6.2 (s,1H); 8.9 (s,1H);
50	2-Benzthienyl	Me	-S$(CH_2)_3$-	Piperazinyl		m.p.. 143°C

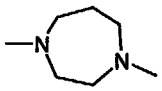
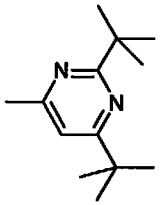
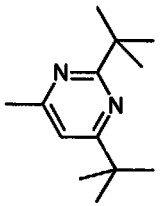
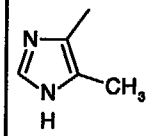
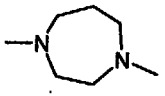
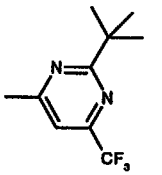
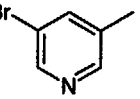
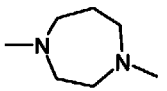
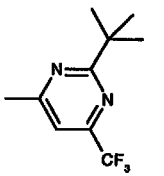
51		Me	-S-CH_2-C(=CH_2)-CH_2-	Piperazinyl		1H-NMR ($CDCl_3$) 1.2 (d,6H); 1.4 (s,9H); 2.5 (m,7H); 2.9-3.0 (m,3H); 3.5 (s,3H); 3.8 (s,2H); 5.0 (s,1H); 5.2 (s,1H); 6.2 (s,1H); 8.9 (s,1H).
52		Me	-S-CH_2-C(=CH_2)-CH_2-	Piperazinyl		m.p.. 150°C
53	Phenyl	n-Propyl	-CO-$(CH_2)_3$-	Piperazinyl		Bishydrochloride 1H-NMR (DMSO-d_6) 1.0 (t,3H); 1.5 (s,9H); 1.7 (m,2H), 2.2 (m,2H); 3.0 (t,2H); 3.3 (m,4H); 3.4 (m,2H); 3.7 (m,3H); 3.9 (m,4H); 4.5 (m,1H); 5.0 (m,1H); 7.2 (s,1H); 7.6 (m,3H); 7.8 (m,2H).
54		Me	-S$(CH_2)_3$-	Piperazinyl		Hydrochloride m.p.. 150°C MS: m/z=641 [M^+]

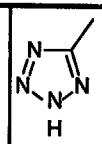
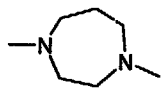
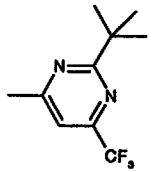
55		Propyl	-S(CH_2)$_3$-	Piperazinyl		1H-NMR ($CDCl_3$) 0.9 (t,3H); 1.3 (s,9H); 1.7 (m,3H); 1.9 (q,2H); 2.6 (m,9H); 3.3 (t,2H); 3.7 (m,4H); 4.3 (t,2H); 6.6 (s,1H); 8.2 (s,1H).
56	2-Pyrrolyl	Me	-S(CH_2)$_3$-	Piperazinyl		1H-NMR ($CDCl_3$): 1.0 (t, 3H); 1.3 (s, 9H); 1.7 (m,2H); 2.0 (m,3H); 2.5 (m,8H); 3.3 (t, 2H); 3.6 (t,4H); 3.8 (s,3H); 6.2 (s,1H); 6.3 (m,1H); 6.6 (m,1H); 7.1 (m,1H).
57		Me	-S-CH_2-C(=CH_2)-CH_2-			Hydrochloride m.p.. 116°C
58		Propyl	-S-CH_2-C(=CH_2)-CH_2-			Hydrochloride m.p.. 76°C (Decomp.) MS: m/z=525[M+]

59	4-Ethinylphe-nyl	Me	-S$(CH_2)_3$-	Piperazinyl		MS: m/z=532 [M+]
60	3-Thienyl	Me	-$(CH_2)_4$-			1H-NMR ($CDCl_3$): 1.7-1.9 (m,4H); 2.5-2.7 (m,6H); 2.9 (t,2H); 3.2 (m,2H); 3.7 (s,3H); 7.3-7.5 (m, 6H); 7.8 (m,1H). MS: m/z= 395 [M+]
61	3-Thienyl	Me	-$(CH_2)_4$-			1H-NMR ($CDCl_3$): 1.7-2.0 (m,8H); 2.5 (m,2H); 2.9 (t,2H); 3.1-3.3 (m,4H); 3.7 (s,3H); 7.5 (m,2H); 7.8 (m,1H). MS: m/z= 393 [M+]
62	3,4-Dichloro-phenyl	Me	-$(CH_2)_4$-	Piperazinyl		1H-NMR ($CDCl_3$): 1.3 (s,9H); 1.4 (s,9H); 1,7 (m,2H); 1.9 (m,2H); 2.5 (m,6H); 2.9 (t,2H); 3.6-3.8 (m,7H); 6.2 (s,1H); 7.4 (dd 1H); 7.6 (d,1H); 8.2 (d,1H).

O.Z. 0050/48151

63	N-Methyl-2-pyrrolyl	Et	$-(CH_2)_4-$	Piperazinyl		1H-NMR ($CDCl_3$): 1.3 (s,9H); 1.7-2.0 (m,6H); 2.5 (m,6H); 2.9 (t,2H); 3.7-4.1 (9H); 6.2 (s,1H); 6.4 (m,1H); 6.6 (s,1H); 6.8 (m,1H).
64	3-Bromopyridin-5-yl	cProp	$-S(CH_2)_3-$	Piperazinyl		1H-NMR ($CDCl_3$) 1.0 (m,4H); 1.3 (s,9H; 2.1 (m,2H); 2.8 (m,1H); 3.6 (m,6H); 3.3 (m,3H); 3.8 (m,4H); 6.6 (s,1H); 8.2 (s,1H); 8.9 (m,2H).
65		Me	$-S(CH_2)_3-$	Piperazinyl		m.p.. 133°C
66	4-CF_3-Phenyl	Me	$-S(CH_2)_3-$	Piperazinyl		MS: m/z= 576 [M^+]

67	Pyrazinyl	Me	-S(CH$_2$)$_3$-			Hydrochloride m.p.. 131°C MS: m/z= 524 [M$^+$]
68	2,4-Dinitro-phenyl	Me	-S(CH$_2$)$_3$-	Piperazinyl		1H-NMR (CDCl$_3$) 1.3 (s,9H); 1.4 (s,9H); ; 2.0 (m,2H); 2.6 (m,6H); 3.3 (t,3H); 3.8 (mbr,7H); 6.2 (s,1H);7.8 (d1H); 8.6 (dd,1H); 9.1 (d,1H).
69		Me	-S(CH$_2$)$_3$-			1H-NMR (CDCl$_3$) 1.3 (s,9H); 1.9 (m,4H); 2.3 (s, 3H); 2.6 (m,4H); 2.8 (m,2H); 3.3 (t,2H); 3.5 (mbr,2H); 3.8 (s,3H); 3.9-4.1 (m,2H); 6.6 (s,1H); 7.6(s, 1H); 12.8 (br,1H).
70		Me	-S(CH$_2$)$_3$-			1H-NMR (CDCl$_3$) 1.3 (s,9H); 2.0 (m,4H); 2.3 (s, 3H); 2.6 (m,4H); 2.8 (m,2H); 3.3 (t,2H); 3.6 (m,2H); 3.7 (s,3H); 4.1 (m,2H); 6.6 (s,1H); 8.2 (m, 1H); 8.8 (m,2H).

71		Me	$-S(CH_2)_3-$			1H-NMR ($CDCl_3$) 1.3 (s,9H); 1.8-2.1 (m, 4H), 2.6-2.9 (m,6H); 3.1 (m,2H); 3.6 (mbr,2H); 3.8-4.1 (m,5H); 6.6 (s, 1H).

c = cyclo, for example cProp = cyclopropyl

0.Z. 0050/48151

The compounds of Examples 20-25 and 65 in the table were obtained in the following manner.

EXAMPLE 20

3-{3-[4-(2-t-Butyl-6-trifluoromethylpyrimidin-4-yl)piperazin-1-yl]propoxy}-4-methyl-5-phenyl-1,2,4-(4H)-triazole

855 mg (3mmol) of 3-iodo-4-methyl-5-phenyl-1,2,4-(4H)-triazole (prepared by iodinating 4-methyl-5-phenyl-1,2,4-(4H)-triazole by a method similar to Izv. Akad. Nauk SSSR, Ser. Khim (1975), 616-619), were stirred, at 60°C for 6 h, with 1.04 g (3 mmol) of 2-t-butyl-4-[4-(3-hydroxypropyl)piperazin-1-yl]-6-trifluoromethyl pyrimidine (prepared, by a method similar to Example 1, A.3, by reacting the product obtained as described in Example 1, A.2 with 3-chloropropanol) and sodium hydride in DMF. For the working-up, ice water was added to the mixture and the whole was extracted several times with methyl t-butyl ether. The residue which was obtained after drying with sodium sulfate and removing the solvent was purified by column chromatography (silica gel, methylene chloride/methanol). Yield, 140 mg (9 % of theory) of oil

$C_{25}H_{32}F_3N_7O$ (503)

1H NMR ($CDCl_3$):
1.3 (s,9H); 2.1 (m,2H); 2.6-2.8 (m,6H); 3.5 (s,3H); 3.8 (mbr,4H); 4.6 (t,2H); 6.5 (s,1H); 7.6 (m,3H); 7.8 (m,2H);

EXAMPLE 21

3-{4-[4-(2,6-Di-t-butylpyrimidin-4-yl)piperazin-1-yl]but-1-enyl}-4-methyl-5-phenyl-1,2,4-(4H)-triazole

a. 3-Formyl-4-methyl-5-phenyl-1,2,4-(4H)-triazole

18.5 g (116 mmol) of 4-methyl-5-phenyl-1,2,4-(4H)-triazole were dissolved in 235 ml of absolute THF and the solution was cooled down to -70°C; 85 ml (139 mmol) of a 15% strength solution of butyllithium in hexane were then added at this temperature over the course of 15 min. After 45 min, 72 ml (1.16 mmol) of methyl formate were added over the space of 5 min, in association with which the temperature rose to -50°C. The mixture was subsequently stirred for a further 2 h at -50 to -70°C and for 30 min at -25°C; solid ammonium chloride was then added, after which ice water was added and

the whole was extracted 3 times with methylene chloride. After drying and evaporating off the solvent, 22.8 g of residue remained, which residue was purified by means of flash chromatography (silica gel, ethyl acetate/methanol). Yield: 10.9 g (46 % of theory)

$C_{10}H_9N_3O$ (187)

1H NMR ($CDCl_3$):
3.9 (s,3H); 7.6 (m,3H); 7.7 (m,2H); 10.2 (s,1H).

b. 3-[4-(2,6-Di-t-butylpyrimidin-4-yl)piperazin-1-yl]propyl-triphenylphosphonium chloride

3.52 g (10 mmol) of 1-chloro-3-[4-(2,6-di-t-butylpyrimidin-4-yl)piperazin-1-yl]propane (prepared by a method similar to Example 1, A.3) were dissolved, together with 1.8 g of sodium iodide (12 mmol) and 3.41 g (13 mmol) of triphenylphosphine in 75 ml of acetone and the solution was refluxed for 24 h.

After the mixture had been cooled down, the precipitate was filtered off with suction, the filtrate was concentrated by evaporation under reduced pressure and the residue was purified by column chromatography (silica gel, methylene chloride containing 3.5 % methanol). Yield: 6.25 g (88 % of theory).

$C_{37}H_{48}IN_4P$ (706).

1H NMR ($CDCl_3$):
1.3 (s,9H); 1.4 (s,9H); 1.9 (m,2H); 2.4 (m,4H); 2.7 (m,2H); 3.6 (m,4H); 3.9 (mbr, 2H); 6.3 (s,1H); 7.6-7.9 (m,15H).

c. 5.88 g (8.3 mmol) of the phosphonium salt which was prepared above under b. were dissolved in 15 ml of ethylene glycol dimethyl ether, the solution was cooled down to 0°C and 280 mg (9.2 mmol) of sodium hydride were added and, after the mixture had been stirred at room temperature for 15 min, 1.56 g of the aldehyde described above under a., dissolved in 10 ml of ethylene glycol dimethyl ether, were subsequently added dropwise at 0°C.

After the mixture had been stirred at room temperature for 1.5 h and at 40°C for a further 2 h, it was worked up using toluene and water and the insoluble material was removed by filtration. 2.6 g of oil were obtained from the toluene phase

after drying and evaporating. Yield: crude product, 65 % of theory.

The product was purified by chromatography (silica gel, methylene chloride/methanol).

$C_{29}H_{41}N_7$ (487).

c) 1H NMR ($CDCl_3$):
1.3 (s,9H); 1.4 (s,9H); 2.6 (m,8H); 3.7 (m,7H); 6.2 (s,1H); 6.4 (d,1H); 7.0 (td,1H); 7.5 (m,3H); 7.7 (m,2H).

EXAMPLE 22

3-{4-[4-(2,6-Di-t-butylpyrimidin-4-yl)piperazin-1-yl]butyl}-4-methyl-5-phenyl-1,2,4-(4H)-triazole

a. 2-[4-Methyl-5-phenyl-1,2,4-(4H)-triazol-3-yl]-1,3-dithiane

6.12 g (32.6 mmol) of the aldehyde prepared as described in Example 21 a. were dissolved in 16 ml of chloroform, after which 16 ml of acetic acid, 3.28 ml (32.6 mmol) of 1,3-dimercaptopropane and 160 µl of boron trifluoride etherate were added at 0°C. After the mixture had been refluxed for 2.5 h, a further 2.4 ml of dimercaptopropane and boron trifluoride etherate were slowly added and the mixture was heated for a further 6 h until the aldehyde had been completely reacted.

After the mixture had been cooled down to 0°C, it was adjusted to pH 9-10 with 10% strength sodium hydroxide solution, stirred at 0°C for 1 h and then extracted 3 times with methylene chloride. 13.2 g of a yellow oil were obtained from the dried and evaporated solvent phase and were purified by column chromatography (silica gel, ethyl acetate). Yield: 4.3 g (48 % of theory), colorless solid.

$C_{13}H_{15}N_3S_2$ (277).

1H NMR ($CDCl_3$):
2.1 (m,2H); 2.9 (m,2H); 3.3 (m,2H); 3.7 (s,3H); 5.3 (s,1H); 7.5 (m,3H); 7.7 (m,2H).

b. 831 mg (3 mmol) of the above-described dithiane were dissolved in 7.5 ml of dried THF, and the solution was treated, at -70°C, with 2.2 ml (3.6 mmol) of a 15% strength solution of butyllithium in n-hexane. After the mixture had

been stirred at from -70°C to -50°C for 60 min, 1.06 g (3 mmol) of 1-chloro-3-[4-(2,6-di-t-butylpyrimidin-4-yl)piperazin-1-yl]propane (prepared by a method similar to Example 1, A.3), dissolved in 5 ml of THF, were added dropwise. The mixture was then warmed slowly to room temperature and heated at 30 to 50°C for a further 60 min in order to achieve complete reaction. For the working-up, solid ammonium chloride was added to the cooled-down mixture. The latter was then added to ice/water; this mixture was then extracted several times with methylene chloride and methyl-t-butyl ether. Drying and concentrating left a residue of 1.74 g (98 % of theory) of the substituted dithiane, which was subsequently hydrogenated in tetrahydrofuran, at 40°C and over the course of 12 h, using Raney nickel and hydrogen. After the catalyst had been separated off, the residue was purified by chromatography (silica gel, methylene chloride/methanol). Yield: 700 mg (49 % of theory). Colorless solid, m.p. 144-145°C.

$C_{29}H_{43}N_7$ (489).

EXAMPLE 23

3-{4-[4-(2-t-Butyl-6-trifluoromethylpyrimidin-4-yl)piperazin-1-yl]butyl}-4-methyl-5-phenyl-1,2,4-(4H)-triazole hydrochloride

The compound was prepared, by a method similar to Example 22, using the chlorine compound from Example 1, A.3.

$C_{29}H_{34}F_3N_7$ (502.)

1H NMR ($CDCl_3$):
1.3 (s,9H); 1.7 (m,2H); 1.9 (q,2H); 2.4 (t,2H); 2.5 (t,4H); 2.8 (t,2H); 3.6 (s,3H); 3.75 (m,4H); 6.6 (s,1H); 7.4 (m,3H); 7.6 (m,2H).

EXAMPLE 24

3-{3-[4-(2-t-Butyl-6-trifluoromethylpyrimidin-4-yl)piperazin-1-yl]propylmercapto}-5-(2,5-dimethylfuran-3-yl)-4-methyltriazole hydrochloride

2,5-Dimethylfuran-3-yl-3-mercapto-4-methyl-1,2,4-(4H)-triazole was obtained by reacting 2,5-dimethylfuran-3-carbonyl chloride with N-methylthiosemicarbazide and subsequently cyclizing in

accordance with the method of Kubota and Uda, Chem. Pharm. Bull. (1975), 23, 955-966.

$C_9H_{11}N_3OS$ (209).

1H NMR ($CDCl_3$):
2.2 (s,3H); 2.3 (s,3H); 3.5 (s,3H); 6.5 (1H).

The abovementioned compound was obtained by reacting by a method similar to Example 1B. M.p. 190-192°C

$C_{25}H_{34}F_3N_7OS$ HCl (574)

EXAMPLE 25

3-{3-[4-2-t-Butyl-6-trifluoromethylpyrimidin-4-yl)piperazin-1-yl]propylmercapto}-5-(pyrazin-2-yl)-4-methyltriazole hydrochloride

3-Mercapto-4-methyl-5-pyrazin-2-yl-1,2,4-(4H)-triazole was obtained by reacting pyrazine-2-carbonyl chloride by a method similar to the method of Kubota and Uda in Example 24.

The abovementioned compound was likewise prepared by a method similar to Example 1B. M.p. 164-169°C.

$C_{23}H_{31}F_3N_9$ (522).

EXAMPLE 65

3-(3-(4-(2-tert-Butyl-6-trifluoromethylpyrimidin-4-yl)piperazin-1-yl)propylmercapto-4-methyl-5(1H)-tetrazolyl-5)-1,2,4(4H)-triazole.

a) 3-(3-(4-(2-tert-Butyl-6-trifluoromethylpyrimidin-4-yl)-piperazin-1-yl)propylmercapto-4-methyl-1,2,4(4H)-triazole-5-carboxamide

950 mg (6.0 mmol) of 5-mercapto-4-methyl-1,2,4(4H)-triazole-3-carboxamide were heated at 100°C for 3 h, while stirring, with 2.2 g (6.0 mmol) of the chlorine base prepared in accordance with Example 1.A3 and 144 mg of lithium hydroxide (6.0 mmol) in 17 ml of DMF. After having been cooled down, the mixture was treated with 100 ml of water and extracted with methyl tert-butyl ether; the solvent phase was then dried and evaporated. The residue was purified by

chromatography (silica gel, methylene chloride/methanol 95:5).

Yield: 1.65 g (57% of theory)
M.p. 141-143°C
$C_{20}H_{29}F_3N_8OS$ (MW 486)

b) 3-(3-(4-(2-tert-Butyl-6-trifluoromethylpyrimidin-4-yl)-piperazin-1-yl)propylmercapto-5-cyano-4-methyl-1,2,4(4H)-triazole.

1.15 g (24.0 mmol) of the above-described compound were dissolved in 20 ml of methylene chloride and 2 ml (12.0 mmol) of dipropylethylamine, after which the solution was cooled down to 0°C and 0.5 ml of trifluoroacetic anhydride was added slowly. After the mixture had been stirred at room temperature for 3 h, it was washed twice with water, then with a 20% solution of $NaHSO_4$, a saturated solution of $NaHCO_3$ and a solution of sodium chloride; the organic phase was then dried and evaporated. 0.9 g of oil (81% of theory) remained. A sample was converted with ethereal hydrochloric acid into the hydrochloride.

M.p. 220-222°C
$C_{20}H_{27}F_3N_8S$ (MW 468)
$C_{20}H_{28}ClF_3N_8S$ (MW 503.5)

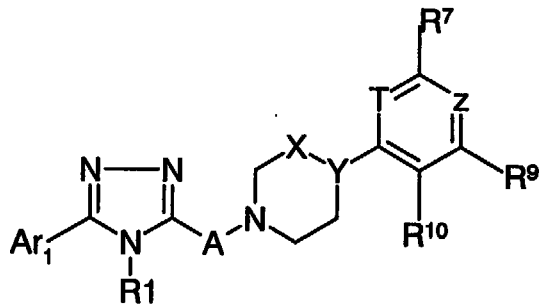
c) 5-(3-(4-(2-tert-Butyl-6-trifluoromethylpyrimidin-4-yl)-piperazin-1-yl)propylmercapto-4-methyl-3((1H)-tetrazolyl-5)-1,2,4(4H)-triazole.

0.8 g (1.7 mmol) of the above-described substance was dissolved in 1 ml of DMF, after which 122 mg (1.9 mmol) of sodium azide and 100 mg (1.9 mmol) of ammonium chloride were added; the mixture was then heated at 85°C for 2 h while stirring. For the working up, a little water was added and the solution was adjusted to pH 7 with NaOH and extracted with methylene chloride. After drying and concentrating, approx. 1 g of residue was obtained, with this residue being purified by column chromatography. (Silica gel, methylene chloride/methanol 8:2).

Yield: 0.38 g (43% of theory)
M.p. 133° (decomposition)
$C_{20}H_{28}F_3N_{11}S$ (MW 511)

The following compounds listed in Tables 2 to 9 were obtained in an analogous manner:

Table 2:

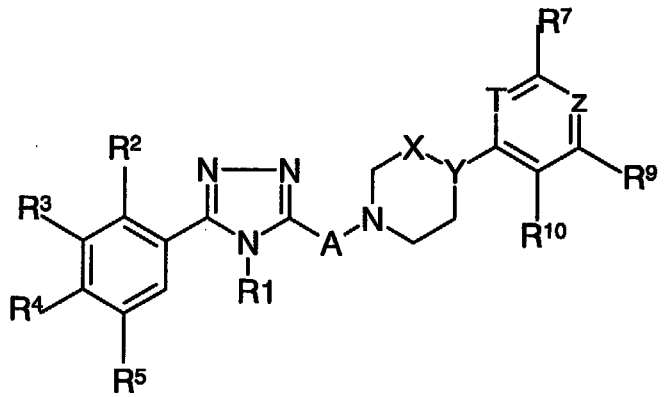


Ar1	R1	T	R7	Z	R9	R10	X-Y	A
N-Me-2-Pyrrolyl	Et	N	tBut	N	4-MeOPh	H	CH_2-N	COO-$(CH_2)_4$-
2-Me-4-Oxazolyl	But	N	tBut	N	H	OMe	CH_2-N	S-CH_2-CH=CH-CH_2-
N-Me-2-Pyrrolyl	But	N	iProp	CH	tBut	H	CH_2-CH	S -$(CH_2)_3$-
4-Imidazolyl	Me	N	tBut	CH	iProp	H	CH_2-N	S -$(CH_2)_7$-
2,5-Dimethylfuranyl-3-	cBut	N	Pyrrolyl	N	Me	H	CH=C	NH-$(CH_2)_4$
N-Me-2-pyrrolyl	Me	N	tBut	N	tBut	H	CH_2-CH	S -$(CH_2)_3$-
2-Pyrrolyl	Me	N	2,4 OMe-Ph	N	Cl	H	CH_2-N	O -$(CH_2)_3$-
2-Pyrazinyl-	$(CH_2)_4$-OMe	N	tBut	N	1-Pyrrolyl	H	CH_2-N	-$(CH_2)_8$-
2-Methylpyridin-3-yl	CH_2Ph	CH	iProp	N	H	OMe	CH_2-N	-$(CH_2)_4$-
2-Pyrazinyl-	cProp	CH	H	N	CH_3	OMe	CH=C	O-$(CH_2)_3$-
3-Br-Pyrimidin-5-yl	Et	N	Prop	N	cHex	H	CH=C	O -$(CH_2)_4$-
Pyrimidin-3-yl	Et	N	tBut	N	nHex	H	CH_2-N	S-CH_2-C(CH_3)=CH-CH_2-
N-Propyltetrazolyl	CH_2Ph	N	iProp	N	H	OMe	CH_2-N	S-$(CH_2)_4$-

2-Methylpyridin-3-yl	cProp	N	H	N	CH_3	OMe	CH=C	O-$(CH_2)_3$-
N-Ethylindol-3-yl	Me	N	H	N	iProp	OMe	CH_2-N	S -$(CH_2)_3$-
Tetrazolyl-	Et	N	tBut	N	H	CH_3	CH_2-N	-$(CH_2)_4$-
6-Chlorobiphenyl-2	Me	CH	tBut	N	tBut	OMe	CH_2-N	CONH-$(CH_2)_4$-
4-Methylthiazole	Me	N	4-OMePh	N	Me	Me	CH_2-N	S -$(CH_2)_7$-
Tetrazonyl-	iProp	N	tBut	N	Ph	H	CH_2-N	CO-$(CH_2)_3$-
N-Me-2-Pyrrolyl	Prop	N	Me	CH	Pyrrolyl	H	CH=C	CH_2-CH_2-C(CH_3)=CH-CH_2-
4-Imidazolyl	cProp	N	nPropyl	N	tBut	H	CH=C	NH-$(CH_2)_3$-
2-Pyrrolyl	Me	N	4-OMePh	N	Me	Me	CH=C	S -$(CH_2)_8$-
3-Thienyl	Me	CH	4-OMePh	N	Me	Me	CH_2-N	CH_2-CH_2-C(=CH_2)-CH_2-
2-Me-4-Oxazolyl	Et	N	tBut	N	Pyrrolyl	H	CH_2-N	S-CH_2-C(=CH_2)-CH_2-
2-Me-4-Oxazolyl	cProp	N	tBut	CH	Me	H	CH_2-N	S-CH_2-CH=CH-CH_2-
N-Propyltetrazolyl	Me	N	CF_3	CH	Me	Butyl	CH=C	CH_2-CH_2-CH(CH_3)-CH_2
3-Thienyl	cProp	N	CF_3	N	Me	Butyl	CH=C	CH_2-CH_2-CH(CH_3)-CH_2
N-Propyltetrazolyl	Me	N	CF_3	N	H	H	CH_2-N	-$(CH_2)_4$-
3-Thienyl	cBut	N	CHF_2	CH	H	H	CH_2-N	-$(CH_2)_4$-
2,5-Dimethylfuranyl-3-	Me	N	Pyrrolyl	CH	Me	H	CH=C	NH-$(CH_2)_4$-
Oxadiazol-2-yl	Prop	N	Me	N	Pyrrolyl	H	CH_2-N	-$(CH_2)_4$-
N-Propyl-2-pyrrolyl	Prop	N	Me	N	Pyrrolyl	H	CH=C	CH_2-CH_2-C(CH_3)=CH-CH_2-
3-Benzthienyl	iProp	N	tBut	N	Ph	H	CH_2-N	CH_2-CH_2-CH(CH_3)-CH_2-
5-Methylimidazol-4-yl	Me	N	2,4 OMe-Ph	CH	Cl	H	CH_2-N	O -$(CH_2)_3$-
2-Aminothiazol-4yl	Prop	N	Cl	CH	iProp	H	CH_2-N	CH_2-CH_2-C(CH_3)=CH-CH_2-
N-Me-2-Pyrrolyl	iProp	CH	tBut	N	tBut	H	CH_2-CH	S -$(CH_2)_3$-
N-Propyl-2-pyrrolyl	Prop	N	Me	CH	tBut	H	CH=C	CH_2-CH_2-CH(CH_3)-CH_2-
3-Benzthienyl	iProp	N	tBut	CH	H	Ne	CH_2-N	S-CH_2-C(CH_3)=CH-CH_2-
2-Pyrrolyl	Me	CH	iProp	N	Me	H	CH_2-CH	NH-$(CH_2)_3$-
2-Phenylfuran-3yl	cProp	N	CF_3	CH	CH	CH	CH=C	S-$(CH_2)_3$
3-Br-Pyrimidin-5-yl	Me	CH	iProp	N	tBut	H	CH_2-N	CO-$(CH_2)_7$-
2-Aminothiazol-4yl	Et	N	CH	Cl	CH	CH	CH_2-N	CONH-$(CH_2)_4$-
6 Me-Benzoindol-3-yl	Me	N	iProp	CH	Furanyl	H	CH_2-N	CH_2-CH_2-C(CH_3)=CH-CH_2-

2,5-Dimethylfuranyl-3-	cBut	CH	Pyrrolyl	N	Me	H	CH=C	NH-$(CH_2)_4$-
Tetrazolyl-	iProp	N	tBut	CH	H	Cl	CH_2-N	CO-$(CH_2)_8$-
4-Imidazolyl	$(CH_2)_4$-OMe	CH	tBut	N	H	H	CH_2-N	-$(CH_2)_8$-
Pyrimidin-3-yl	Et	CH	Pyrrolyl	N	cHex	H	CH=C	S -$(CH_2)_4$-
4-Imidazolyl	Me	N	iProp	N	iProp	H	CH_2-N	S -$(CH_2)_7$-
N-Propyltetrazolyl	Et	CH	tBut	N	nHex	H	CH_2-N	S-CH_2-C(CH_3)=CH-CH_2-

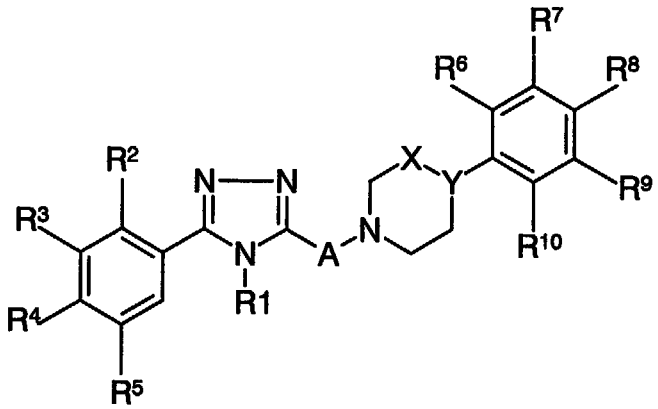
Table 3:



R1	R2	R3	R4	R5	T	R7	Z	R9	R10	X-Y	A
Me	H	CN	H	CN	N	tBut	N	tBut	H	CH_2-CH	S -$(CH_2)_3$-
Me	OMe	H	OMe	H	N	iProp	N	iProp	H	CH_2-N	S -$(CH_2)_7$-
Me	H	H	$MeSO_2$	H	N	H	N	CF_2Cl	H	CH_2-N	O -$(CH_2)_3$-
Me	H	Me	CN	H	CH	tBut	N	tBut	H	CH_2-N	CONH-$(CH_2)_4$-
cProp	H	Me	CN	H	N	nPropyl	N	tBut	H	CH=C	NH-$(CH_2)_3$-
Me	OMe	H	tBut	H	N	4-OMePh	N	Me	Me	CH=C	S -$(CH_2)_8$-
Me	H	iProp	H	Me	CH	4-OMePh	N	Me	Me	CH_2-N	S -$(CH_2)_7$-
Et	H	H	H	H	N	Me	N	Pyrrolyl	H	CH_2-N	-$(CH_2)_4$-
iProp	H	H	H	H	N	Pyrrolyl	N	Me	H	CH_2-N	CO-$(CH_2)_8$-
Et	Me	H	Br	Br	CH	tBut	N	Pyrrolyl	H	CH_2-N	S-CH_2-C(=CH_2)-CH_2-
Et	H	H	4-MePh	H	N	tBut	N	2-Napht	H	CH_2-N	COO-$(CH_2)_4$-
-$(CH_2)_4$-OMe	H	Cl	Cl	H	N	tBut	N	1-Pyrrolyl	H	CH_2-N	-$(CH_2)_8$-
Prop	Me	H	Br	H	CH	Me	N	Pyrrolyl	H	CH_2-N	S-CH_2-C(=CH_2)-CH_2-
Et	H	$MeSO_2$	Me	$MeSO_2$	N	Prop	N	cHex	H	CH=C	O -$(CH_2)_4$-

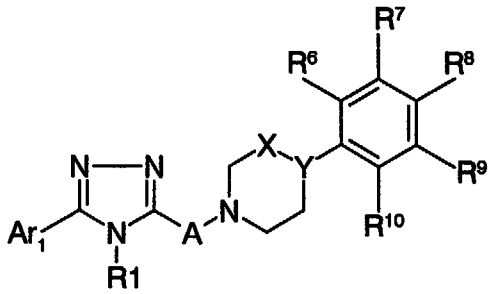
Et	Me	H	Br	H	N	tBut	N	nHex	H	CH_2-N	S-CH_2-C(CH_3)=CH-CH_2-
But	H	OMe	H	OMe	N	tBut	N	H	OMe	CH_2-N	S-CH_2-CH=CH-CH_2-
CH_2Ph	I	OMe	H	H	N	iProp	N	H	OMe	CH_2-N	S-$(CH_2)_4$-
cProp	H	Me	CN	H	N	nPropyl	CH	tBut	Me	CH=C	S -$(CH_2)_7$-
cProp	F	H	F	H	N	H	N	CH_3	OMe	CH=C	O-$(CH_2)_3$-
Me	H	iProp	H	H	N	4-OMePh	N	Me	Me	CH_2-N	S -$(CH_2)_7$-
Me	OMe	H	tBut	H	N	4-OMePh	N	Me	Me	CH_2-N	CH_2-CH_2-C(=CH_2)-CH_2-
iProp	H	CN	CN	H	N	tBut	CH	H	Me	CH=C	S-CH_2-CH(CH_3)-CH_2-
Et	Me	H	Br	H	N	tBut	N	Pyrrolyl	H	CH_2-N	S-CH_2-C(=CH_2)-CH_2-
Me	H	OMe	H	Prop	N	iProp	N	Furanyl	H	CH_2-N	CH_2-CH_2-C(CH_3)=CH-CH_2-
Me	H	CN	H	H	N	tBut	CH	tBut	H	CH_2-CH	S -$(CH_2)_3$-
Me	OMe	H	OMe	H	N	iProp	CH	iProp	H	CH_2-N	-$(CH_2)_4$-
Me	H	H	$MeSO_2$	H	N	H	C-Me	CF_3	H	CH_2-N	CONH-$(CH_2)_4$
Me	H	iProp	H	H	N	Me	CH	Me	H	CH_2-N	S -$(CH_2)_7$-
Prop	SO_2Me	H	SO_2Me	H	N	4-OMePh	CH	Pyrrolyl	H	CH=C	CH_2-CH_2-C(CH_3)=CH-CH_2-
Me	OMe	H	tBut	H	N	4-OMePh	CH	Me	Me	CH_2-N	CH_2-CH_2-C(=CH_2)-CH_2-
Prop	SO_2Me	H	SO_2Me	H	N	Me	N	Pyrrolyl	H	CH=C	CH_2-CH_2-C(CH_3)=CH-CH_2-
iProp	OMe	Ph	H	H	N	tBut	N	Ph	H	CH_2-N	CH_2-CH_2-CH(CH_3)-CH_2-
H	H	Br	H	NH_2	N	Cl	CH	tBut	H	CH_2-N	S-CH_2-C(=CH_2)-CH_2-
Prop	H	C≡CH	H	H	CH	tBut	N	H	CH_3	CH_2-N	CH_2-CH_2-CH(CH_3)-CH_2-
cProp	SO_2Me	H	SO_2Me	H	CH	Me	N	Pyrrolyl	H	CH=C	CH_2-CH_2-C(CH_3)=CH-CH_2-
iProp	OMe	Ph	H	H	CH	tBut	N	4-OMePh	H	CH_2-N	-$(CH_2)_4$-
Me	H	H	H	H	N	Me	N	H	But	CH=C	-$(CH_2)_8$-
Prop	NO_2	H	H	Me	N	Me	N	Pyrrolyl	H	CH_2-N	-$(CH_2)_4$-
iProp	H	iProp	H	Me	N	tBut	N	Ph	H	CH_2-N	CO-$(CH_2)_3$-
Me	OMe	H	tBut	H	CH	4-OMePh	N	Me	Me	CH_2-CH	CH_2-CH_2-C(=CH_2)-CH_2-

Table 4:



R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	X-Y	A
Me	OMe	H	tBut	H	H	tBut	H	tBut	H	CH_2-N	S-CH_2-C(=CH_2)-CH_2-
cProp	H	H	$MeSO_2$	H	H	tBut	F	Ph	H	CH_2-N	O -$(CH_2)_4$-
Me	H	iProp	H	H	H	tBut	H	1-Pyrrolyl	H	CH_2-N	S-CH_2-C(CH_3)=CH-CH_2-
Prop	SO_2Me	H	SO_2Me	H	H	nPropyl	H	tBut	H	CH=C	S-CH_2-CH=CH-CH_2-
Me	H	Me	CN	H	H	CF_3	H	tBut	H	CH_2-N	S-$(CH_2)_4$-
Me	OMe	H	tBut	H	Me	Me	H	iProp	H	CH_2-N	S-CH_2-CH(CH_3)-CH_2
Me	H	H	Cl	Cl	H	iProp	H	p-OMe-Ph	H	CH_2-N	O-$(CH_2)_3$-
cProp	H	Me	CN	H	OMe	tBut	CN	CF_3	H	CH=C	S-$(CH_2)_7$-
Et	Me	H	Br	Br	H	iProp	H	Me	Me	CH=C	CH_2-CH_2-C(=CH_2)-CH_2-
Et	H	H	4-MePh	H	H	iProp	H	F	OMe	CH_2-N	S-$(CH_2)_7$-
-$(CH_2)_4$-OMe	H	Cl	Cl	H	H	CHF_2	H	But	H	CH_2-N	S-CH_2-C(=CH_2)-CH_2-
Prop	SO_2Me	H	SO_2Me	H	H	Ph	C≡CH	tBut	H	CH_2-N	CH_2-CH_2-C(CH_3)=CH-CH_2-
iProp	OMe	Ph	H	H	H	CHF_2	H	H	H	CH=C	S -$(CH_2)_3$-
cProp	F	H	F	H	H	CF_3	H	H	H	CH_2-CH	-$(CH_2)_4$-

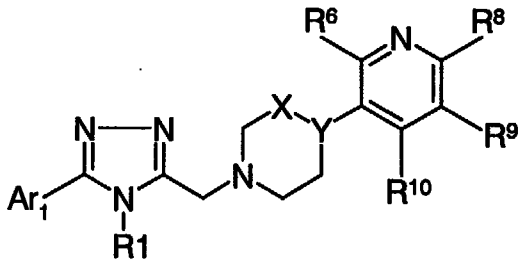
Table 5:



Ar1	R1	R6	R7	R8	R9	R10	X-Y	A
4-Imidazolyl-	Me	H	tBut	H	tBut	H	CH_2-N	S-CH_2-C(=CH_2)-CH_2-
2-Pyrazinyl-	cProp	H	tBut	F	Ph	H	CH_2-N	O -$(CH_2)_4$-
2-Me-4-oxazolyl-	Me	H	tBut	H	1-Pyrrolyl	H	CH_2-N	S-CH_2-C(CH_3)=CH-CH_2-
2-Pyrrolyl	Prop	H	nPropyl	H	tBut	H	CH=C	S-CH_2-CH=CH-CH_2-
3-Br-pyrimidin-5-yl-	Me	H	CF_3	H	tBut	H	CH_2-N	S-$(CH_2)_4$-
Pyrimidin-3-yl-	Me	Me	Me	H	iProp	H	CH_2-N	S-CH_2-CH(CH_3)-CH_2
6-Chlorobiphenyl-2-	Me	H	iProp	H	p-OMe-Ph	H	CH_2-N	O-$(CH_2)_3$-
2,5-Dimethylfuranyl-3-	cProp	OMe	tBut	CN	CF_3	H	CH=C	S -$(CH_2)_7$-
N-propyltetrazolyl-	Et	H	iProp	H	Me	Me	CH=C	CH_2-CH_2-C(=CH_2)-CH_2-
N-methyl-2-Pyrrolyl-	Et	H	iProp	H	F	OMe	CH_2-N	S -$(CH_2)_7$-
3-Thienyl	-$(CH_2)_4$-OMe	H	CHF_2	H	But	H	CH_2-N	S-CH_2-C(=CH_2)-CH_2-
3-Benzthienyl-	Prop	H	Ph	C≡CH	tBut	H	CH_2-N	CH_2-CH_2-C(CH_3)=CH-CH_2-
2-Me-4-Oxazolyl-	iProp	H	CHF_2	H	H	H	CH=C	S -$(CH_2)_3$-
4-Methylthiazol-	Et	H	CHF_2	H	But	H	CH_2-N	CH_2-CH_2-C(CH_3)=CH-CH_2-
3-Benzthienyl-	iProp	H	iProp	H	p-OMe-Ph	H	CH_2-N	NH-$(CH_2)_4$-
5-Methylimidazol-4-yl-	Me	But	Me	H	H	H	CH_2-N	O-$(CH_2)_3$-
2-Aminothiazol-4yl-	Prop	H	H	C≡CH	But	H	CH_2-N	-$(CH_2)_4$-

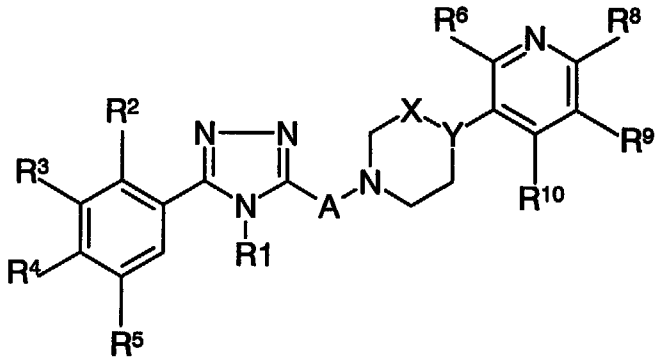
N-Me-2-pyrrolyl	Me	H	CF_3	H	tBut	H	CH=C	CO-$(CH_2)_3$-
2-Me-4-oxazolyl	iProp	H	tBut	F	Ph	H	CH=C	S -$(CH_2)_3$-
2,5-Dimethylfuranyl-	Me	Me	H	CN	H	H	CH_2-N	S-CH_2-CH=CH-CH_2
N-ethylindol-3-yl	-$(CH_2)_4$-OMe	H	CHF_2	H	H	H	CH=C	S -$(CH_2)_3$-
2,5-Dimethylfuranyl-3-	iProp	H	iProp	H	2,4-OMe-Ph	Me	CH_2-CH-	-COO-$(CH_2)_4$-
2-Aminothiazol-4yl-	Me	H	iProp	H	2,4-OMe-Ph	H	CH=C-	-S-CH_2-CH=CH-CH_2-
3-Br-Pyrimidin-5-yl-	Me	H	Me	H	Et	Me	CH_2-N	S -$(CH_2)_3$-
5-Ethylimidazol-4-yl-	cProp	Prop	H	C≡CH	But	H	CH_2-N	-$(CH_2)_4$-
n-Butyltetrazolyl-	But	H	Et	CN	OH	H	CH=C	-$(CH_2)_4$-
3-Benzthienyl-	Me	H	CHF_2	H	H	H	CH_2-CH-	S -$(CH_2)_3$-
N-Me-2-pyrrolyl	Me	H	CF_3	H	tBut	H	CH_2-CH-	S -$(CH_2)_3$
Tetrazolyl-	cProp	H	CF_3	H	iProp	H	CH_2-CH-	-$(CH_2)_4$-
Oxadiazol-2-yl-	cProp	H	CF_3	H	H	H	CH=C	-$(CH_2)_4$-

Table 6:



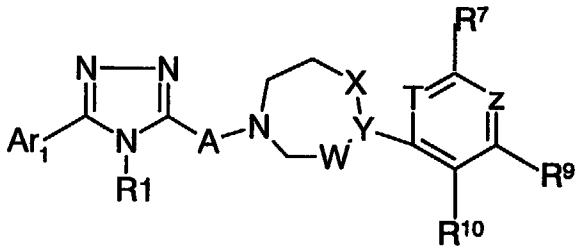
Ar1	R1	R6	R8	R9	R10	X-Y	A
N-Me-2-pyrrolyl	Prop	4-MeOPh	H	tBut	H	CH_2-N	-S -$(CH_2)_7$-
2-Me-4-oxazolyl	Me	H	H	iProp	Me	CH_2-N	S-CH_2-CH=CH-CH_2-
4-Imidazolyl	Me	iProp	Me	But	H	CH_2-N	COO-$(CH_2)_4$
2,5-Dimethylfuranyl-	But	Me	CC	Me	H	CH=C	$(CH_2)_4$-
3-Thienyl-	Me	H	H	Pyrrolyl	Cl	CH_2-CN	S-CH_2-C(CH_3)=CH-CH_2-
2-Pyrazinyl-	cProp	H	CN	iProp	OMe	CH_2-N	-$(CH_2)_4$-
3-Br-pyrimidin-5-yl	Hex	H	H	iProp	OMe	CH_2-N	O-$(CH_2)_3$-
Pyrimidin-3-yl	Et	cHex	H	Prop	H	CH=C	NH-$(CH_2)_4$
2-Pyrazinyl-	Et	H	H	Pent	Et	CH_2-N	-$(CH_2)_4$-
2-Methylpyridin-3-yl	Me	H	Cl	Me	H	CH_2-N	CONH-$(CH_2)_4$-
2,5-Dimethylfuranyl-3-	cProp	CH_3	H	H	OMe	CH=C	- $(CH_2)_4$-
N-ethylindol-3-yl-	cProp	CH_3	Me	H	OMe	CH=C	S-CH_2-C(=CH_2)CH_2
Tetrazolyl-	Et	cHex	H	Prop	H	CH=C	S-$(CH_2)_3$-
3-Benzthienyl-	iProp	H	H	cProp	But	CH_2-N	S-$(CH_2)_8$-
N-propyltetrazolyl	CH_2Ph	H	H	iProp	OMe	CH_2-N	S-$(CH_2)_4$-
2-Aminothiazol-4yl-	Me	H	CN	CHF2	H	CH_2-N	-$(CH_2)_4$-

Table 7:



R1	R2	R3	R4	R5	R6	R8	R9	R10	X-Y	A
Prop	H	$MeSO_2$	Me	$MeSO_2$	Et	H	tBut	H	CH_2-N	COO-$(CH_2)_4$-
Me	Me	H	Br	H	H	H	tBut	H	CH_2-N	S-CH_2-CH=CH-CH_2-
Me	H	OMe	H	OMe	iProp	Me	tBut	H	CH_2-N	-$(CH_2)_4$-
But	OMe	H	OMe	H	Me	C≡CH	Pyrrolyl-	H	CH=C	CONH-$(CH_2)_4$
Me	H	Me	CN	H	H	H	Me	Cl	CH_2-N	-$(CH_2)_4$-
cProp	F	H	F	H	H	H	iProp	OMe	CH_2-N	S-CH_2-C(=CH_2)CH_2-
cProp	H	iProp	H	Me	CH_3	Me	H	OMe	CH=C	O-$(CH_2)_3$-
Et	OMe	H	tBut	H	cHex	H	Prop	H	CH=C	S-$(CH_2)_3$-
Et	H	H	H	CN	nHex	CN	tBut	H	CH_2-N	S-CH_2-C(CH_3)=CH-CH_2-
iProp	H	CF_3	H	Me	H	CC	4OMe-Ph	H	CH_2-CH	S-CH_2-CH=CH-CH_2-
Hex	H	H	H	H_2NSO_2	H	H	CHF_2	H	CH_2-N	-CO-$(CH_2)_3$-
Me	H	H	H	H	H	H	iProp	H	CH=C	S-$(CH_2)_3$-
CH_2Ph	NO_2	H	NO_2	H	H	H	iProp	OMe	CH_2-N	S-$(CH_2)_4$-

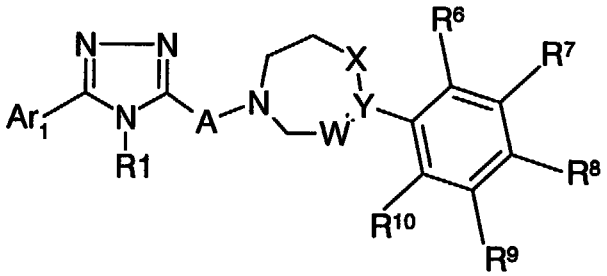
Table 8:



Ar1	R1	T	R7	Z	R9	R10	X-Y-W	A
N-Me-2-pyrrolyl-	Et	N	tBut	N	4-MeOPh	H	CH_2-N-CH_2	COO-$(CH_2)_4$-
2-Me-4-oxazolyl-	But	N	tBut	N	H	OMe	CH=C-CH_2	S-CH_2-CH=CH-CH_2-
Oxadiazol-2-yl-	Prop	N	Me	N	Pyrrolyl	H	CH_2-CH-CH_2	-$(CH_2)_4$-
Tetrazolyl-	iProp	N	tBut	N	Ph	H	CH_2-CH-CH_2	CO-$(CH_2)_3$-
N-Me-2-pyrrolyl	Prop	N	Me	CH	Pyrrolyl	H	CH=C-CH_2	CH_2-CH_2-C(CH_3)=CH-CH_2-
4-Imidazolyl-	cProp	N	nPropyl	N	tBut	H	CH_2-C=CH	NH-$(CH_2)_4$-
2-Pyrrolyl	Me	N	4-OMePh	N	Me	Me	CH_2-N-CH_2	S -$(CH_2)_8$-
N-Me-2-pyrrolyl	But	N	iProp	CH	tBut	H	CH_2-C=CH	S -$(CH_2)_3$-
N-Me-2-pyrrolyl	Me	N	tBut	N	tBut	H	CH_2-N-CH_2	S -$(CH_2)_3$-
2-Pyrrolyl	Me	N	2,4 OMe-Ph	N	Cl	H	CH_2-C=CH	CONH-$(CH_2)_4$-
2-Pyrazinyl-	$(CH_2)_4$-OMe	N	tBut	N	1-Pyrrolyl	H	CH_2-C=CH	O-$(CH_2)_3$-
2-Methylpyridin-3-yl-	CH_2Ph	CH	iProp	N	H	OMe	CH_2-N-CH_2	-$(CH_2)_4$-
2-Pyrazinyl-	cProp	CH	H	N	CH_3	OMe	CH_2-N-CH_2	-$(CH_2)_8$-
3-Br-pyrimidin-5-yl--	Et	N	Prop	N	cHex	H	CH=C-CH_2	O -$(CH_2)_4$-
Pyrimidin-3-yl-	Et	N	tBut	N	nHex	H	CH_2-C=CH	S-CH_2-C(CH_3)=CH-CH_2-
N-propyltetrazolyl-	CH_2Ph	N	iProp	N	H	OMe	CH_2-N-CH_2	S-$(CH_2)_4$-
2-Methylpyridin-3-yl-	cProp	N	H	N	CH_3	OMe	CH_2-N-CH_2	O-$(CH_2)_3$-
4-Imidazolyl--	Me	N	tBut	CH	iProp	H	CH_2-N-CH_2	S -$(CH_2)_7$-
2,5-Dimethylfuranyl-3-	cBut	N	Pyrrolyl	N	Me	H	CH_2-N-CH_2	NH-$(CH_2)_4$

N-ethylindol-3-yl-	Me	N	H	N	iProp	OMe	$CH=C-CH_2$	S $-(CH_2)_3-$
Tetrazolyl-	Et	N	tBut	N	H	CH_3	$CH_2-C=CH$	$-(CH_2)_4-$
6-Chlorobiphenyl-2	Me	CH	tBut	N	tBut	OMe	$CH=C-CH_2$	$CONH-(CH_2)_4$
4-Methylthiazole-	Me	N	4-OMePh	N	Me	Me	$CH=C-CH_2$	S $-(CH_2)_7-$
3-Thienyl-	cBut	N	CHF_2	CH	H	H	CH_2-N-CH_2	$-(CH_2)_4$
2,5-Dimethylfuranyl-3-	Me	N	Pyrrolyl	CH	Me	H	CH_2-N-CH_2	$NH-(CH_2)_4$
3-Thienyl	Me	CH	4-OMePh	N	Me	Me	CH_2-N-CH_2	$CH_2-CH_2-C(=CH_2)-CH_2-$
2-Me-4-oxazolyl	Et	N	tBut	N	Pyrrolyl	H	$CH_2-C=CH$	$S-CH_2-C(=CH_2)-CH_2-$
2-Me-4-oxazolyl-	cProp	N	tBut	CH	Me	H	CH_2-N-CH_2	$CH_2-CH_2-CH(CH_3)-CH_2$
N-propyltetrazolyl-	Me	N	CF_3	CH	Me	Butyl	CH_2-N-CH_2	$CH_2-CH_2-CH(CH_3)-CH_2$
3-Thienyl-	cProp	N	CF_3	N	Me	Butyl	CH_2-N-CH_2	$S-CH_2-CH=CH-CH_2-$
N-propyltetrazolyl-	Me	N	CF_3	N	H	H	$CH_2-CH-CH_2$	$-(CH_2)_4$
N-propyl-2-pyrrolyl-	Prop	N	Me	N	Pyrrolyl	H	CH_2-N-CH_2	$CH_2-CH_2-C(CH_3)=CH-CH_2-$
3-Benzthienyl-	iProp	N	tBut	N	Ph	H	CH_2-N-CH_2	$CH_2-CH_2-CH(CH_3)-CH_2$
5-Methylimidazol-4-yl-	Me	N	2,4 OMe-Ph	CH	Cl	H	$CH=C-CH_2$	O $-(CH_2)_3-$
2-Aminothiazol-4yl-	Prop	N	Cl	CH	iProp	H	$CH=C-CH_2$	$CH_2-CH_2-C(CH_3)=CH-CH_2-$
N-Me-2-pyrrolyl	iProp	CH	tBut	N	tBut	H	$CH_2-CH-CH_2$	S $-(CH_2)_3-$
N-propyl-2-pyrrolyl	Prop	N	Me	CH	tBut	H	$CH=C-CH_2$	$CH_2-CH_2-CH(CH_3)-CH_2$
3-Benzthienyl-	iProp	N	tBut	CH	H	Ne	CH_2-N-CH_2	$S-CH_2-C(CH_3)=CH-CH_2-$
2-Pyrrolyl	Me	CH	iProp	N	Me	H	CH_2-N-CH_2	N $-(CH_2)_3-$
2-Phenylfuran-3yl-	cProp	N	CF_3	CH	CH	CH	$CH_2-CH-CH_2$	$S-(CH_2)_3$
3-Br-pyrimidin-5-yl-	Me	CH	iProp	N	tBut	H	$CH=C-CH_2$	$CO-(CH_2)_7-$
2-Aminothiazol-4yl-	Et	N	CH	Cl	CH	CH	CH_2-N-CH_2	$CONH-(CH_2)_4-$
6 Me-benzoindol-3-yl	Me	N	iProp	CH	Furanyl	H	CH_2-N-CH_2	$CH_2-CH_2-C(CH_3)=CH-CH_2-$
2,5-Dimethylfuranyl-3-	cBut	CH	Pyrrolyl	N	Me	H	$CH_2-CH-CH_2$	$NH-(CH_2)_4$
Tetrazolyl-	iProp	N	tBut	CH	H	Cl	CH_2-N-CH_2	$CO-(CH_2)_8$
4-Imidazolyl-	$(CH_2)_4$-OMe	CH	tBut	N	H	H	CH_2-N-CH_2	$-(CH_2)_8-$
Pyrimidin-3-yl-	Et	CH	Pyrrolyl	N	cHex	H	$CH=C-CH_2$	S $-(CH_2)_4-$
4-Imidazolyl-	Me	N	iProp	N	iProp	H	$CH_2-CH-CH_2$	S $-(CH_2)_7-$
N-propyltetrazolyl-	Et	CH	tBut	N	nHex	H	CH_2-N-CH_2	$S-CH_2-C(CH_3)=CH-CH_2-$

Table 9:



Ar1	R1	R6	R7	R8	R9	R10	X-Y-W	A
2-Pyrrolyl	Prop	H	nPropyl	H	tBut	H	CH_2-CH-CH_2	S-CH_2-CH=CH-CH_2-
N-ethylindol-3-yl	-$(CH_2)_4$-OMe	H	CHF_2	H	H	H	CH_2-C=CH	S -$(CH_2)_3$-
2,5-Dimethylfuranyl-3-	iProp	H	iProp	H	2,4-OMe-Ph	Me	CH=C-CH_2	-COO-$(CH_2)_4$-
3-Br-pyrimidin-5-yl-	Me	Me	Me	H	iProp	H	CH_2-C=CH	S-CH_2-CH(CH_3)-CH_2
Pyrimidin-3-yl-	Hexyl	H	CF_3	H	tBut	H	CH=C-CH_2	S-$(CH_2)_4$-
6-Chlorobiphenyl-2-	Me	H	iProp	H	p-OMe-Ph	H	CH_2-N-CH_2	O-$(CH_2)_3$-
N-propyltetrazolyl-	Et	H	iProp	H	Me	Me	CH_2-N-CH_2	CH_2-CH_2-C(=CH_2)-CH_2-
N-methyl-2-pyrrolyl-	Et	H	iProp	H	F	OMe	CH_2-C=CH	S -$(CH_2)_7$-
3-Thienyl	-$(CH_2)_4$-OMe	H	CHF_2	H	But	H	CH_2-C=CH	S-CH_2-C(=CH_2)-CH_2-
2,5-Dimethylfuranyl-3-	cProp	OMe	tBut	CN	CF_3	H	CH_2-C=CH	CO-$(CH_2)_3$-
2-Aminothiazol-4yl-	Me	H	iProp	H	2,4-OMe-Ph	H	CH=C-CH_2	-S-CH_2-CH=CH-CH_2-
3-Benzthienyl-	Pentyl	H	Ph	C≡CH	tBut	H	CH_2-N-CH_2	CH_2-CH_2-C(CH_3)=CH-CH_2-
4-Methylthiazol-	Et	H	CHF_2	H	But	H	CH=C-CH_2	CH_2-CH_2-C(CH_3)=CH-CH_2-
3-Benzthienyl-	iProp	H	iProp	H	p-OMe-Ph	H	CH_2-C=CH	-CONH-$(CH_2)_4$
5-Methylimidazol-4-yl-	Me	But	Me	H	H	H	CH_2-N-CH_2	O-$(CH_2)_3$-
2-Aminothiazol-4yl-	Prop	H	H	C≡CH	But	H	CH_2-N-CH_2	-$(CH_2)_4$-
2-Me-4-oxazolyl-	iProp	H	CHF_2	H	H	H	CH_2-N-CH_2	S -$(CH_2)_3$-
N-Me-2-pyrrolyl	Me	H	CF_3	H	tBut	H	CH_2-C-CH_2	S -$(CH_2)_7$-

2-Me-4-oxazolyl	iProp	H	tBut	F	Ph	H	CH_2-N-CH_2	$CONH(CH_2)_4$-
2,5-Dimethylfuranyl-	Me	Me	H	CN	H	H	CH=C-CH_2	S-CH_2-CH=CH-CH_2
3-Br-pyrimidin-5-yl-	Me	H	Me	H	Et	Me	CH_2-N-CH_2	S -$(CH_2)_3$-
n-Butyltetrazolyl-	But	H	Et	CN	OH	H	CH_2-N-CH_2	-$(CH_2)_4$-
3-Benzthienyl-	Me	H	CHF_2	H	H	H	CH_2-C≡CH	S -$(CH_2)_3$-
N-Me-2-pyrrolyl	Me	H	CF_3	H	tBut	H	CH_2-C-CH_2	S -$(CH_2)_3$
Tetrazolyl-	cProp	H	iProp	H	CF_3	H	CH_2-N-CH_2	-$(CH_2)_4$-
Propyltetrazolyl-	Et	H	CF_3	H	nProp	H	CH_2-N-CH_2	-$(CH_2)_4$-
Oxadiazol-2-yl-	cProp	H	CF_3	H	H	H	CH_2-N-CH_2	-$(CH_2)_4$-
5-Ethylimidazol-4-yl-	cProp	Prop	H	C≡CH	But	H	CH_2-N-CH_2	-$(CH_2)_4$-
4-Imidazolyl-	Me	H	tBut	H	tBut	H	CH_2-N-CH_2	S-CH_2-C(=CH_2)-CH_2-
2-Pyrazinyl-	cProp	H	tBut	F	Ph	H	CH=C-CH_2	O -$(CH_2)_4$-
2-Me-4-oxazolyl-	Me	H	tBut	H	1-Pyrrolyl	H	CH_2-CH-CH_2	S-CH_2-C(CH_3)=CH-CH_2-
4-Pyrimidyl-	Et	H	Pent	H	2,4-OMe-Ph	H	CH_2-N-CH_2	
Oxadiazol-2-yl-	Hex	H	CF_3	H	tBut	H	CH_2-N-CH_2-	S-$(CH_2)_4$-

Examples of pharmacological administration forms

A) Tablets

Tablets of the following composition were molded, in a customary manner, on a compressed-tablet machine:

40 mg	of the substance of Example 1
120 mg	of corn starch
13.5 mg	of gelatin
45 mg	of lactose
2.25 mg	of Aerosil® (chemically pure silicic acid which is finely divided to the submicroscopic level)
6.75 mg	of potato starch (as a 6 % strength paste)

B) Coated tablets

20 mg	of the substance of Example 4
60 mg	of core mass
70 mg	of saccharifying mass

The core mass consists of 9 parts of corn starch, 3 parts of lactose and 1 part of vinylpyrrolidone/vinyl acetate 60:40 mixed polymer. The saccharifying mass consists of

5 parts of cane sugar, 2 parts of corn starch, 2 parts of calcium carbonate and 1 part of talc. The coated tablets which have been prepared in this way are then provided with a gastric juice-resistant coating.

Biological investigations - receptor-binding studies

1) D_3-binding test

Cloned human D_3 receptor-expressing CCL 1,3 mouse fibroblasts, which can be obtained from Res. Biochemicals Internat., One Strathmore Rd., Natick, MA 01760-2418 USA, were used for the binding studies.

Cell preparation

The D_3-expessing cells were multiplied in RPMI-1640 containing 10 % fetal calf serum (GIBCO No. 041-32400 N); 100 U/ml penicillin and 0.2 % streptomycin (GIBCO BRL, Gaithersburg, MD, USA). After 48 h, the cells were washed with PBS and incubated for 5 min with 0.05 % trypsin-containing PBS. After that, the mixture was neutralized with medium and the cells were collected by centrifuging at 300 g. In order to lyse the cells, the pellet was briefly washed with lysis buffer (5mM tris-HCl, pH 7.4, containing 10 % glycerol) and then incubated, at 4°C for 30 min, at a concentration of 10^7 cells/ml of lysis buffer. The cells were centrifuged at 200 g for 10 min and the pellet was stored in liquid nitrogen.

Binding tests

For the D_3 receptor-binding test, the membranes were suspended in incubation buffer (50 mM tris-HCl, pH 7.4, containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, 10µM quinolinol, 0.1 % of ascorbic acid and 0.1 % BSA) at a concentration of approx. 10^6 cells/250 µl of test mixture and incubated at 30°C with 0.1 nM ^{125}iodosulpiride [sic] in the presence and absence of test substance. The nonspecific binding was determined using 10^{-6}M spiperone.

After 60 min, the free and the bound radio ligand were separated by filtration through GF/B glass fiber filters (Whatman, England) on a Skatron cell collector (Skatron, Lier, Norway) and the filters were washed with ice-cold tris-HCl buffer, pH 7.4. The radioactivity which had collected on the filters was quantified using a Packard 2200 CA liquid scintillation counter.

The K_i values were determined by means of nonlinear regression analysis using the LIGAND program.

2) D_2-binding test

Cell culture

HEK-293 cells, possessing stably expressed human dopamine D2A receptors, were cultured in RPMI 1640 containing Glutamax I™ and 25 mM HEPES containing 10% fetal calf serum albumin. All the media contained 100 units of pencillin per ml and

100 µg/ml streptomycin. The cells were kept at 37°C in a moist atmosphere containing 5% CO_2.

The cells were prepared for the binding studies by being trypsinized (0.05% trypsin solution) at room temperature for 3-5 minutes. After that, the cells were centrifuged at 250 g for 10 minutes and treated, at 4°C for 30 minutes, with lysis buffer (5 mM tris-HCl, 10% glycerol, pH 7.4). Following centrifugation at 250 g for 10 minutes, the residue was stored at -20°C until used.

Receptor binding tests

1) Dopamine D_2 receptor "low affinity state" using ^{125}I-spiperone (81 TBq/mmol, Du Pont de Nemours, Dreieich)

The mixtures (1 ml) were composed of 1 x 10^5 cells in incubation buffer (50 mM tris, 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$ and 2 mM $CaCl_2$, pH 7.4 with HCl) and 0.1 nM ^{125}I-spiperone (total binding) or, in addition, 1 µM haloperidol (nonspecific binding) or test substance.

After having been incubated at 25°C for 60 minutes, the mixtures were filtered through GF/B glass fiber filters (Whatman, England) on a Skatron cell collector (from Zinsser, Frankfurt) and the filters were washed with ice-cold 50 mM tris-HCl buffer, pH 7.4. The radioactivity which had collected on the filters was quantified using a Packard 2200 CA liquid scintillation counter.

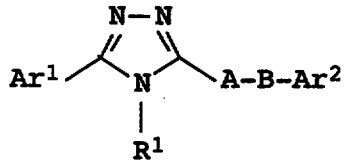
The evaluation was carried out as described under a).

The K_i values were determined by means of nonlinear regression analysis using the LIGAND program or by converting the IC_{50} values with the aid of the formula of Cheng and Prusoff.

In these tests, the novel compounds exhibit very good affinities for the D_3 receptor (<1 µmolar, in particular <100 molar) and high selectivities in relation to the D_3 receptor.

We claim:

1. A triazole compound of the formula I



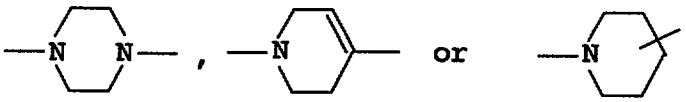
(I)

where

Ar^1 is phenyl, naphthyl or a 5- or 6-membered heterocyclic aromatic ring having from 1 to 4 heteroatoms which are selected, independently of each other, from O, S and N, where Ar^1 may have 1, 2, 3 or 4 substituents which are selected, independently of each other, from C_1-C_6-alkyl, which may be substituted by OH, OC_1-C_6-alkyl, halogen or phenyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_6-cycloalkyl, halogen, CN, $COOR^2$, NR^2R^2, NO_2, SO_2R^2, $SO_2NR^2R^2$ and phenyl, which may be substituted by C_1-C_6-alkyl, OC_1-C_6-alkyl, NR^2R^2, CN, CF_3, CHF_2, or halogen, and where the heterocyclic, aromatic ring mentioned may also be fused to a phenyl ring;

A is straight-chain or branched C_4-C_{10}-alkylene or straight-chain or branched C_3-C_{10}-alkylene which comprises at least one Z group which is selected from O, S, NR^2, $CONR^2$, COO, CO, or a double or triple bond,

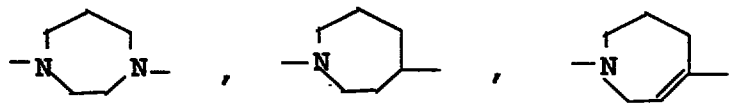
B is a radical of the formula:



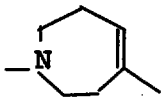
or if Ar^1 is the 5- or 6-membered heterocyclic aromatic ring which can be substituted as above, B is also a radical of the formulae

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or



* C L M S *

Ar^2 is phenyl, pyridyl, pyrimidinyl or triazinyl, where Ar^2 may have from one to four substituents which are selected, independently of each other, from OR^2, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-C_1-C_6-alkyl, halogen-C_1-C_6-alkoxy, halogen, CN, NO_2, SO_2R^2, NR^2R^2, $SO_2NR^2R^2$, a 5- or 6-membered carbocyclic, aromatic or non-aromatic ring and a 5- or 6-membered, heterocyclic aromatic or non-aromatic ring having 1 or 2 heteroatoms which are selected from O, S and N, where the carbocyclic or heterocyclic ring may be substituted by C_1-C_6-alkyl, phenyl, phenoxy, halogen, OC_1-C_6-alkyl, OH, NO_2 or CF_3 and/or fused to a phenyl ring and where Ar^2 may be fused to a carbocyclic, aromatic or non-aromatic ring and a 5- or 6-membered, heterocyclic aromatic or non-aromatic ring having 1 or 2 heteroatoms which are selected from O, S and N,

R^1 is H, C_3-C_6-cycloalkyl or C_1-C_6-alkyl which may be substituted by OH, OC_1-C_6-alkyl or phenyl;

the radicals R^2, which can be identical or different, are H or C_1-C_6-alkyl, which may be substituted by OH, OC_1-C_6-alkyl or phenyl;

and their salts with physiologically tolerated acids.

2. A compound of the formula I as claimed in claim 1, where

Ar^1 is phenyl, naphthyl or a 5- or 6-membered heterocyclic aromatic ring having from 1 to 3 heteroatoms which are selected from O, S and N, where Ar^1 may have 1, 2, 3 or 4 substituents which are selected, independently of each other, from C_1-C_6-alkyl, which may be substituted by OH, OC_1-C_6-alkyl, halogen or phenyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_6-cycloalkyl, halogen, CN, $COOR^2$, NR^2R^2, NO_2, SO_2R^2, $SO_2NR^2R^2$ or phenyl, which may be substituted by C_1-C_6-alkyl, OC_1-C_6-alkyl, NR^2R^2, CN,

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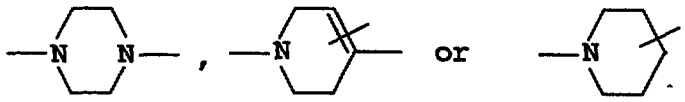


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CF_3, CHF_2, or halogen, and where the heterocyclic, aromatic ring mentioned may be fused to a phenyl ring;

A is straight-chain or branched C_4-C_{10}-alkylene or straight-chain or branched C_3-C_{10}-alkylene which comprises at least one group which is selected from O, S, NR^2, $CONR^2$, COO, CO, or a double or triple bond,

B is a radical of the formula:



Ar^2 is phenyl, pyridyl, pyrimidinyl or triazinyl, where Ar^2 may have from one to four substituents which are selected, independently of each other, from OR^2, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-C_1-C_6-alkyl, halogen-C_1-C_6-alkoxy, halogen, CN, NO_2, SO_2R^2, NR^2R^2, $SO_2NR^2R^2$, a 5- or 6-membered carbocyclic, aromatic or non-aromatic ring and a 5- or 6-membered, heterocyclic aromatic or non-aromatic ring having 1 or 2 heteroatoms which are selected from O, S and N, where the carbocyclic or heterocyclic ring may be substituted by C_1-C_6-alkyl, phenyl, phenoxy, halogen, OC_1-C_6-alkyl, OH, NO_2 or CF_3 and where Ar^2 may be fused to a carbocyclic or heterocyclic ring of the above-defined nature,

R^1 is H, C_3-C_6-cycloalkyl or C_1-C_6-alkyl which may be substituted by OH, OC_1-C_6-alkyl or phenyl;

the radicals R^2, which can be identical or different, are H or C_1-C_6-alkyl, which may be substituted by OH, OC_1-C_6-alkyl or phenyl;

and their salts with physiologically tolerated acids.

3. A compound of the formula I as claimed in claim 1 or 2, where A is C_4-C_{10}-alkylene or C_3-C_{10}-alkylene which may comprise at least one Z group which is selected from O, S and a double or triple bond.

4. A compound of the formula I as claimed in one of the preceding claims, where Ar^1 is phenyl, naphthyl, pyrrolyl, thienyl, furanyl, thiazolyl, imidazolyl, oxazolyl,

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oxadiazolyl, tetrazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyrimidinyl, benzthiophenyl, indolyl or benzofuranyl, where Ar^1 can, as indicated in claim 1, be substituted or fused.

5. A compound of the formula I as claimed in claim 4, where Ar^1 is phenyl, thienyl, furanyl, tetrazolyl, pyrrolyl or pyrazinyl and can, as indicated in claim 1, be substituted.

6. A compound of the formula I as claimed in one of the preceding claims, where Ar^1 is unsubstituted or has 1, 2, 3 or 4 substituents which are selected, independently of each other, from CN, C_1-C_6-alkyl, OH, OC_1-C_6-alkyl, phenyl and halogen.

7. A compound of the formula I as claimed in one of the preceding claims, where R^1 is H, C_1-C_6-alkyl or C_3-C_6-cycloalkyl.

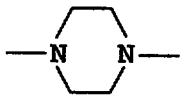
8. A compound of the formula I as claimed in one of the preceding claims, where Ar^2 is phenyl, pyridinyl or pyrimidinyl which may have one or two substituents which are selected, independently of each other, from C_1-C_6-alkyl, C_2-C_6-alkynyl, halogen, CN, haloalkyl, Oalkyl, NO_2, phenyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, indolyl, cyclopentyl and cyclohexyl.

9. A compound of a formula I as claimed in claim 8, wherein the substituent(s) is/are selected, independently of each other, from C_1-C_6-alkyl, phenyl, NO_2, and halogenoalkyl, in particular CF_3, CHF_2 and CF_2Cl.

10. A compound of the formula I as claimed in claim 1, where

Ar^1 is phenyl which may be substituted by C_1-C_6-alkyl, OC_1-C_6-alkyl, CN, phenyl or halogen;

A has the meanings given in claim 2;

B is  and

Ar^2 is pyrimidinyl which may be substituted by C_1-C_6-alkyl, halogen-C_1-C_6-alkyl, halogen-C_1-C_6-alkoxy, pyrrolyl or indolyl.

11. A compound of the formula I as claimed in claim 10, where

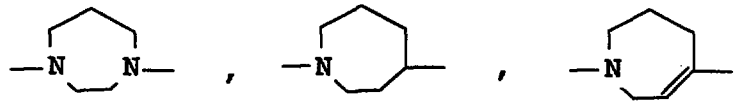
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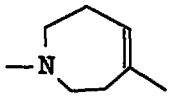
Ar^1 is phenyl which may be substituted by C_1-C_6-alkyl, OC_1-C_6-alkyl or halogen, and

A is $-S(CH_2)_{3-10}-$ or $-(CH_2)_{4-10}-$.

12. A compound of the formula I as claimed in one of claims 1 to 9, where Ar^1 is a 5- or 6-membered heterocyclic aromatic ring having from 1 to 4 heteroatoms which are selected, independently of each other, from O, S and N, where the ring can, as indicated in claim 1, be substituted or fused, B is



or

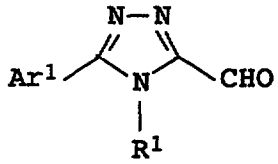


and A and Ar^2 have the meanings given in claim 1.

13. A pharmaceutical which comprises at least one compound as claimed in one of claims 1 to 12, with or without physiologically acceptable carrier substances and/or auxiliary substances.

14. The use of at least one compound as claimed in one of claims 1 to 12 for preparing a pharmaceutical for the treatment of diseases which respond to dopamine D_3 receptor antagonists or dopamine D_3 agonists.

15. A compound of the formula VIII



(VIII)

where Ar^1 and R^1 have the meanings given in one of the claims 1, 2, 4 to 7, 10 and 11.

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