WO00/42036 *166166* PCT/EP00/00177

TRIAZOLE COMPOUNDS WITH DOPAMINE D3 RECEPTOR AFFINITY

The invention relates to triazole compounds and to the use of these compounds. These compounds possess valuable therapeutic properties and can be used for treating diseases which respond to the influence of dopamine D_3 receptor ligands.

Compounds of the type which is under discussion here and which possess physiological activity are already known. Thus, WO 94/25013; 96/02520; 97/43262; 97/47602; 98/06699; 98/49145; 98/50363; 98/50364 and 98/51671 describe compounds which act on the dopamine receptors. DE 44 25 144 A, WO 96/30333, WO 97/25324, WO 97/40015, WO 97/47602, WO 97/17326, EP 887 350, EP 779 284 A and Bioorg. & Med. Chem. Letters 9 (1999) 2059-2064 disclose further compounds which possess activity as dopamine D_3 receptor ligands. US 4,338,453; 4,408,049 and 4,577,020 disclose triazole compounds which possess antiallergic or antipsychotic activity. WO 93/08799 and WO 94/25013 describe compounds of the type which is under discussion here and which constitute endothelin receptor antagonists. Additional triazole compounds, which inhibit blood platelet aggregation and which have a hypotensive effect are described in *Pharmazie* 46 (1991), 109-112. Further triazole compounds which possess physiological activity are disclosed in EP 691 342, EP 556 119, WO 97/10210, WO 98/24791, WO 96/31512 and WO 92/20655.

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

A number of facts about the presence of dopamine, and its physiological function as a neuron transmitter, are known with certainty. Disturbances of the dopaminergic

transmitter system result in diseases such as schizophrenia, depression and Parkinson's disease. These, and other, diseases are treated with drugs which interact with the dopamine receptors.

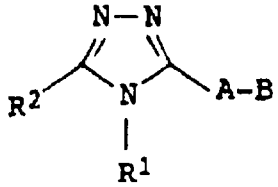
By 1990, two subtypes of dopamine receptor had been clearly defined pharmacologically, namely the D_1 and D_2 receptors.

More recently, a third subtype has been found, namely the D_3 receptor, which appears to mediate some of the effects of the antipsychotic and anti-Parkinson agents (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; M. Dooley et al., Drugs and Aging 1998, 12, 495-514).

Since D_3 receptors are chiefly expressed in the limbic system, it is assumed that while a selective D_3 ligand would probably have the properties of known antipsychotic agents, it would not have their dopamine D_2 receptor-mediated neurological side-effects (P. Sokoloff et al., Localization and Function of the D_3 Dopamine Receptor, Arzneim. Forsch./Drug Res. 42(1), 224 (1992); P. Sokoloff 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 consequently selective D_3 ligands.

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



(I)

where

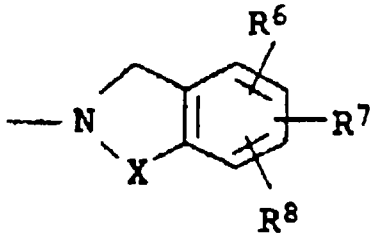
R^1 is H, C_1-C_6-alkyl, which may be substituted by OH, OC_1-C_6-alkyl, halogen or phenyl, C_3-C_6-cycloalkyl or phenyl;

R^2 is H, 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_1-C_6-alkylthio, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_6-cycloalkyl, halogen, CN, $COOR^3$, $CONR^3R^4$, NR^3R^4, SO_2R^3, $SO_2NR^3R^4$ or an aromatic radical which is selected from phenyl, naphthyl and a 5- or 6-membered heterocyclic radical having 1, 2, 3 or 4 heteroatoms which are selected, independently of each other, from O, N and S, with it being possible for the aromatic radical to have one or two 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, COR^3, NR^3R^4, NO_2, SO_2R^3, $SO_2NR^3R^4$ and phenyl which may be substituted by one or two radicals which are selected, independently of each other, from C_1-C_6-alkyl, C_1-C_6-alkoxy, NR^3R^4, CN, CF_3, CHF_2 or halogen;

R^3 and R^4 are, independently of each other, H, C_1-C_6-alkyl, which may be substituted by OH, OC_1-C_6-alkyl, halogen or phenyl, or phenyl;

A is C_4-C_{10}-alkylene or C_3-C_{10}-alkylene which comprises at least one group Z which is selected from O, S, $CONR^3$, COO, CO, C_3-C_6-cycloalkyl and a double or triple bond;

B is a radical of the following formula:



where

X is CH_2 or CH_2CH_2;

R^6, R^7 and R^8 are, independently of each other, selected from H, C_1-C_6-alkyl, which may be substituted by OH, OC_1-C_6-alkyl, which may be substituted by amino, mono- or di-C_1-C_4-alkylamino, C_1-C_6-alkylthio, halogen or phenyl, OH, C_1-C_6-alkoxy, OCF_3, OSO_2CF_3, SH, C_1-C_6-alkylthio, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halogen, CN, NO_2, CO_2R^3, SO_2R^3, $SO_2NR^3R^4$, where R^3 and R^4 have the abovementioned meanings and may also form together with the N atom to which they are bonded a saturated or unsaturated heterocycle with 5 to 7 ring atoms and 1 or 2 N and/or O heteroatoms, $CONR^3R^4$, $NHSO_2R^3$, NR^3R^4, a 5- or 6-membered carbocyclic, aromatic or nonaromatic ring and a 5- or 6-membered heterocyclic, aromatic or nonaromatic ring with 1 or 2 heteroatoms which are selected, independently of each other, from O, N and S, with the carbocyclic or heterocyclic ring being able to have one or two substituents which are selected, independently of each other, from C_1-C_6-alkyl, phenyl, phenoxy, halogen, C_1-C_6-alkoxy, OH, NO_2, CF_3 and CHF_2, and with two of the substituents R^6, R^7 and R^8 being able to form, together with the carbon atoms of the phenyl ring to which they are bonded, a phenyl, cyclopentyl or cyclohexyl ring which is fused to the phenyl ring, in which one or two of the CH or CH_2 groups can be replaced by a nitrogen atom or an NH or N-(C_1-C_6-alkyl) group;

and the salts thereof with physiologically tolerated acids.

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The compounds according to the invention are selective dopamine D_3 receptor ligands which act in the limbic system in a regioselective manner and which, as a result of their low affinity for the D_2 receptor, have fewer side-effects than do the classic neuroleptic agents, which are D_2 receptor antagonists. The compounds can therefore be used for treating diseases which respond to dopamine D_3 ligands, i.e. they are effective for treating those diseases in which affecting (modulating) the dopamine D_3 receptors leads to an improvement in the clinical picture or to the disease being cured. Examples of such diseases are diseases of the cardiovascular system and the kidneys, diseases of the central nervous system, in particular schizophrenia, affective disorders, neurotic stress and somatoform disorders, psychoses, Parkinsonism, attention deficit disorders, hyperactivity in children, epilepsy, amnesic and cognitive disorders such as learning and memory impairment (impaired cognitive function), anxiety states, dementia, delirium, personality disorders, sleep disturbances (for example restless legs syndrome), disorders of the sex life (male impotence), eating disorders and addictive disorders. The compounds are also suitable for treating stroke.

Addictive disorders include the psychological disorders and behavioral disturbances caused by the abuse of psychotropic substances such as pharmaceuticals or drugs, and other addictive disorders such as, for example, compulsive gambling (impulse control disorders not elsewhere classified). Addictive substances are, for example: opioids (for example morphine, heroin, codeine); cocaine; nicotine; alcohol; substances which interact with the GABA chloride channel complex, sedatives, hypnotics or tranquilizers, for example benzodiazepines; LSD; cannabinoids; psychomotor stimulants such as 3,4-methylenedioxy-N-methyl-

amphetamine (ecstasy); amphetamine and amphetamine-like substances such as methylphenidate or other stimultants including caffeine. Addictive substances of particular concern are opioids, cocaine, amphetamine or amphetamine-like substances, nicotine and alcohol.

The compounds according to the invention are preferably used for treating affective disorders; neurotic, stress and somatoform disorders and psychoses, for example schizophrenia.

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

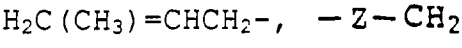
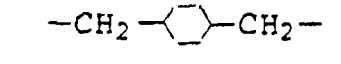
Alkyl (also in radicals such as alkoxy, alkylthio, alkylamino etc.) is a straight-chain or branched alkyl group having from 1 to 6 carbon atoms and, in particular from 1 to 4 carbon atoms. The alkyl group can have one or more substituents which are selected, independently of each other, from OH, OC_1-C_6-alkyl,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

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 a 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 four 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.

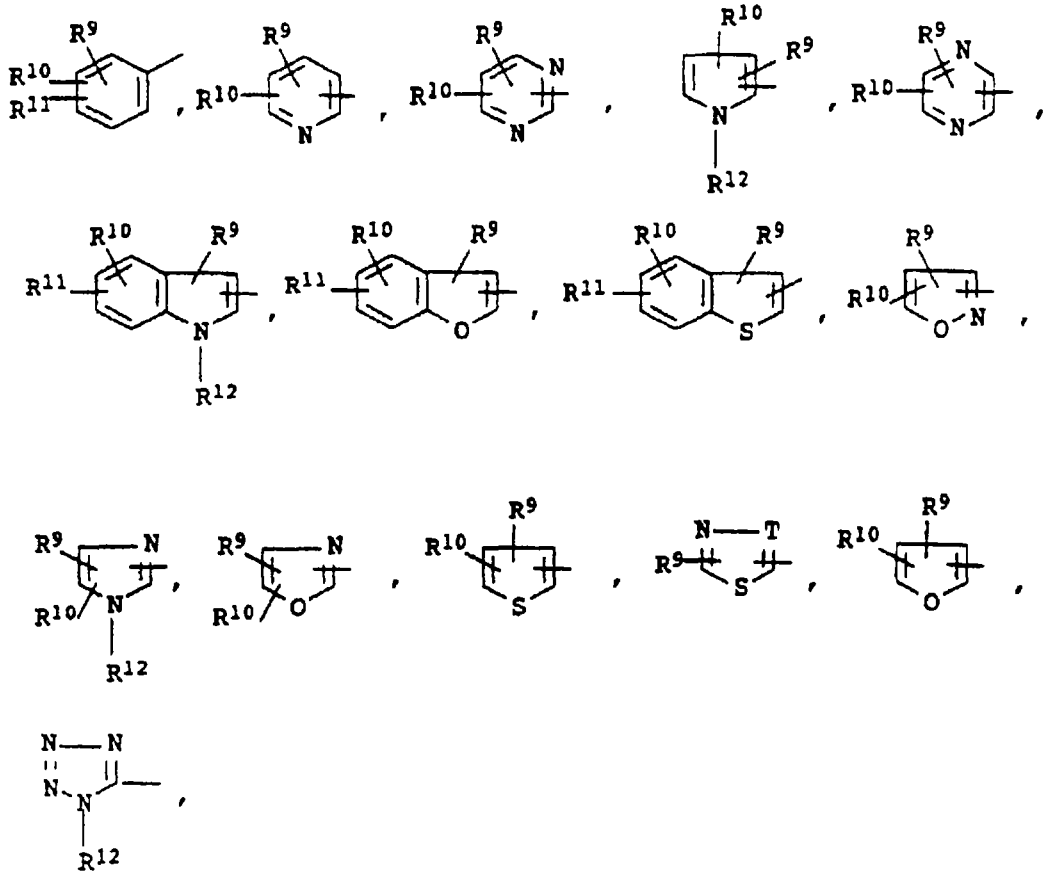
If the alkylene groups comprise at least one of the Z groups, this or these groups can then be arranged in the alkylene chain at an arbitrary site or in position 1 or 2 of the A group (seen from the triazole radical). The radicals $CONR^2$ and COO are preferably arranged such that the carbonyl group is in each case facing the triazole ring. Particular preference is given to the 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-$CH_2CH(CH_3)CH_2$- 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. Preference is additionally given to A being -$(CH_2)_4$-, -$(CH_2)_5$-, -CH_2CH_2CH=$CHCH_2$-, , -$CH_2CH_2C(CH_3)$=$CHCH_2$- or -$CH_2CH_2CH(CH_3)CH_2$-.

Halogen is F, Cl, Br or I, preferably F or Cl.

X is preferably -CH_2-CH_2-.

R^1 is preferably H, C_1-C_6-alkyl or C_3-C_6-cycloalkyl.

If R^2 is an aromatic radical, this radical is then preferably one of the following radicals:



where

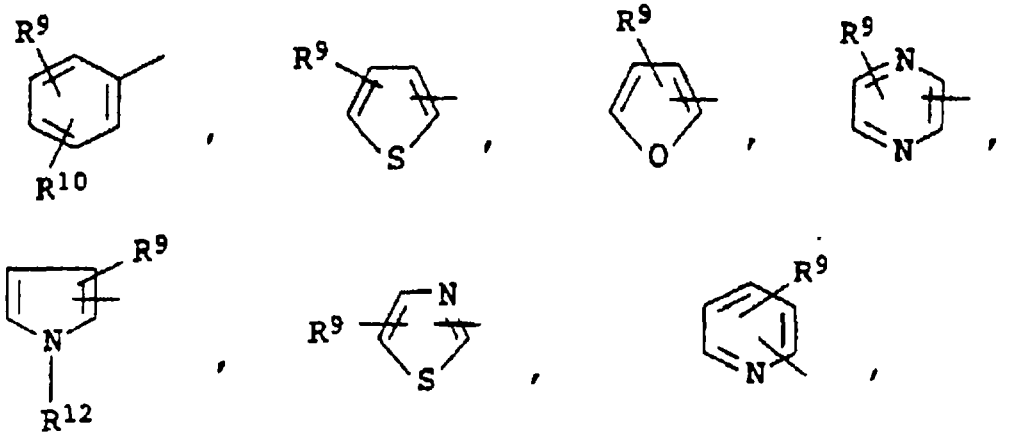
R^9 to R^{11} are H or the abovementioned substituents of the aromatic radical,

R^{12} is H, C_1-C_6-alkyl or phenyl, and

T is N or CH.

If the phenyl radical is substituted, the substituents are preferably in the m position or the p position.

The aromatic radical is particularly preferably a group of the formula:



where R^9, R^{10} and R^{12} have the abovementioned meanings. The indicated phenyl, pyridine, thiazolyl and pyrrole radicals are particularly preferred.

The radicals R^9 to R^{11} are preferably H, C_1-C_6-alkyl, OR^3, CN, phenyl, which may be substituted by C_1-C_6-alkyl, C_1-C_6-alkoxy or halogen, CF_3 and halogen, and are, in particular, H, C_1-C_6-alkyl, OR^3 and halogen. In this context, R^3 has the abovementioned meanings.

Particularly preferably, R^2 is H, C_1-C_6-alkyl, NR^3R^4 (R^3 and R^4 are, independently of each other, H or C_1-C_6-alkyl), phenyl or a 5-membered aromatic heterocyclic radical which has 1 or 2 heteroatoms which are independently selected from N, S and O. The heterocyclic radical is preferably a pyrrole radical or a pyridine radical.

A is preferably C_4-C_{10}-alkylene or C_3-C_{10}-alkylene which comprises at least one group Z which is selected from O, S, COO, CO, a double bond and cyclohexyl.

Preferably, at least one of the radicals R^6, R^7 and R^8 is H.

The radicals R^6, R^7 and R^8 are preferably, and independently of each other, selected from H, C_1-C_6-alkyl, OH, C_1-C_6-alkoxy, C_1-C_6-alkylthio-C_1-C_6-alkyl,

halogen, CN, NO_2, SO_2R^3, $SO_2NR^3R^4$ and $CONR^3R^4$. Particularly preferably, the fused phenyl group has one or two substituents, i.e. one or two of the radicals R^6, R^7 and R^8 is/are C_1-C_6-alkyl, halogen, CN, NO_2, SO_2R^3 and, in particular, $SO_2NR^3R^4$, where R^3 and R^4, together with the N atom to which they are attached, can also be a 5-, 6- or 7-membered heterocycle which, in addition to the nitrogen atom, can also possess one or two additional heteroatoms, selected from N, O or S, and/or be substituted, e.g. can be pyrrolidine, piperidine, morpholine or azepine.

If one of the radicals R^6, R^7 and R^8 is a 5- or 6-membered heterocyclic ring, this 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.

If one of the radicals R^6, R^7 and R^8 is a carbocyclic radical, this radical is then, in particular, a phenyl, cyclopentyl or cyclohexyl radical.

Particular preference is given to the compounds of formula I where

R^1 is H, C_1-C_6-alkyl or phenyl,
R^2 is H, C_1-C_6-alkyl, phenyl, thienyl, furanyl, pyridyl, pyrrolyl, thiazolyl or pyrazinyl,
A is -SC_3-C_{10}-alkylene which may comprise a double bond, and
R^6, R^7 and R^8 are selected from H, C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, $SO_2NR^3R^4$, CN, NO_2, CF_3, $CONR^3R^4$, CHF_2, OSO_2CF_3, OCF_3 and $NHSO_2$-C_1-C_6-alkyl,
here is X particularly preferably CH_2CH_2.

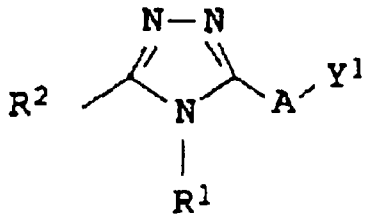
The invention also encompasses the acid addition salts of the compounds of the formula I with physiologically

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 acids which can be used are described in Fortschritte der Arzneimittelforschung [Advances in pharmaceutical research], Volume 10, pages 224 ff., Birkhauser Verlag, Basle and Stuttgart, 1966.

The compounds of the formula I can exhibit one or more centers of asymmetry. The invention therefore includes not only the racemates but also the relevant enantiomers and diastereomers. The respective tautomeric forms are also included in the invention.

The process for preparing the compounds of the formula I consist in

a) reacting a compound of the formula (II)



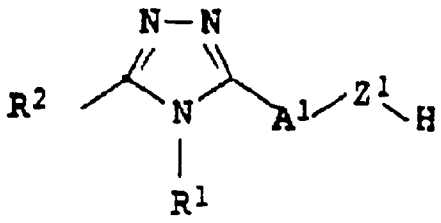
(II)

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

HB (III);

or

b) reacting a compound of the formula (IV)



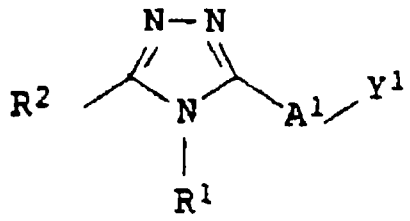
(IV)

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

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

where Y^1 has the abovementioned meaning and A^2 is C_2-C_{10}-alkylene, with A^1 and A^2 together having from 3 to 10 C atoms and A^1 and/or A^2 where appropriate comprising at least one group Z; or

c) reacting a compound of the formula (VI)



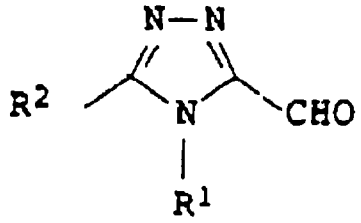
(VI)

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

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

where Z^1 has the abovementioned meanings; or

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

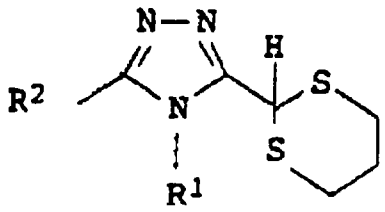


(VIII)

using reagents which are known from the literature, such as 1,3-propanedithiol, KCN/water, TMSCN (trimethylsilyl cyanide) 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)



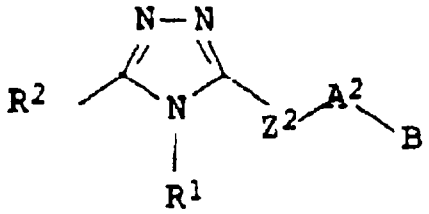
(VIIIa)

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

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

where Y^1 has the abovementioned meaning and A^3 is C_3-C_9-alkylene which can contain a group Z,

with compounds of the formula (Ia)



(Ia)

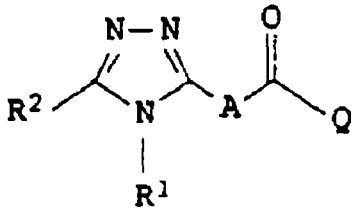
where Z^2 is CO or a methylene group, and Z^2 and A^2 have together from 4 to 10 C atoms, being obtained after deprotecting or reducing, or

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

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

where Y^2 is a phosphorane or a phosphonic ester, in analogy with customary methods, as described, for example, in Houben Weyl *"Handbuch der Organischen Chemie"* [Textbook of Organic Chemistry], 4th Edition, Thieme Verlag Stuttgart, Volume V/1b p. 383 ff, or Vol. V/1c p. 575 ff, or

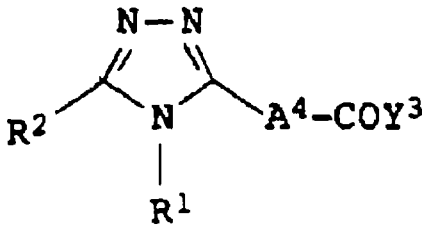
f) reacting a compound of the formula (XI)



(XI)

where Q is H or OH, with a compound of the formula III under reductive conditions in analogy with methods known from the literature, for example as described in *J. Org. Chem.* **1986**, 50, 1927; or WO 92/20655.

The process for preparing a compound of the formula I where A comprises the group COO or $CONR^3$ consists in reacting a compound of the formula (XII)



(XII)

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

$$B - A - Z^3 \qquad \text{(XIII)}$$

where Z^3 is OH or NHR^3

Compounds of the formula B-H can be prepared as described, for example, in

Synth. Commun. **1984**, 14, 1221
S. Smith et al., *Bioorg. Med. Chem. Lett.* **1998**, 8, 2859;
WO 97/47602 or WO 920655, or
J. Med. Chem. **1987**, 30, 2111 and 2208 and **1999**, 42, 118.

The compounds of the formula (IV) type are either known or can be prepared using known methods, as described, for example, in 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 which is cited therein, or in S. Kubota et al. *Chem. Pharm. Bull.* **1975**, 23, 955 or Vosilevskii et al. Izv. Akad. Nauk. SSSR Ser. Khim. **1975**, 23, 955.

In the above formulae, R^1, R^2, R^6, R^7, R^8, A, B and X have the meanings given in connection with formula I.

The compounds according to the invention, and the starting materials and the intermediates, can also be prepared in analogy with the methods which are described in the patent publications which were mentioned at the outset.

The above-described reactions are generally effected in a solvent at temperatures of 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, acetonitrile, ketones, such as acetone or methyl ethyl ketone, or alcohols, such as ethanol or butanol.

If desired, the reactions can be carried out in the presence of an acid-binding agent. Suitable acid-binding agents are inorganic bases, such as sodium carbonate or potassium carbonate, or sodium hydrogencarbonate or potassium hydrogencarbonate, sodium methoxide, sodium ethoxide, sodium hydride, or organometallic compounds, such as butyl lithium or alkyl magnesium compounds, or organic bases, such as triethylamine or pyridine. The latter can also simultaneously serve as the solvent.

Process (f) is effected under reducing conditions, e.g. using sodium borohydride, sodium cyanoborohydride or triacetoxy borohydride, where appropriate in an acid medium or in the presence of a Lewis acid, such as zinc chloride, or by way of catalytic hydrogenation.

The crude product is isolated in a customary manner, for example by means of filtering, distilling off the solvent or 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 converting into an acid addition compound.

The acid addition salts are prepared in a customary manner by mixing the free base with the corresponding 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 tert-butyl ether, a ketone, such as acetone or methyl ethyl ketone, or an ester, such as ethyl acetate.

For treating the abovementioned diseases, the compounds according to the invention are administered orally or parenterally (subcutaneously, intravenously, intramuscularly or intraperitoneally) in a customary manner. The administration can also be effected through the nasopharyngeal space using vapors or sprays.

The dosage depends on the age, condition and weight of the patient and on the type of administration. As a rule, the daily dose of active compound is from about 10 to 1000 mg per patient and day when administered orally and from about 1 to about 500 mg per patient and day when administered parenterally.

The invention also relates to pharmaceuticals which comprise the compounds according to the invention. In the customary pharmacological administration forms, these pharmaceuticals are present in solid or liquid form, for example as tablets, film tablets, capsules, powders, granules, sugar-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, flow-regulating agents, plasticizers, wetting agents, dispersants, emulsifiers, solvents, retarding agents, antioxidants and/or propellent gases (cf. H. Sucker et

al., Pharmazeutische Technologie, 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

6,7-Dimethoxy-2-{3-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline

1A Preparation of the starting materials

2-(3-Chloropropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

7.2 g (37 mmol) of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline were heated together with 4.05 ml (40 mmol) of 1-bromo-3-chloropropane, 11.3 g (81 mmol) of potassium carbonate and 610 mg (40 mmol) of sodium iodide in 250 ml of acetonitrile with stirring at 70°C for four hours. After the reaction was complete, the solvent was distilled off, and the residue was taken up in water and extracted with methylene chloride. The combined organic phases were dried and concentrated, and the crude product was purified by chromatography on silica gel (mobile phase: methylene chloride/methanol = 9/1).

4.8 g (45% of theory) of a yellowish oil were obtained.

^{1}H-NMR ($CDCl_3$): δ = 2.0 (m, 2H); 2.6-2.8 (m, 6H); 3.5 (s, 2H); 3.6 (t, 2H); 3.8 (2s, 6H); 6.5 (s, 1H); 5.6 (s, 1H).

$C_{14}H_{20}ClNO_2$ (269)

1B Preparation of the final product

380 mg (1.7 mmol) of 3-mercapto-4-methyl-5-phenyl-1,2,4(4H)-triazole were heated with 450 mg (1.7 mmol) of the chlorinated base 1A and 40 mg (1.7 mmol) of lithium hydroxide in 5 ml of DMF while stirring at 100°C for five hours. Workup entailed addition of 50 ml of water, extraction several times with methyl tert-butyl ether, drying of the combined organic phases, evaporation and purification by chromatography on silica gel (mobile phase: methylene chloride/2-5% methanol).
Yield: 0.2 g (49% of theory)

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.6 (m, 2H); 2.7 (m, 2H); 2.8 (m, 2H); 3.3 (t, 2H); 3.5 (m, 2H); 3.6 (s, 3H); 3.8 (2s, 6H); 6.3 (s, 1H); 6.5 (s, 1H); 7.5 (m, 3H); 7.8 (m, 2H).

The title compound was obtained by treatment with ethereal hydrochloric acid
$C_{23}H_{28}N_4O_2S$ x HCl
Melting point: 180-183°C

Example 2
6-Methoxy-2-{3-[(4-methyl-5-pyrrol-2-yl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline

2A Preparation of the starting compound
2-(3-Chloropropyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline

The above substance was prepared using 6-methoxy-1,2,3,4-tetrahydroisoquinoline in a manner analogous to 1A.

^{1}H-NMR ($CDCl_3$): δ = 2.0 (q, 2H); 2.5-2.6 (m, 4H); 2.9 (m, 2H); 3.5 (s, 2H); 3.6 (m, 2H); 3.8 (s, 3H); 6.6 (δ, 1H); 6.7 (dd, 1H); 6.9 (δ, 1H).

2B Preparation of the final product

Preparation took place in analogy to Example 1 by reacting the chlorinated base prepared in 2A with 3-mercapto-4-methyl-5-(2-pyrrolyl)-1,2,4(4H)-triazole.
Yield: 52% of theory.
$C_{20}H_{25}N_5OS$ (383.5)
Melting point: 179-181°C

Example 3
2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-6-methoxy-1,2,3,4-tetrahydroisoquinoline

3A Preparation of the starting material

3-(3-Chloropropylmercapto)-4-methyl-5-phenyl-1,2,4(4H)-triazole

A suspension of 2.6 g (16.5 mmol) of 1-bromo-3-chloropropane, 0.22 g (1.5 mmol) of sodium iodide, 2.7 g (15 mmol) of 3-mercapto-4-methyl-5-phenyl-1,2,4(4H)-triazole and 2.1 g (15 mmol) of potassium carbonate in 70 ml of ethanol were heated to boiling for one hour. After hot filtration, the filtrate was concentrated, taken up in water and extracted with dichloromethane. The combined organic phases were dried, filtered and concentrated, and the residue was chromatographed (mobile phase: methylene chloride/2% methanol).
Yield: 1.35 g (34% of theory) of white solid

^{1}H-NMR ($CDCl_3$): δ = 2.3 (q, 2H); 3.4 (t, 2H); 3.6 (s, 3H); 3.7 (t, 2H); 7.5-7.7 (m, 5H).

$C_{12}H_{14}ClN_3S$ (267.8)

Melting point: 137-141°C

3B Preparation of the final product

0.7 g (2.5 mmol) of compound 3A described above was stirred with 0.6 g (2.5 mmol) of 6-methoxy-1,2,3,4-tetrahydroisoquinoline oxalic acid salt in the presence of 1.1 ml (7.5 mmol) of triethylamine and catalytic amounts of sodium iodide in 6 ml of butanol at 120°C for four hours. After the reaction was complete it was worked up by extraction with water and methyl tert-butyl ether, drying over sodium sulfate and concentrating, and the crude product was chromatographed on silica gel (mobile phase: methylene chloride with 0-3% methanol). 110 mg of a white solid were isolated.

$C_{22}H_{26}N_4OS$ (394.5) MS (m/z): 395 $[M]^+$

Example 4

2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(piperidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

4A Preparation of N-acetyl-7-(piperidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

21.1 g (77 mmol) of 2-acetyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride (prepared as described in G. Grunewald et al. J. Med. Chem 1999, 42, 118-134) in 50 ml of THF were added dropwise to a solution of 6.0 g (70 mmol) of piperidine and 10.9 g (84 mmol) of diisopropylethylamine in 230 ml of THF, and the mixture was heated under reflux for two hours. After the reaction was complete, the solvent was removed in vacuo, the residue was taken up in dichloromethane/water and, after making alkaline with 10% strength sodium hydroxide solution and separating the phases, the organic phase was dried over sodium

sulfate. The crude product remaining after filtration and removal of the solvent was purified by column chromatography on silica gel (mobile phase: methylene chloride with 3% methanol).
Yield: 18.6 g (57.6 mmol); 82%
Melting point:171-174°C

4B 7-(Piperidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

The compound described above was heated to boiling with 50% concentrated hydrochloric acid for two hours. The product formed a white precipitate on cooling. The residue was isolated, washed with water, digested in diethyl ether and dried in vacuo.
Yield: 12.1 g (38.2 mmol) 56% of theory

4C 2-(3-Chloropropyl)-7-(piperidin-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

12.1 g (38.2 mmol) of 7-(piperidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline and 8.4 g (84 mmol) of triethylamine were dissolved in DMF at 40°C, 9.0 g (57.2 mmol) of 1-bromo-3-chloropropane were added dropwise, and the mixture was stirred at 50°C for 7 h. For workup, the mixture was concentrated, and the residue was taken up in water and extracted with dichloromethane. Drying over sodium sulfate, filtration and removal of the solvent were followed by purification by chromatography (silica gel; mobile phase: methylene chloride with 3% methanol) to result in 11.7 g (323.7 mmol) of a yellowish oil.
Yield: 86% of theory.

4D Preparation of the final compound

10.0 g (28.0 mmol) of the chlorinated base 4C described above, 6.4 g (28 mmol) of 3-mercapto-4-methyl-5-phenyl-

4H-1,2,4-triazole and 0.7 g (28.0 mmol) of lithium hydroxide were heated in 77 ml of DMF at 100°C for three hours. After the reaction was complete, the solvent was removed, and the residue was mixed with water and extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and evaporated. Chromatography of the crude product (silica gel; mobile phase: methylene chloride with 0-5% methanol) afforded 3.9 g (7.5 mmol) of a white solid.
Yield: 27% of theory

^{1}H-NMR ($CDCl_3$): δ = 1.4 (m, 2H); 1.7 (m, 4H); 2.1 (q, 2H); 2.7 (t, 2H); 2.8 (t, 2H); 3.0 (m, 6H); 3.35 (t, 2H); 3.6 (s, 3H); 3.7 (s, 2H); 7.2 (δ, 1H); 7.4 (s, 1H); 7.5 (m, 4H); 7.7 (m, 2H).

$C_{26}H_{33}N_5O_2S_2$ (511.7) MS (m/z): 512.3 $[M+H]^+$
Melting point: 105-108°C

Example 5
2-[4-(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)butyl]-7-(morpholin-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

Preparation of the starting compound

5A N-Acetyl-7-(morpholin-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

was obtained as described in Example 4A by reacting morpholine with 2-acetyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride in the presence of diisopropylamine in THF and by heating with 50% concentrated hydrochloric acid and, after alkaline workup, converted into the corresponding 7-(morpholin-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline.
$C_{13}H_{18}N_2O_3S$ (282) MS (m/z): 283 $[M+H]^+$

5B 2-(3-Chloropropyl)-7-(morpholin-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

1.2 g (4.4 mmol) of 7-(morpholin-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline and 1.0 g (10 mmol) of triethylamine were dissolved in DMF at 40°C, 1.1 g (6.6 mmol) of 1-bromo-3-chloropropane were added dropwise, and the mixture was stirred at 40°C for 3 h. For workup, the mixture was concentrated, and the residue was taken up in water and extracted with methyl tert-butyl ether. Drying over sodium sulfate, filtration and removal of the solvent were followed by purification by chromatography (silica gel; mobile phase: methylene chloride with 2% methanol) to afford 0.7 g (2 mmol) of a pale oil.
Yield: 46% of theory.
^{1}H-NMR ($CDCl_3$): δ = 2.0 (q, 2H); 2.7 (t, 2H); 2.8 (t, 2H); 3.0 (m, 6H); 3.6-3.8 (m, 8H); 7.3 (δ, 1H); 7.4 (s, 1H); 7.5 (δ, 1H).
$C_{16}H_{23}N_2O_3S$ (359)

Preparation of the final compound

280 mg (1 mmol) of 2-[4-methyl-5-phenyl-1,2,4-(4H)-triazol-3-yl]-1,3-dithiane (described in WO 9902503) were dissolved in 2.5 ml of dry THF and, at -70°C, with the addition of 0.15 g of sodium iodide, treated with 0.75 ml (1.2 mmol) of a 15% strength solution of butyllithium in n-hexane. After stirring at -70°C for 45 min, 0.37 g (1 mmol) of 2-[3-chloropropyl]-7-(morpholin-4-yl-sulfonyl)-1,2,3,4-tetrahydroisoquinoline 5B dissolved in THF was added dropwise. The mixture was then slowly warmed to room temperature and subsequently heated at 40°C for 90 min in order to achieve complete conversion. Workup entailed addition to ice/water and extraction several times with methylene chloride. After drying and concentration, 0.5 g (82% of theory) of the substituted

09 JUL 2003

dithiane remained and was then hydrogenated with Raney nickel and hydrogen in tetrahydrofuran at 40°C over the course of 3 hours. After removal of the catalyst, the residue was purified by chromatography (silica gel, methylene chloride with 5% methanol).
Yield: 120 mg (29% of theory)
^{1}H-NMR ($CDCl_3$): δ = 1.8 (m, 2H); 2.0 (q, 2H); 2.6 (m, 2H); 2.7 (t, 2H); 2.9 (t, 2H); 3.0 (m, 6H); 3.6 (s, 3H); 3.7 (m, 6); 7.2 (δ, 1H); 7.4 (s, 1H); 7.5 (m, 4H); 7.7 (m, 2H).

The title compound was obtained by adding ethereal HCl
$C_{26}H_{33}N_5O_3S \cdot HCl$ (531.6)
Melting point: 87-89°C

The following were obtained in an analogous way:

Example 6
1-(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)-4-(7-(piperidin-1-yl-sulfonyl)-1,2,3,4-dihydroisoquinolin-2-yl)butan-1-one

$C_{27}H_{33}N_5O_3S$ (507.7) MS: 508.3 $[M+H]^+$

Example 7
2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline-7-carbonitrile

$C_{22}H_{23}N_5S$ (389.5)
Melting point: 116-118°C

Example 8
5-[2-(Diethylammonio)ethoxy]-2-{3-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline dihydrochloride

$C_{27}H_{37}N_5OS \cdot 2HCl$ (552.6)

Melting point: 110-112°C

Example 9
N-Benzyl-2-(3-{[4-methyl-5-(4-methyl-1,3-thiazol-5-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide

$C_{26}H_{30}N_6O_2S_3$ (554.8)
Melting point: 67-70°C

Example 10
N-Benzyl-2-{3-[(4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide

$C_{27}H_{30}N_6O_2S_2 \cdot 2HCl$ (607.6)
Melting point: 81-84°C

Example 11
5-Methoxy-2-{3-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline

$C_{22}H_{26}N_4OS$ (394.5)
Melting point: 73-75°C

Example 12
2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-nitro-1,2,3,4-tetrahydroisoquinoline

$C_{21}H_{24}ClN_5O_2S$ (446)
Melting point: 190-192°C

Example 13
2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.65 (t, 2H); 2.7 (t, 2H); 2.9 (t, 2H); 3.4 (t, 2H); 3.5 (s, 3H); 3.7 (s, 2H); 7.0 (m, 1H); 7.2 (m, 3H); 7.5 (m, 3H); 7.7 (m, 2H).

$C_{21}H_{24}N_4S$ (365.5)

Example 14

2-(3-{[4-Methyl-5-(4-methyl-1,3-thiazol-5-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.55 (s, 3H); 2.7 (t, 2H); 2.75 (t, 2H); 2.9 (t, 2H); 3.4 (t, 2H); 3.5 (s, 3H); 3.65 (s, 2H); 7.0 (m, 1H); 7.1 (m, 3H); 8.9 (s, 1H).

$C_{19}H_{23}N_5S_2$ (386.5)

Example 15

2-{3-[(4-Methyl-5-pyridinium-3-yl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline dihydrochloride

$C_{20}H_{23}N_5S \cdot 2HCl$ (438.4)
Melting point: 87-89°C

Example 16

7-[(Dimethylamino)sulfonyl]-2-{3-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.65 (m, 8H); 2.75 (t, 2H); 3.0 (t, 2H); 3.3 (t, 2H); 3.6 (s, 3H); 3.7 (s, 2H); 7.2 (δ, 1H); 7.4-7.6 (m, 7H).

$C_{23}H_{29}N_5O_2S_2$ (472.6)

Example 17
7-[(Dimethylamino)sulfonyl]-2-(3-{[4-methyl-5-(4-methyl-1,3-thiazol-5-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.5 (s, 3H); 2.6-2.8 (m, 10H); 2.9 (m, 2H); 3.4 (t, 2H); 3.5 (s, 3H); 3.7 (s, 2H); 7.2 (m, 1H); 7.5 (m, 2H); 8.9 (s, 1H).

$C_{21}H_{28}N_6O_2S_3$ (493.7)

Example 18
Methyl 2-{3-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)-sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxylate oxalate

$C_{23}H_{27}N_4O_2S \cdot C_2HO_4$ (512.6)
Melting point: 160-163°C

Example 20
2-(3-{[4-Methyl-5-(4-methyl-1,3-thiazol-5-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-7-(piperidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 1.4 (m, 2H); 1.7 (m, 4H); 2.1 (q, 2H); 2.5 (s, 3H); 2.6 (t, 2H); 2.7 (t, 2H); 3.0 (m, 6H); 3.3 (t, 2H); 3.5 (s, 3H); 3.6 (s, 2H); 7.2 (δ, 1H); 7.45 (s, 1H); 7.5 (δ, 1H); 8.9 (s, 1H).

$C_{24}H_{32}N_6O_2S_3$ (532.8)

Example 21
2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.6 (t, 2H); 2.7 (t, 2H); 2.9 (t, 2H); 3.35 (t, 2H); 3.5 (s, 3H); 3.6 (m, 2H); 7.2 (δ, 1H); 7.4- 7.7 (m, 10H); 7.9 (δ, 2H).

$C_{27}H_{28}N_4O_2S_2$ (504.7)

Example 22
2-(3-{[4-Methyl-5-(4-methyl-1,3-thiazol-5-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl phenyl sulfone

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.5 (s, 3H); 2.7 (t, 2H); 2.8 (t, 2H); 2.95 (t, 2H); 3.4 (t, 2H); 3.5 (s, 3H); 3.65 (m, 2H); 7.2 (δ, 1H); 7.4-7.7 (m, 5H); 7.9 (δ, 2H); 8.9 (s, 1H).

$C_{25}H_{29}N_5O_2S_3$ (525.7)

Example 23
2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(morpholin-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.7 (t, 2H); 2.8 (t, 2H); 3.0 (t, 4H); 3.35 (t, 2H); 3.6 (s, 3H); 3.7 (m, 6H); 7.3 (m, 1H); 7.4- 7.6 (m, 5H); 7.9 (δ, 2H).

$C_{25}H_{31}N_5O_3S_2$ (525.7)

Example 24
2-[4-(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)butyl]-7-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

$C_{28}H_{30}N_4O_2S$ (486.6)

Example 25

2-{3-[(4-Methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-N-phenyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide

^{1}H-NMR ($CDCl_3$): δ = 1.3 (m, NH); 2.1 (q, 2H); 2.6 (m, 4H); 2.8 (t, 2H); 3.3 (t, 2H); 3.6 (s, 3H); 3.7 (m, 6H); 7.3 (m, 1H); 7.4-7.6 (m, 5H); 7.9 (δ, 2H).

$C_{26}H_{28}N_6O_2S_2$ (520.7)
Melting point: 58-61°C

Example 26
2-(3-{[4-Methyl-5-(4-methyl-1,3-thiazol-5-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-N-phenyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.5 (s, 3H); 2.7 (m, 4H); 2.9 (m, 2H); 3.3 (t, 2H); 3.5 (s, 3H); 3.6 (s, 32H); 7.0-7.2 (m, 6H); 7.5 (m, 2H); 8.9 (s, 1H).

$C_{25}H_{28}N_6O_2S_3$ (540.7)
Melting point: 77-81°C

Example 27
2-(3-{[5-(2,4-Dimethoxy)phenyl)-4-methyl-4H-1,2,4-triazol-3-yl]-sulfanyl}propyl)-7-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 2.2 (q, 2H); 2.9 (m, 2H); 3.0 (m, 2H); 3.05 (s, 3H); 3.1 (m, 2H); 3.3 (m, 5H); 3.7 (s, 3H); 3.85 (s, 3H); 3.9 (s, 2H); 6.5 (s, 1H); 6.65 (δ, 1H); 7.25 (δ, 1H); 7.3 (δ, 1H); 7.7 (s, 1H); 7.8 (δ, 1H).

$C_{24}H_{30}N_4O_4S_2$ (502.7) MS: 503.5 $[M+H]^+$

Example 28

6,7-Dichloro-2-{3-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline

$C_{21}H_{22}Cl_2N_4S$ (433.4)
Melting point: 138-139°C

Example 29
7,8-Dichloro-2-{3-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline hydrochloride

1H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.7 (m, 4H); 2.9 (t, 2H); 3.3 (t, 2H); 3.6 (s, 3H); 3.7 (s, 2H); 6.95 (δ, 1H); 7.2 (δ, 1H); 7.5 (m, 3H); 7.7 (m, 2H), [free base].

Salt precipitation with ethereal HCl led to the title compound

$C_{21}H_{22}Cl_2N_4S \cdot x$ HCl (469.9)
Melting point: 109°C

Example 30
7-Cyano-2-[4-(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)butyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride

$C_{23}H_{25}N_5 \cdot HCl$ (407.9)
Melting point: 175°C

Example 31
2-{3-[(4-Methyl-5-thien-3-yl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

$C_{20}H_{21}F_3N_4S_2 \cdot Cl \times HCl$ (475)
Melting point: 184-185°C

Example 32

1-{2-[3-({4-Methyl-5-[4-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-yl}sulfanyl)propyl]-1,2,3,4-tetrahydroisoquinolin-7-yl}ethanone

^{1}H-NMR ($CDCl_3$): δ = 2.15 (q, 2H); 2.4 (s, 3H); 2.7 (t, 2H); 2.8 (t, 2H); 3.0 (t, 2H); 3.3 (t, 2H); 3.6 (s, 3H); 3.75 (s, 2H); 7.1 (δ, 1H); 7.6-7.8 (m, 6H).

$C_{24}H_{25}F_3N_4OS$ (474.5)

The hydrochloride of the title compound was obtained by treatment with ethereal hydrochloric acid:

Melting point: 183°C

Example 33
6,7-Dichloro-2-(3-{[4-methyl-5-(4-methylphenyl)-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.4 (s, 3H); 2.7 (m, 4H); 2.8 (t, 2H); 3.3 (t, 2H); 3.5 (s, 2H); 3.6 (s, 3H); 7.1 (s, 1H); 7.2 (s, 1H); 7.3 (δ, 2H); 7.5 (δ, 2H); [free base].

The title compound was obtained by treatment with ethereal hydrochloric acid

$C_{22}H_{24}Cl_2N_4S \cdot HCl$ (483.9)
Melting point: 207-210°C

Example 34
6-Chloro-2-{3-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline hydrochloride

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.4 (s, 3H); 2.7 (m, 4H); 2.8 (t, 2H); 3.3 (t, 2H); 3.5 (s, 2H); 3.6 (m,

5H); 6.9 (δ, 1H); 7.1 (m, 2H); 7.5 (δ, 3H); 7.5 (δ, 2H); [free base].

Salt precipitation with ethereal HCl led to the title compound

$C_{21}H_{23}ClN_4S \cdot HCl$ (435.4)
Melting point: 188-191°C

Example 35
2-(3-{[4-Methyl-5-(1-methyl-1H-pyrrol-2-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-7-(piperidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 1.4 (m, 2H); 1.7 (m, 4H); 2.1 (q, 2H); 2.7 (t, 2H); 2.8 (t, 2H); 3.0 (m, 6H); 3.35 (t, 2H); 3.6 (s, 3H); 3.7 (s, 2H); 3.9 (s, 3H); 6.2 (m, 1H); 6.4 (m, 1H); 6.8 (m, 1H); 7.2 (δ, 1H); 7.4 (s, 1H); 7.5 (m, 2H).

$C_{25}H_{34}N_6O_2S_2$ (514.7)
Melting point: 96-100°C

Example 36
2-[4-(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)butyl]-7-(piperidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

$C_{27}H_{35}N_5O_2S$ (493.7) MS: 494.3 $[M+H]^+$

Example 37
2-(3-{[4-Methyl-5-thien-3-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-7-(piperidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 1.4 (m, 2H); 1.7 (m, 4H); 2.15 (q, 2H); 2.7 (t, 2H); 2.8 (t, 2H); 3.0 (m, 6H); 3.3 (t, 2H); 3.7 (m, 5H); 7.2 (δ, 1H); 7.4 (s, 1H); 7.5 (m, 3H); 7.7 (s, 1H).

$C_{24}H_{31}N_5O_2S_3$ (517.7) MS: 518.3 $[M+H]^+$
Melting point: 192-195°C

Example 38
2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-N-phenyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.6 (t, 2H); 2.7 (t, 2H); 2.9 (t, 2H); 3.3 (t, 2H); 3.55 (s, 2H); 3.6 (s, 3H); 7.0 (m, 2H); 7.2 (m, 4H); 7.5 (m, 5H); 7.7 (m, 2H).

$C_{27}H_{29}N_5O_2S_2$ (519.7) MS: 520.3 $[M+H]^+$

Example 39
6-Chloro-2-{3-[(4-methyl-5-thien-3-yl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline

$C_{19}H_{21}ClN_4S_2$ (405)
Melting point: 99-100°C

Example 40
7-[(Diethylammonio)methyl]-2-{3-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline dihydrochloride

$C_{26}H_{35}N_5S \cdot 2HCl$ (522.6)
Melting point: 75°C

Example 41
2-{3-[(4-Methyl-5-thien-3-yl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

Preparation of the starting material

41A 7-Trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

10.0 ml of concentrated sulfuric acid were slowly added dropwise to a solution of 1.77 g (6.2 mmol) of N-trifluoroacetyl-2-(4-trifluorophenyl)ethylamine [prepared from 2-(4-trifluorophenyl)ethylamine and trifluoroacetic anhydride at -5°C] in 7.5 ml of glacial acetic acid, and, while cooling in ice, 2 ml of formalin solution were added dropwise. After 18 hours at room temperature, the reaction mixture was poured into 130 ml of ice-water and extracted with dichloromethane, and the combined organic phases were washed with sodium hydrogencarbonate solution and then with water. After drying over sodium sulfate, filtration and evaporation, 1.7 g of 2-trifluoroacetyl-7-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline were isolated and were converted into 7-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline by heating under reflux in ethanol/3N HCl (1:1) and alkaline workup.
Yield: 1.0 g (4.7 mmol) 75% of theory.

^{1}H-NMR ($CDCl_3$): δ = 2.0 (sbr, 1H); 2.9 (t, 2H); 3.2 (t, 2H); 4.0 (s, 2H); 7.2 (δ, 1H); 7.3 (s, 1H); 7.4 (s, 1H).

41B 2-(3-Chloropropyl)-7-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

0.95 g (4.7 mmol) of the compound described above was reacted with 1-bromo-3-chloropropane in the same way as described in Example 4B at room temperature, and purified by chromatography (silica gel, mobile phase dichloromethane with 2% methanol).
Yield: 0.9 g (3.2 mmol) 69% of theory.

^{1}H-NMR ($CDCl_3$): δ = 2.0 (m, 2H); 2.65 (m, 2H); 2.75 (m, 2H); 2.9 (m, 2H); 3.65 (m, 4H); 7.2 (dd, 1H); 7.3 (δ, 1H); 7.4 (dd, 1H).

41C Preparation of the final product

0.45 g (1.6 mmol) of 2-(3-chloropropyl)-7-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline, 0.36 g (1.6 mmol) of 3-mercapto-4-methyl-5-thien-3-yl-4H-1,2,4-triazole and 40 mg of lithium hydroxide were stirred in 6 ml of DMF at 100°C for 4 hours. Workup entailed pouring into ice/water, extraction with methyl tert-butyl ether, drying over sodium sulfate and purification after filtration and evaporation by column chromatography (silica gel, mobile phase dichloromethane with 3-5% methanol).
Yield: 0.3 g (0.7 mmol) 42% of theory.

^{1}H-NMR ($CDCl_3$): δ = 2.1 (m, 2H); 2.7 (t, 2H); 2.8 (t, 2H); 3.0 (m, 2H); 3.35 (t, 2H); 3.7 (m, 5H); 7.1 (δ, 1H); 7.2 (s, 1H); 7.3 (δ, 1H); 7.5 (m, 2H); 7.7 (s, 1H); [free base].

The title compound was obtained by treatment with ethereal HCl

$C_{20}H_{21}F_3N_4S_2 \cdot HCl$ (475)
Melting point: 192-194°C

Example 42
2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-8-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

Preparation of the starting materials

42A 6/8-Trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

5.3 g (18.6 mmol) of N-trifluoroacetyl-2-(3-trifluorophenyl)ethylamine [prepared from 2-(3-trifluorophenyl)ethylamine and trifluoroacetic anhydride at -5°C]

and 0.9 g (29 mmol) of paraformaldehyde were added to a mixture of 22 ml of glacial acetic acid and 30 ml of concentrated sulfuric acid. After 18 hours at room temperature, the reaction mixture was poured into 350 ml of ice-water and extracted with ethyl acetate, and the combined organic phases were washed with sodium hydrogencarbonate solution and then with water. After drying over sodium sulfate, filtration and evaporation, 5.4 g of a mixture of 2-trifluoroacetyl-6- and -8-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline were isolated. The protective group was eliminated by heating in ethanol/3N HCl (1:1) under reflux. The two isomers were separated after workup and purification by chromatography (silica gel, mobile phase dichloromethane with 2-4% methanol):

F1 1.2 g (5.7 mmol) 32% of theory of 8-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline
^{1}H-NMR ($CDCl_3$): δ = 1.9 (sbr, 1H); 2.8 (t, 2H); 3.1 (t, 2H); 4.2 (s, 2H); 7.2 (m, 2H); 7.5 (δ, 1H).

F2 1.4 g (6.8 mmol) 38% of theory of 6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline
^{1}H-NMR ($CDCl_3$): δ = 1.8 (sbr, 1H); 2.8 (t, 2H); 3.1 (t, 2H); 4.0 (s, 2H); 7.1 (δ, 1H); 7.4 (m, 2H).

42 B 2-(3-Chloropropyl)-8-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline
2-(3-Chloropropyl)-8-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline was obtained in 73% yield by reacting 42-A F1 with bromochloropropane in a manner analogous to the description in Example 4C.

^{1}H-NMR ($CDCl_3$): δ = 2.0 (q, 2H); 2.7-2.8 (m, 4H); 3.0 (t, 2H); 3.6 (t, 2H); 3.8 (s, 2H); 7.2-7.3 (m, 2H); 7.4 (δ, 1H).

42C Preparation of the final compound

Reaction of 0.7 g (3.0 mmol) of 3-mercapto-4-methyl-5-phenyl-1,2,4(4H)-triazole with 0.83 g (3.0 mmol) of 2-(3-chloropropyl)-8-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline [42B1] in 10 ml of DMF in the presence of 70 mg of lithium hydroxide at 100°C afforded, after workup as described under 4D, 0.84 g (1.9 mmol) of the final compound.
Yield: 0.84 g (1.9 mmol) 65% of theory

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.6-2.7 (m, 4H); 2.9 (t, 2H); 3.4 (t, 2H); 3.6 (s, 3H); 3.8 (s, 2H); 7.1 (t, 1H); 7.25 (δ, 1H); 7.4 (δ, 1H), 7.5 (m, 3H); 7.6 (m, 2H).

The title compound was obtained by treatment with ethereal HCl.

$C_{22}H_{23}F_3N_4S \cdot HCl$ (469)
Melting point: 118°C

Example 43
2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

Preparation of the starting materials

43 B2 2-(3-Chloropropyl)-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

2-(3-Chloropropyl)-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline was obtained in 96% yield by reacting 6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline [42AF2] (obtained as described in 42A) with bromochloropropane in a manner analogous to that described for 4C.

^{1}H-NMR ($CDCl_3$): δ = 2.0 (m, 2H); 2.6-2.8 (m, 4H); 2.9 (t, 2H); 3.6 (m, 4H) 7.1 (δ, 1H); 7.4 (m, 2H).

43C Preparation of the final compound

Reaction of 0.7 g (3.0 mmol) of 3-mercapto-4-methyl-5-phenyl-1,2,4(4H)-triazole with 0.83 g (3.0 mmol) of 2-(3-chloropropyl)-8-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline in 10 ml of DMF in the presence of 70 mg of lithium hydroxide at 100°C afforded, after workup as described under 4D, 0.75 g (1.7 mmol) of the final compound.
Yield: 0.75 g (1.7 mmol) 58% of theory

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.6 (t, 2H); 2.7 (t, 2H); 2.9 (t, 2H); 3.3 (t, 2H); 3.6 (s, 3H); 3.7 (s, 2H); 7.1 (δ, 1H); 7.3 (m, 2H); 7.5 (m, 3H); 7.7 (m, 2H); [free base].

The title compound was obtained by treatment with ethereal HCl

$C_{22}H_{23}F_3N_4S \cdot HCl$ (469)
Melting point: 200-202°C

Example 44
2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

$C_{22}H_{23}F_3N_4S \cdot HCl$ (469)
Melting point: 205-207°C

Example 45
2-{3-[(4-Methyl-5-(thien-3-yl)-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(4-methylpiperazin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.2 (s, 3H); 2.4 (m, 4H); 2.7 (t, 2H); 2.8 (t, 2H); 2.9 (t, 2H); 3.0 (m, 4H); 3.3 (t, 2H); 3.6 (m, 5H); 7.2 (δ, 2H); 7.45 (m, 4H); 7.7 (m, 1H).

$C_{24}H_{32}N_6O_2S_3$ (538.8)

Example 46

2-{3-[(4-Methyl-5-(phenyl)-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(4-methylpiperazin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.2 (s, 3H); 2.5 (m, 4H); 2.7 (t, 2H); 2.8 (t, 2H); 2.9-3.0 (m, 6H); 3.3 (t, 2H); 3.6 (s, 3H); 3.7 (s, 2H); 7.2 (δ, 1H); 7.5 (m, 5H); 7.6 (m, 2H).

$C_{26}H_{34}N_6O_2S_3$ (564.8)

Example 47

2-{3-[(4-Methyl-5-(thien-3-yl)-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(1,2,3,4-tetrahydroisoquinolin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$): δ = 2.1 (q, 2H); 2.7 (t, 2H); 2.8 (t, 2H); 2.9 (t, 2H); 3.2-3.3 (m, 4H); 3.6 (m, 2H); 3.7 (m, 5H); 4.2 (m, 2H); 7.1 (m, 4H); 7.2 (δ, 1H); 7.4-7.6 (m, 4H); 7.7 (m, 1H).

$C_{28}H_{31}N_5O_2S_3$ (565)

Example 48

2-{3-[(4-Methyl-5-(pyrid-3-yl)-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(1,2,3,4-tetrahydroisoquinolin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR ($CDCl_3$) δ = 2.1 (q, 2H); 2.7 (t, 2H); 2.8 (t, 2H); 2.9 (m, 4H); 3.3 (m, 4H); 3.6 (s, 3H); 3.7 (s,

2H); 4.2 (s, 2H); 7.0-7.2 (m, 5H); 7.2 (m, 1H); 7.4-7.6 (m, 3H); 8.0 (m, 1H); 8.7 (m, 1H); 8.9 (m, 1H).

$C_{29}H_{32}N_6O_2S_2$ (558)

Example 49

7-[(3,3-Dimethylpiperidin-1-yl)sulfonyl]-2-{3-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline

$C_{28}H_{37}N_5O_2S_2$ (539.8)
Melting point: 75-76°C

Example 50

2-{3-[(4-Cyclopropyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-[(3,3-dimethylpiperidin-1-yl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline

$C_{30}H_{39}N_5O_2S_2$ (558)

Example 51

2-[(4-{[(4-Methyl-5-(1-methyl-1H-pyrrol-3-yl)-4H-1,2,4-triazol-3-yl)sulfanyl]methyl}cyclohexyl)methyl]-7-nitro-1,2,3,4-tetrahydroisoquinoline

$C_{26}H_{31}N_5O_2S$ (477.6)
Melting point: 160°C

Example 52

2-{(E)-4-[(4-Methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)sulfanyl]but-2-enyl}-7-nitro-1,2,3,4-tetrahydroisoquinoline

$C_{21}H_{22}N_6O_2S$ (422) MS: 423 $[M+H]^+$

Example 53

2-[(4-{[(4-Methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)sulfanyl]methyl}cyclohexyl)methyl]-1,2,3,4-tetrahydroisoquinoline-7-carbonitrile

$C_{27}H_{31}N_5S$ (457.6)
Melting point: 156-158°C

Example 54

1-(2-{3-[(4-Methyl-5-(3-cyano)phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinolin-7-yl-ethanone hydrochloride

$C_{24}H_{25}N_5OS$ x HCl (468)
Melting point: 185°C

Example 55

7-Nitro-2-[(4-{[(4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)sulfanyl]methyl}cyclohexyl)methyl]-1,2,3,4-tetrahydroisoquinoline

$C_{26}H_{31}N_6O_2S$ (477.6)
Melting point: 160°C

Example 56

1-{2-[3-({4-Methyl-5-phenyl]-4H-1,2,4-triazol-3-yl}sulfanyl)propyl]-1,2,3,4-tetrahydroisoquinolin-7-yl}ethanone hydrochloride

$C_{23}H_{27}N_4OS$ x HCl (443)
Melting point: 165°C

Example 57

7,8-Dichloro-2{3-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline

$C_{21}H_{22}ClN_4S$ (399)
Melting point: 72-75°C

Example 58

1-{2-[3-({5-(2,4-Dinitrophenyl)-4-methyl]-4H-1,2,4-triazol-3-yl}sulfanyl)propyl]-1,2,3,4-tetrahydroisoquinolin-7-yl}ethanone hydrochloride

$C_{23}H_{25}N_6O_5S$ x HCl (500.6)
Melting point: 193°C

Example 59

2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(octahydroisoquinolin-2(1H)-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

$C_{30}H_{39}N_5O_2S_2$ (565.8) MS: 567 $[M+H]^+$

Example 60
2-{3-[(4-Methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(octahydroisoquinolin-2(1H)-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

$C_{29}H_{38}N_6O_2S_2$ (566.8) MS: 568 $[M+H]^+$

Example 61

2-{3-[(4-Cyclopropyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(azepan-1-ylsulfonyl]-1,2,3,4-tetrahydroisoquinoline

$C_{29}H_{37}N_5O_2S_2$ (551.8) MS: 552 $[M+H]^+$

Example 62

2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(pyrrolidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

$C_{25}H_{31}N_5O_2S_2$ (497.7)

Example 63

2-{3-[(4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(azepan-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

$C_{27}H_{35}N_5O_2S_2$ (525.7)

Example 64

7-Chloro-2-(3-{[4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl]sulfanyl}but-2-en-yl)-1,2,3,4-tetrahydroisoquinoline

$C_{21}H_{23}ClN_4S$ (399)
Melting point: 72-75°C

Example 65

2-(3-{([4-Methyl-5-methylamino-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-7-(azepan-1-ylsulfonyl)-1,2,3,4-tetrahydroquinoline

Example 66

N,4-Dimethyl-5-{[3-(7-(piperidin-1-ylsulfonyl)-3,4-dihydroisoquinolin-2(1H)-yl)propyl]sulfanyl}-4H-1,2,4-triazol-3-amine

Example 67

7-tert-Butyl-2-(3-{[4-methyl-5-(4-methyl-1,3-thiazol-5-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-1,2,3,4-tetrahydroisoquinoline

Example 68

2-{3-[(4-Methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(azepan-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

Example 69

7-{4-[2-tert-Butyl-6-(trifluoromethyl)pyrimidin-4-yl]piperazin-1-yl}sulfonyl)-2-{3-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline

Example 70

8-Bromo-2-(3-{[5-cyclohexyl-4-methyl-4H-1,2,4-triazol-3-yl]sulfanyl}but-2-en-yl)-1,2,3,4-tetrahydroisoquinoline

Example 71

4-Methyl-5-phenyl-N-[4-(7-(pyrrolidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)butyl]-4H-1,2,4-triazole-3-carboxamide

Example 72

6-Methyl-2-(3-{[-4-methyl-5-(1-methyl-1H-pyrrol-3-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-7-(pyrrolidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

Example 73

7-Cyano-2-[(2-{[4-methyl-5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)sulfanyl]methyl}cyclopropyl)methyl]-1,2,3,4-tetrahydroisoquinoline

Example 74

1-(2-{3-[(4-Methyl-5-(3-methoxy)phenyl-4H-1,2,4-triazol-3-yl)oxy]propyl}-1,2,3,4-tetrahydroisoquinolin-7-yl)ethanone

Example 75

4-(7-(Pyrrolidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)butyl-4-methyl-5-phenyl-4H-1,2,4-triazol-3-carboxylate

Example 76

2-{2-{[5-(N-Methylpyrrol-2-yl)-4-methyl-4H-1,2,4-triazol-3-yl]sulfanyl}methyl)prop-2-enyl]-1,2,3,4-tetrahydroisoquinolin-7-carboxamide

Example 77

2-{3-[(4-Cyclopropyl-5-(4-methylsulfonyl)phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(pyrrolidin-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

Example 78

6-tert-Butyl-2-(3-{[5-(2,4-dinitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-1,2,3,4-tetrahydroisoquinoline

Example 79

N-[2-(8-{[5-(dimethylamino)-4-butyl-4H-1,2,4-triazol-3-yl]sulfanyl}octyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]methanesulfonamide

Example 80

2-{3-[(4-Methyl-5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-7-(octahydroisoquinolin-2(1H)-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

Example 81

7-Cyano-2-{3-[(4-methyl-5-(2-methyloxazol-4-yl)-4H-1,2,4-triazol-3-yl)sulfanyl]propyl}-1,2,3,4-tetrahydroisoquinoline

Example 82

2-{6-[5-(2,5-Dimethylfuran-3-yl)-4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]hexyl}-7-trifluoromethanesulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Example 83

2-[2-({[4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl]sulfanyl}methyl)prop-2-enyl]-7-nitro-1,2,3,4-tetrahydroisoquinoline hydrochloride

$C_{22}H_{23}N_5O_2S \times HCl$ (460)

Melting point: 146-150°C

Example 84

N-[2-(3-{[4-Methyl-5-phenyl-4H-1,2,4-triazol-3-yl]sulfanyl}propyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]methanesulfonamide

$C_{22}H_{27}N_5O_2S_2 \times HCl$ (494.1)

Melting point: 90°C

The following compounds can in principle be prepared in an analogous manner:

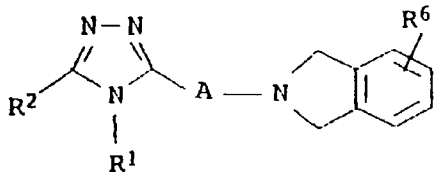


Table 1:

Ex.	R^1	R^2	A	R^6	R^7	R^8
85	Me	Ethoxycarbonyl	S-$(CH_2)_4$-	7-(Piperidin-1-yl-sulfonyl)	8-methyl	
86	Me	N,N-Dimethylamino-	S-CH_2-CH=CH-CH_2-	6-methyl	7-cyano	
87	Et	tert-Butyl	$(CH_2)_4$-	7-cyano		
88	Butyl	Methylsulfanyl	$(CH_2)_4$-	6-fluoro		
89	cycProp	Methyl	S-$(CH_2)_3$-	6-chloro	7-chloro	
90	Me	2,5-Dimethylfuranyl-3-	S-CH_2-CH=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
91	Me	3-Thienyl	COO-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
92	Me	Phenyl-	$(CH_2)_4$-	7-(3,3-dimethyl-piperidin-1-yl-sulfonyl)		
93	Me	2,4-Dimethoxyphenyl	S-$(CH_2)_2$-	7-methanesulfonamide		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
94	Me	Amino-	$S-CH_2-C-(=CH_2)-CH_2$	7-(piperidin-1-yl-sulfonyl)		
95	Prop	Phenyl	$S-CH_2-C(CH_3)=CH-CH_2-$	8-trifluoromethyl		
96	Me	2-Me-4-oxazolyl-	$S-(CH_2)_4-$	7-(dimethylamino-sulfonyl)		
97	Me	3-Benzthienyl	$S-(CH_2)_6-$	7-(pyrrolidin-1-yl-sulfonyl)		
98	Me	Phenyl-	$S-(CH_2)_1-$	7-(pyrrolidin-1-yl-sulfonyl)		
99	Me	Phenyl	$CONH-(CH_2)_4-$	7-(piperidin-1-yl-sulfonyl)		
100	Me	2-Pyrazinyl-	$S-(CH_2)_4-$	7-trifluoromethyl		
101	Phenyl	Methyl	$(CH_2)_4-$	7-(morpholin-1-yl-sulfonyl)		
102	Me	Tetrazolyl-	$S-(CH_2)_3-$	7-methoxy		
103	Et	4-Methylthiazol-5-yl	$S-(CH_2)_3-$	7-methylsulfonyl		
104	Et	3-Iodophenyl	$S-(CH_2)_3-$	7-methanesulfonamide		
105	Et	4-Methylphenyl	$S-CH_2-C(=CH_2)-CH_2$	7-(piperidin-1-ylsulfonyl)		
106	Me	N-Methyl-2-pyrrolyl-	$S-(CH_2)_3-$	7-(dimethylamino-sulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
107	Me	4-Methylthiazol-5-yl	S-CH_2-C-(=CH_2)-CH_2	7-(pyrrolidin-1-yl-sulfonyl)		
108	Me	2,5-Dimethylfuranyl-3-	S-$(CH_2)_3$-	7-phenylsulfonyl		
109	Me	2-Me-4-oxazolyl-	$(CH_2)_2$-CH(CH_3)-CH_2-CH_2-	7-(morpholin-1-yl-sulfonyl)		
110	Me	Phenyl-	S-$(CH_2)_2$-	7-(pyrrolidin-1-yl-sulfonyl)		
111	Hexyl	3-Pyridyl-	S-$(CH_2)_3$-	6-chloro	7-chloro	
112	Me	3-Cyanophenyl-	S-$(CH_2)_4$-	7-(dimethylamino-sulfonyl)		
113	Me	2-Pyrazinyl-	CO-$(CH_2)_4$-	7-(morpholin-1-yl-sulfonyl)		
114	Prop	Phenyl	S-$(CH_2)_4$-	7-(morpholin-1-yl-sulfonyl)		
115	Me	3-Methoxypentyl	$(CH_2)_4$-	6-trifluoromethyl		
116	Me	3-Pyrrolyl	S-$(CH_2)_4$-	7-nitro		
117	Et	3-Pyridyl	S-$(CH_2)_2$-	6-methyl	7-cyano	
118	Me	4-Methylthiazol-5-yl	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
119	Me	Phenyl	CONH-$(CH_2)_4$	7-cyano		
120	Et	2,5-Dimethylfuranyl-3-	S-$(CH_2)_3$-	7-nitro		
121	Et	N-Methyl-2-pyrrolyl-	S-$(CH_2)_3$-	7-nitro		

09 JUL 2003

Ex.	R^1	R^2	A	R^4	R^7	R^8
122	Prop	Phenyl-	S-$(CH_2)_3$-	6-methyl	7-(azepan-1-yl-sulfonyl)	
123	Et	N-Propyl-tetrazolyl-	S-$(CH_2)_3$-	7-cyano		
124	Me	3-Thienyl	S-$(CH_2)_3$-	7-methylsulfonyl		
125	Me	4-Methoxyphenyl	S-$(CH_2)_3$-	4-methoxy		
126	Me	Tetrazolyl-	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
127	Me	4-Methylthiazol-5-yl	S-CH_2-cycHex-CH_2-CH_2-	7-phenylsulfonyl		
128	Me	2-Chlorophenyl	CO-$(CH_2)_3$-	7-trifluoromethoxy		
129	Et	Phenyl-	S-$(CH_2)_3$-	6-CH_2-CH_2-CH_2-CH_2-7		
130	Et	4-Methoxyphenyl	$(CH_2)_2$-$CH(CH_3)$-CH_2-CH_2-	7-(piperidin-1-yl-sulfonyl)		
131	Et	4-Methylthiazol-5-yl	S-CH_2-C(=CH_2)-CH_2	7-(azepan-1-yl-sulfonyl)		
132	Me	2-Me-4-oxazolyl-	S-$(CH_2)_6$-	7-nitro		
133	Me	5-Methylimidazol-4-yl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
134	Me	3-Iodophenyl	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
135	Me	Phenylmethyl	S-CH_2-CH=CH-CH_2-	7-(azepan-1-yl-sulfonyl)		
136	Et	Phenyl-	S-$(CH_2)_3$-	6-$CH(CH_3)CH_2$-N(CH_3)-7		
137	Et	3-Thienyl	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
138	Me	3-Iodophenyl	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
139	Et	Phenyl	S-$(CH_2)_3$-	8-trifluoromethyl		
140	Me	Phenyl	CONH-$(CH_2)_5$-	8-trifluoromethyl		
141	Me	Phenyl-	S-CH_2-CH=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
142	Me	Cyclohexyl-	S-$(CH_2)_3$-	7-nitro		
143	iProp	3-Pyridyl	S-$(CH_2)_7$-	7-chloro	8-chloro	
144	Me	Amino-	S-$(CH_2)_3$-	7-cyano		
145	Me	2-Aminothiazol-4-yl-	S-$(CH_2)_3$-	7-cyano		
146	Me	3-Pyrrolyl	S-CH_2-cycProp-CH_2-	6-trifluoromethyl		
147	cycProp	Phenyl-	S-$(CH_2)_3$-	6-CH_2-CH_2-CH_2-CH_2-7		
148	Me	2-Pyrazinyl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
149	Me	Cyclohexyl-	S-$(CH_2)_3$-	7-cyano		
150	Me	5-Methylimidazol-4-yl-	$(CH_2)_2$-CH(CH_3)-CH_2-CH_2-	tert-butyl		
151	Me	Methylamino-	S-$(CH_2)_3$-	7-cyano		
152	Me	3-Benzthienyl-	S-$(CH_2)_3$-	7-(dimethylamino-sulfonyl)		
153	Me	Phenyl	S-CH_2-cycHex-CH_2-CH_2-	5-methoxy		

09 JUL 2003

Ex.	R^1	R^2	A	R^4	R^7	R^8
154	Me	Pyridin-4-yl-	S-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
155	Prop	Phenyl-	S-CH_2-C(=CH_2)-CH_2	7-(azepan-1-yl-sulfonyl)		
156	Me	3-Pyridinyl	S-$(CH_2)_8$-	7-CHF_2		
157	Me	Tetrazolyl-	$(CH_2)_4$-	7-(pyrrolidin-1-yl-sulfonyl)		
158	Me	4-Phenyl	S-CH_2-cycProp-$(CH_2)_2$-	7-bromo		
159	Me	4-Methylphenyl	COO-$(CH_2)_4$-	7-nitro		
160	Et	3-Cyanophenyl	S-CH_2-cycHex-CH_2-CH_2-	6-methyl		
161	Et	2-Aminothiazol-4-yl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
162	Et	Phenyl-	$(CH_2)_4$-	7-(3,3-dimethylpiperidin-1-yl-sulfonyl)		
163	Me	4-Methylthiazol-5-yl	S-$(CH_2)_3$-	7-trifluoromethyl		
164	Me	Oxadiazol-2-yl	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
165	Me	6-Chlorobiphenyl-2-	S-$(CH_2)_3$-	7-methylsulfonyl		
166	Et	3-Pyridinyl	S-$(CH_2)_8$-	7-CHF_2		
167	Me	Pyridin-3-yl-	S-$(CH_2)_3$-	7-methylsulfonyl		
168	Me	Phenyl	CONH-$(CH_2)_4$-	7-phenylsulfonyl		
169	Et	2-Me-4-oxazolyl-	S-$(CH_2)_3$-	8-trifluoromethyl		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
170	Me	5-Methylimidazol-4-yl-	S-$(CH_2)_3$-	7-nitro		
171	iProp	Phenyl	S-$(CH_2)_3$-	6-bromo		
172	Prop	4-Imidazolyl-	S-$(CH_2)_3$-	7-methoxy		
173	Me	Tetrazolyl-	S-$(CH_2)_3$-	7-cyano		
174	Et	Phenyl	CONH-$(CH_2)_3$-	6-chloro	7-chloro	
175	Me	2-Pyrazinyl-	S-$(CH_2)_3$-	7-methoxy		
176	Prop	Phenyl-	S-$(CH_2)_3$-	6-methyl	7-nitro	
177	Me	4-Iodophenyl	COO-$(CH_2)_3$-	7-cyano		
178	iProp	4-Imidazolyl-	S-CH_2-CH=CH-CH_2	7-(azepan-1-yl-sulfonyl)		
179	Et	4-Methylsulfonylphenyl-	S-$(CH_2)_8$-	7-(piperidin-1-yl-sulfonyl)		
180	Butyl	N-Propyltetrazolyl-	S-$(CH_2)_3$-	7-cyano		
181	Me	2-Me-4-oxazolyl-	S-CH_2-C(CH_3)=CH-CH_2-	7-(azepan-1-yl-sulfonyl)		
182	Et	3-Pyrrolyl	S-$(CH_2)_3$-	7-nitro		
183	Me	N-Propyltetrazolyl-	S-CH_2-C(=CH_2)-CH_2	7-(piperidin-1-yl-sulfonyl)		
184	Me	Propyl	CO-$(CH_2)_3$-	5-methoxy		
185	Me	2-Pyrazinyl-	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
186	Me	Oxadizol-2-yl	S-$(CH_2)_3$-	7-nitro		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
187	Prop	2-Me-4-oxazolyl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
188	Hexyl	Phenyl	$(CH_2)_4$-	8-nitro		
189	Prop	Phenyl	O-$(CH_2)_3$-	7-methoxy		
190	Me	3-Pyridyl	S-$(CH_2)_7$-	7-chloro	8-chloro	
191	Et	Oxadiazol-2-yl	S-$(CH_2)_4$-	7-nitro		
192	Et	Phenyl-	S-$(CH_2)_3$-	6-$CH(CH_3)CH_2$-NH-7		
193	Me	3-Iodophenyl	S-$(CH_2)_3$-	7-methanesulfonamide		
194	Me	Pyridin-4-yl-	S-$(CH_2)_3$-	7-nitro		
195	Me	4-Imidazolyl-	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
196	Me	Phenyl	$(CH_2)_4$-	8-nitro		
197	Me	4-Methylphenyl	S-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
198	cycProp	Phenyl	S-$(CH_2)_3$-	7-carboxamide		
199	Me	3-Iodophenyl	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
200	Me	Cyclohexyl	S-$(CH_2)_6$-	7-(piperidin-1-yl-sulfonyl)		
201	Me	3-Iodophenyl	S-CH_2- $C(CH_3)$=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
202	Me	3-Iodophenyl	S-$(CH_2)_3$-	7-phenylsulfonyl		
203	Butyl	Pyridin-3-yl-	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
204	cycProp	2,4-Dimethoxyphenyl	S-$(CH_2)_3$-	7-methanesulfonamide		
205	Me	N-Propyltetrazolyl-	S-$(CH_2)_3$-	7-cyano		
206	Et	4-Methoxyphenyl	S-CH_2-CH=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
207	Et	Phenyl-	S-$(CH_2)_3$-	6-methyl	7-nitro	
208	Et	Phenyl-	$(CH_2)_2$-$CH(CH_3)$-CH_2-CH_2-	6-methoxy		
209	Me	3-Br-Pyridin-5-yl-	S-$(CH_2)_3$-	7-nitro		
210	Me	Methylamino-	S-CH_2-cycHex-CH_2-CH_2-	7-cyano		
211	Et	tert-Butyl	CO-$(CH_2)_3$-	6-methoxy		
212	Me	Phenyl	S-$(CH_2)_3$-	6-fluoro		
213	Me	Phenylmethyl	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
214	iProp	4-Methoxyphenyl	S-CH_2-CH=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
215	iProp	4-Cyanophenyl	S-CH_2-$C(CH_3)$=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
216	Me	3-Br-Pyridin-5-yl-	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
217	Me	Phenyl-	S-$(CH_2)_3$-	6-CH_2-CH_2-CH_2-CH_2-7		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
218	Me	3-Cyanophenyl	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
219	Me	3-Thienyl	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
220	Et	Phenyl	$(CH_2)_4$	8-nitro		
221	Me	Amino	S-$(CH_2)_3$-	7-nitro		
222	Me	4-Methylsulfonylphenyl	S-$(CH_2)_8$-	7-(piperidin-1-yl-sulfonyl)		
223	Me	4-Methylsulfonylphenyl	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
224	Me	4-Methylthiazol-5-yl	S-$(CH_2)_3$-	7-methoxy		
225	Me	2-Me-4-oxazolyl-	S-$(CH_2)_3$-	7-methylsulfonyl		
226	Me	2,5-Dimethylfuranyl-3-	S-$(CH_2)_3$-	7-methoxy		
227	Me	3-Pyrrolyl	S-$(CH_2)_3$-	7-cyano		
228	Phenyl	Cyano	S-$(CH_2)_3$-	7-(pyrrolidin-1-yl-sulfonyl)		
229	Me	Tetrazolyl-	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
230	Me	Phenyl-	S-$(CH_2)_3$-	6-methyl	7-cyano	
231	Et	Carboxamido-	S-$(CH_2)_3$-	7-cyano		
232	Me	Pyridin-3-yl-	S-CH_2-$C(CH_3)$=CH-CH_2-	7-(azepan-1-yl-sulfonyl)		
233	Et	Phenyl	S-$(CH_2)_3$-	6-bromo		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
234	Prop	2-Aminothiazol-4-yl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
235	Me	Pyridin-4-yl-	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
236	Me	4-Methylthiazol-5-yl	S-$(CH_2)_3$-	7-cyano		
237	cycProp	Phenyl-	S-$(CH_2)_3$-	6-CH_2-CH_2-CH_2-7		
238	Me	Pyridin-3-yl-	S-CH_2-C(=CH_2)-CH_2	7-(azepan-1-yl-sulfonyl)		
239	Et	5-Methylimidazol-4-yl-	S-$(CH_2)_{10}$-	7-(piperidin-1-yl-sulfonyl)		
240	Me	Methylamino	S-$(CH_2)_3$-	7-nitro		
241	Me	Pyridin-4-yl-	S-$(CH_2)_6$-	7-(piperidin-1-yl-sulfonyl)		
242	Butyl	Phenyl-	S-$(CH_2)_3$-	6-methyl	7-cyano	
243	Phenyl	3-Pyridyl-	S-$(CH_2)_6$-	7-(piperidin-1-yl-sulfonyl)		
244	Me	Tetrazolyl-	O-$(CH_2)_3$-	7-cyano		
245	Hexyl	3-Iodophenyl-	S-$(CH_2)_3$-	6-chloro	7-chloro	
246	Me	4-Methylsulfonylphenyl	S-CH_2-cycProp-CH_2-	7-cyano		
247	Phenyl	tert-butyl	S-$(CH_2)_3$-	7-(pyrrolidin-1-yl-sulfonyl)		
248	Me	tert-butyl	$(CH_2)_4$-	6-methoxy		
249	cycProp	tert-butyl	CO-$(CH_2)_3$-	6-methoxy		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
250	Me	Amino-	S-$(CH_2)_3$-	7-methylsulfonyl		
251	Me	Amino-	S-$(CH_2)_3$-	6-methoxy		
252	Et	N-Methyl-2-pyrrolyl-	S-$(CH_2)_4$-	7-cyano		
253	Me	Methylamino-	S-$(CH_2)_3$-	7-methoxy		
254	Me	Phenyl	S-$(CH_2)_3$-	8-ethenyl		
255	Et	Phenyl	S-CH_2-cycHex-CH_2-	7-trifluoromethoxy		
256	Me	N-Methyl-2-pyrrolyl-	S-CH_2-cycProp-CH_2-	8-trifluoromethyl		
257	Prop	3-Iodophenyl	S-$(CH_2)_3$-	7-methanesulfonamide		
258	Me	Methylamino-	S-$(CH_2)_3$-	7-trifluoromethyl		
259	Me	Tetrazolyl-	S-CH_2-cycHex-CH_2-	7-(morpholin-1-yl-sulfonyl)		
260	Me	Methylamino-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
261	Me	N-Methyl-2-pyrrolyl-	S-$(CH_2)_3$-	7-trifluoromethyl		
262	Me	2-Aminothiazol-4-yl-	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
263	Me	3-Pyrrolyl	S-$(CH_2)_3$-	7-methylsulfonyl		
264	Me	4-Imidazolyl-	S-CH_2-CH=CH-CH_2-	7-(azepan-1-yl-sulfonyl)		
265	Me	Propyl	$(CH_2)_4$-	5-methoxy		
266	Me	Oxadiazol-2-yl	S-$(CH_2)_3$-	6-trifluoromethyl		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
267	Me	4-Methylphenyl	O-$(CH_2)_4$-	7-cyano		
268	cycProp	Phenyl	$(CH_2)_4$-	8-nitro		
269	Me	3-Br-Pyridin-5-yl	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
270	iProp	Phenyl	S-$(CH_2)_3$-	7-acetyl		
271	Me	4-Methylsulfonylphenyl	S-$(CH_2)_8$-	7-(piperidin-1-yl-sulfonyl)		
272	Me	3-Cyanophenyl	S-$(CH_2)_3$-	7-nitro		
273	Me	4-Methylthiazol-5-yl	S-$(CH_2)_3$-	7-methanesulfonamide		
274	Me	3-Cyanophenyl	S-$(CH_2)_4$-	7-cyano		
275	Me	Oxadiazol-2-yl	S-$(CH_2)_4$-	7-cyano		
276	Me	Phenyl-	S-$(CH_2)_7$-	6-methyl	7-(pyrrolidin-1-yl-sulfonyl)	
277	Me	Phenyl-	CO-$(CH_2)_4$-	7-cyano		
278	cycProp	4-Methoxyphenyl	$(CH_2)_4$-	8-ethenyl		
279	Me	Phenyl	S-CH_2- $C(CH_3)$=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
280	Me	6-Chloro-biphenyl-2-	S-$(CH_2)_3$-	7-nitro		
281	Me	4-Imidazolyl-	S-$(CH_2)_3$-	8-trifluoromethyl		
282	Me	3-Br-Pyridin-5-yl-	S-$(CH_2)_3$-	7-cyano		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
283	Pentyl	3-Pyridyl-	S-$(CH_2)_3$-	6-chloro	7-chloro	
284	Me	Pyridin-3-yl-	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
285	Me	3-Pyrrolyl	S-$(CH_2)_3$-	7-methoxy		
286	Me	2-Pyrazinyl-	O-$(CH_2)_3$-	7-cyano		
287	Et	Phenyl-	CO-$(CH_2)_3$-	7-cyano		
288	Me	2-Me-4-oxazolyl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
289	Me	4-Methylsulfonylphenyl	S-$(CH_2)_3$-	7-methylsulfonyl		
290	Me	Phenyl	COO-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
291	Me	Oxadiazol-2-yl	S-$(CH_2)_3$-	7-methylsulfonyl		
292	Me	2-Aminothiazol-4-yl-	S-$(CH_2)_3$-	7-methoxy		
293	Me	4-Methylphenyl	CONH-$(CH_2)_4$-	7-cyano		
294	Me	3-Pyrrolyl	S-CH_2-CH=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
295	Me	3-Cyanophenyl	S-$(CH_2)_3$-	7-methanesulfonamide		
296	Me	2-Pyrazinyl-	S-CH_2-cycProp-CH_2)$_2$-	7-(pyrrolidin-1-yl-sulfonyl)		
297	Me	Pyridin-3-yl-	S-CH_2-C(=CH_2)-CH_2	7-(piperidin-1-yl-sulfonyl)		

Ex.	R^1	R^2	A	R^6	R^7	R^8
298	Me	2-Me-4-oxazolyl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
299	Et	3-Br-Pyridin-5-yl-	S-$(CH_2)_3$-	7-cyano		
300	Me	6-Chlorobiphenyl-2-	S-$(CH_2)_3$-	7-trifluoromethyl		
301	iProp	Phenyl-	S-$(CH_2)_2$-	6-methyl	7-(pyrrolidin-1-yl-sulfonyl)	
302	Et	3-Benzthienyl-	S-$(CH_2)_3$-	7-nitro		
303	Me	Phenyl	CONH-$(CH_2)_1$-	7-nitro		
304	Me	Cyclohexyl-	S-$(CH_2)_6$-	7-(piperidin-1-yl-sulfonyl)		
305	Me	3-Pyrrolyl	S-CH_2-CH=CH-CH_2-	6-chloro		
306	Et	2-Pyrazinyl-	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
307	Me	4-Imidazolyl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
308	Me	3-Pyridinyl	S-$(CH_2)_8$-	7-CHF_2		
309	Me	3-Pyridyl	COO-$(CH_2)_4$	7-cyano		
310	Me	3-Benzthienyl-	S-$(CH_2)_3$-	7-cyano		
311	Me	3-Pyrrolyl	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
312	Me	4-Methoxyphenyl	$(CH_2)_2$-CH(CH_3)-CH_2-CH_2-	5-hydroxy		
313	Me	Amino-	S-$(CH_2)_3$-	7-trifluoromethyl		
314	Me	4-Methylthiazol-5-yl	S-CH_2-cycProp-CH_2-	7-(piperidin-1-yl-sulfonyl)		
315	Me	Tetrazolyl-	S-$(CH_2)_3$-	7-phenylsulfonyl		
316	Me	Phenyl	S-CH_2-cycHex-CH_2-	7-trifluoromethyl		
317	Phenyl	3-Thienyl	S-$(CH_2)_3$-	7-nitro		
318	Me	Pyridin-3-yl-	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
319	Me	4-Methylphenyl	S-CH_2-C(=CH_2)-CH_2-	7-(piperidin-1-yl-sulfonyl)		
320	Prop	3-Benzthienyl-	S-$(CH_2)_4$-	7-(dimethylaminosulfonyl)		
321	Me	4-Methylthiazol-5-yl	S-$(CH_2)_3$-	7-methylsulfonyl		
322	Me	4-Methoxyphenyl	S-$(CH_2)_8$-	7-(piperidin-1-yl-sulfonyl)		
323	Me	Oxadiazol-2-yl	S-$(CH_2)_7$-	7-(azepan-1-yl-sulfonyl)		
324	Me	Methylamino-	S-CH_2-cycProp-CH_2-	7-(piperidin-1-yl-sulfonyl)		
325	Me	4-Methoxyphenyl	S-$(CH_2)_3$-	7-cyano		
326	Butyl	2-Aminothiazol-4-yl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
327	iProp	3-Pyrrolyl	S-CH_2-CH=CH-CH -	7-(piperidin-1-yl-sulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R'	R^7	R^8
328	Me	Phenyl	CONH-$(CH_2)_4$-	7-chloro		
329	Butyl	Phenyl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)	8-chloro	
330	Et	4-Imidazolyl-	S-$(CH_2)_3$-	7-methoxy		
331	Me	Phenyl	S-CH_2-cycProp-CH_2-	6-methoxy		
332	Me	3-Furanyl	S-CH_2-cycProp-CH_2-	7-(N-methylanilin-1-sulfonyl)		
333	Me	2-Pyrazinyl-	S-$(CH_2)_3$-	7-cyano		
334	cycProp	2-Pyrazinyl-	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
335	Et	Phenyl	S-$(CH_2)_4$-	7-(morpholin-1-yl-sulfonyl)		
336	Me	Phenyl-	S-$(CH_2)_3$-	7-methylsulfonyl		
337	Me	4-Methylphenyl	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
338	Butyl	Phenyl	S-$(CH_2)_3$-	7-acetyl		
339	Et	4-Cyanophenyl	S-CH_2-C(CH_3)=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
340	Butyl	Phenyl-	S-$(CH_2)_3$-	6-methyl	7-(pyrrolidin-1-yl-sulfonyl)	
341	Butyl	Phenyl	S-$(CH_2)_3$-	8-chloro		
342	Et	Pyridin-3-yl-	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
343	Me	3-Thienyl	S-$(CH_2)_3$-	7-methoxy		
344	Me	N-Methyl-2-pyrrolyl-	S-CH_2-cycHex-CH_2-CH_2-	5-methoxy		
345	Me	4-Imidazolyl-	S-$(CH_2)_3$-	7-methoxy		
346	cycProp	Phenyl	CONH-$(CH_2)_5$-	8-trifluoromethyl		
347	Me	6-Chlorobiphenyl-2-	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
348	Et	3-Pyridyl	S-$(CH_2)_7$-	7-chloro	8-chloro	
349	Me	4-Methylsulfonyl-phenyl	S-CH_2-cycHex-CH_2-	6-methoxy		
350	Me	Methylamino-	S-$(CH_2)_3$-	7-methylsulfonyl		
351	Et	2-Me-4-oxazolyl-	S-$(CH_2)_3$-	7-methoxy		
352	Et	Phenyl-	S-$(CH_2)_3$-	6-CH_2-CH_2-CH_2-7		
353	Et	Phenyl	S-$(CH_2)_4$-	7-(pyrrolidin-1-yl-sulfonyl)		
354	Butyl	2-Pyrazinyl-	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
355	Me	4-Methoxylphenyl	S-$(CH_2)_8$-	7-(piperidin-1-yl-sulfonyl)		
356	Me	Phenyl-	$(CH_2)_2$-$CH(CH_3)$-CH_2-CH_2-	6-methoxy		
357	Me	2-Aminothiazol-4-yl-	S-$(CH_2)_3$-	7-trifluoromethyl		
358	Prop	Phenyl	S-$(CH_2)_3$-	7-acetyl		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
359	Me	4-Methylphenyl	COO-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
360	Et	2-Me-4-oxazolyl-	$(CH_2)_2$-CH(CH_3)-CH_2-CH_2-	7-(morpholin-1-yl-sulfonyl)		
361	Butyl	Carboxamido	S-$(CH_2)_3$-	7-cyano		
362	Me	Pyridin-4-yl-	S-$(CH_2)_3$-	6-trifluoromethyl		
363	Hexyl	3-Pyridyl-	S-$(CH_2)_3$-	7-chloro	8-chloro	
364	Me	N-Propyltetrazolyl-	S-$(CH_2)_3$-	7-methylsulfonyl		
365	Et	Phenyl-	S-CH_2-C(=CH_2)-CH_2	7-(azepan-1-yl-sulfonyl)		
366	cycProp	Phenyl-	$(CH_2)_4$-	7-(3,3-dimethylpiperidin-1-yl-sulfonyl)		
367	Me	Phenyl	CONH-$(CH_2)_4$-	6-chloro	7-chloro	
368	Et	4-Imidazolyl-	S-CH_2-CH=CH-CH_2-	7-(azepan-1-yl-sulfonyl)		
369	Me	Cyclohexyl-	S-$(CH_2)_4$-	7-methoxy		
370	Me	2-Pyrazinyl-	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
371	Prop	2-Me-4-oxazolyl-	S-$(CH_2)_3$-	8-trifluoromethyl		
372	Me	2,4-Dimethoxyphenyl	S-CH_2-C(CH_3)=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
373	Me	Cyclohexyl-	S-$(CH_2)_4$-	7-(dimethylaminosulfonyl)		
374	Me	Pyridin-3-yl-	S-$(CH_2)_3$-	7-methoxy		
375	Me	Phenyl-	S-$(CH_2)_3$-	7-methoxy		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
376	Me	2-Pyrazinyl-	S-CH_2-cycHex-CH_2-	7-(morpholin-1-yl-sulfonyl)		
377	Me	N-Propyltetrazolyl-	S-$(CH_2)_3$-	7-nitro		
378	Me	Phenyl-	$(CH_2)_4$-	8-trifluoromethyl		
379	Prop	4-Methoxyphenyl	$(CH_2)_4$-	8-ethenyl		
380	Me	Phenyl-	S-$(CH_2)_7$-	7-(pyrrolidin-1-yl-sulfonyl)		
381	iProp	4-Methylthiazol-5-yl	S-$(CH_2)_3$-	7-methylsulfonyl		
382	iProp	Phenyl-	S-$(CH_2)_7$-	7-(piperidin-1-yl-sulfonyl)	8-chloro	
383	iProp	Phenyl	S-$(CH_2)_3$-	7-carboxamide		
384	Me	Phenyl	S-CH_2-C(CH_3)=CH-CH_2-	7-trifluoromethyl		
385	Et	Phenyl	CONH-$(CH_2)_6$-	8-trifluoromethyl		
386	iProp	3-Pyrrolyl	S-$(CH_2)_6$-	7-cyano		
387	Me	Phenyl-	S-$(CH_2)_7$-	7-(piperidin-1-yl-sulfonyl)	8-chloro	
388	Et	3-Benzthienyl-	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
389	Me	2-Me-4-oxazolyl-	S-$(CH_2)_3$-	7-methoxy		
390	Me	2-Aminothiazol-4-yl-	S-$(CH_2)_3$-	7-nitro		
391	Prop	3-Br-Pyridin-5-yl-	S-$(CH_2)_3$-	7-cyano		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
392	Me	3-Thienyl	S-$(CH_2)_4$-	7-nitro		
393	Et	Phenyl	CONH-$(CH_2)_4$-	7-chloro		
394	Me	4-Methylthiazol-5-yl	S-$(CH_2)_4$-	7-nitro		
395	Me	2-Me-4-oxazolyl-	S-$(CH_2)_4$-	7-(dimethylaminosulfonyl)		
396	Me	6-Chlorobiphenyl-2-	S-$(CH_2)_4$-	7-cyano		
397	Me	Tetrazolyl-	S-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
398	Me	3-Benzthienyl-	S-$(CH_2)_4$-	7-methylsulfonyl		
399	Me	3-Thienyl-	S-CH_2-CH=CH-CH_2-	7-(pyrrolidin-1-yl-sulfonyl)		
400	Hexyl	Phenyl-	S-$(CH_2)_4$-	6-methyl	7-cyano	
401	Me	3-Pyridyl	S-$(CH_2)_4$-	6-methyl	7-cyano	
402	Me	2-Me-4-oxazolyl-	S-$(CH_2)_3$-	7-methylsulfonyl		
403	Me	3-Thienyl	O-$(CH_2)_3$-	7-cyano		
404	Prop	Phenyl-	S-$(CH_2)_4$-	6-methyl	7-(piperidin-1-yl-sulfonyl)	
405	Et	2,4-Dimethoxyphenyl	S-$(CH_2)_4$-	7-methanesulfonamide		
406	Me	Phenyl-	S-$(CH_2)_3$-	7-trifluoromethyl		
407	Me	4-Methoxyphenyl	$(CH_2)_2$-CH(CH_3)-CH_2-CH_2-	7-(piperidin-1-yl-sulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
408	Me	Phenyl	S-CH_2-cycProp-$(CH_2)_2$-	5-methoxy		
409	Phenyl	3-Thienyl	$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
410	Me	3-Thienyl	S-$(CH_2)_3$-	7-methanesulfonamide		
411	Me	Pyridin-3-yl-	S-$(CH_2)_3$-	7-trifluoromethyl		
412	Phenyl	tert-butyl	O-$(CH_2)_4$-	7-(pyrrolidin-1-yl-sulfonyl)		
413	Me	3-Pyrrolyl	S-$(CH_2)_4$-	7-trifluoromethyl		
414	Me	N-Methyl-2-pyrrolyl-	S-$(CH_2)_3$-	7-nitro		
415	iProp	Phenyl	S-$(CH_2)_4$-	8-trifluoromethyl		
416	Butyl	3-Thienyl	S-$(CH_2)_8$-	7-(pyrrolidin-1-yl-sulfonyl)		
417	Me	Phenyl-	S-CH_2-C(=CH_2)CH_2	7-(piperidin-1-yl-sulfonyl)		
418	Me	2-Me-4-oxazolyl-	S-$(CH_2)_4$-	7-nitro		
419	Me	2-Aminothiazol-4-yl-	S-$(CH_2)_4$-	7-phenylsulfonyl		
420	Me	4-Methylthiazol-5-yl	O-$(CH_2)_3$-	7-cyano		
421	Me	4-Methylsulfonyl-phenyl	S-$(CH_2)_4$-	7-trifluoromethyl		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
422	Me	4-Methylsulfonyl-phenyl	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
423	Butyl	3-Pyridyl-	S-$(CH_2)_3$-	7-chloro	8-chloro	
424	Me	Methylamino-	S-CH_2-$C(CH_3)$=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
425	Me	Carboxamido	S-$(CH_2)_3$-	7-cyano		
426	Me	4-Methoxyphenyl	S-$(CH_2)_3$-	7-phenylsulfonyl		
427	Et	3-Pyrrolyl	S-CH_2-CH=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
428	Me	3-Cyanophenyl	S-$(CH_2)_3$-	7-trifluoromethyl		
429	Me	5-Methylimidazol-4-yl-	S-$(CH_2)_3$-	7-cyano		
430	Prop	N-Propyltetrazolyl-	S-$(CH_2)_4$-	7-cyano		
431	Me	2,5-Dimethylfuranyl-3-	S-$(CH_2)_4$-	7-(dimethylaminosulfonyl)		
432	Prop	Pyridin-3-yl-	S-CH_2-C(=CH_2)-CH	7-(azepan-1-yl-sulfonyl)		
433	Me	4-Methylsulfonyl-phenyl	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
434	Butyl	Phenyl	$(CH_2)_4$-	8-nitro		
435	Me	4-Methylphenyl	COO-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
436	Me	3-Furanyl	S-CH_2-cycHex-CH_2-CH_2-	7-phenylsulfonyl		

09 JUL 2003

Ex.	R^1	R^2	A	$R^{6'}$	R^7	R^8
437	Me	3-Iodophenyl	S-$(CH_2)_3$-	7-trifluoromethyl		
438	Et	2-Pyrazinyl-	O-$(CH_2)_3$-	8-ethenyl		
439	Me	3-Benzthienyl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
440	Me	Cyclohexyl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
441	Me	Pyridin-3-yl-	S-CH_2-cycHex-CH_2-	6-methoxy		
442	Me	2-Me-4-oxazolyl-	S-$(CH_2)_3$-	7-nitro		
443	Me	2-Pyrazinyl-	$(CH_2)_4$-	7-(morpholin-1-yl-sulfonyl)		
444	Prop	2-Pyrazinyl-	S-$(CH_2)_3$-	8-ethenyl		
445	Me	4-Methoxyphenyl	S-$(CH_2)_3$-	7-trifluoromethyl		
446	Me	4-Imidazolyl-	S-$(CH_2)_3$-	7-methylsulfonyl		
447	Me	Phenyl-	S-$(CH_2)_7$-	7-(pyrrolidin-1-yl-sulfonyl)		
448	Me	Cyclohexyl-	S-$(CH_2)_3$-	7-trifluoromethyl		
449	Butyl	Phenyl-	$(CH_2)_4$-	7-(3,3-dimethylpiperidin-1-yl-sulfonyl)		
450	Et	Phenyl	S-$(CH_2)_3$-	8-ethenyl		
451	Me	4-Methoxyphenyl	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
452	iProp	Phenyl	S-$(CH_2)_4$-	7-(morpholin-1-yl-sulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R^I	$R^{I'}$	R^{II}
453	Me	Cyano	S-$(CH_2)_4$-	6,7-dimethoxy		
454	Me	2-Aminothiazol-4-yl-	S-CH_2-CH=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
455	Et	Phenyl	COO-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
456	Me	3-Cyanophenyl	S-$(CH_2)_3$-	7-methylsulfonyl		
457	Me	2-Pyrazinyl-	S-$(CH_2)_3$-	7-nitro		
458	Me	3-Cyanophenyl	S-CH_2-C(=CH_2)-CH_2	7-(piperidin-1-yl-sulfonyl)		
459	cycProp	N-Methyl-2-pyrrolyl-	S-$(CH_2)_4$-	7-cyano		
460	Me	4-Methoxyphenyl	S-$(CH_2)_3$-	7-nitro		
461	Me	Oxadiazol-2-yl	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
462	Me	Tetrazolyl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
463	Butyl	Phenyl	$(CH_2)_4$-	7-(pyrrolidin-1-yl-sulfonyl)		
464	Prop	4-Methylphenyl	S-CH_2-C(=CH_2)-CH_2	7-(piperidin-1-yl-sulfonyl)		
465	Me	Phenyl-	S-$(CH_2)_3$-	6-CH_2-CH_2-CH_2-7		
466	Me	N-Methyl-2-pyrrolyl-	S-$(CH_2)_3$-	7-methylsulfonyl		
467	Me	3-Thienyl	S-$(CH_2)_3$-	7-trifluoromethyl		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
468	Et	Cyano	S-$(CH_2)_8$-	6-methoxy	7-methoxy	
469	cycProp	Phenyl-	S-$(CH_2)_3$-	6-CH$(CH_3)CH_2$-NH-7		
470	Me	3-Br-Pyridin-5-yl-	S-$(CH_2)_4$-	7-methylsulfonyl		
471	Me	Phenyl-	S-$(CH_2)_3$-	6-CH$(CH_3)CH_2$-N(CH_3)-7		
472	Et	4-Methoxyphenyl	$(CH_2)_4$-	8-ethenyl		
473	Me	Tetrazolyl-	S-$(CH_2)_3$-	7-trifluoromethyl		
474	Me	6-Chlorobiphenyl-2-	S-$(CH_2)_4$-	7-methoxy		
475	Me	4-Pyridyl-	$(CH_2)_4$-	7-(pyrrolidin-1-yl-sulfonyl)		
476	cycProp	Phenyl	CONH-$(CH_2)_4$-	6-chloro	7-chloro	
477	Me	2-Me-4-oxazolyl-	S-$(CH_2)_6$-	7-nitro		
478	Me	2-Me-4-oxazolyl-	S-$(CH_2)_4$-	7-methoxy		
479	Me	4-Methoxyphenyl	S-CH_2-CH=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
480	Me	Cyano	S-$(CH_2)_8$-	6-methoxy	7-methoxy	
481	Me	tert-butyl	CO-$(CH_2)_3$-	6-methoxy		
482	Et	3-Cyanophenyl	S-$(CH_2)_3$-	7-methanesulfonamide		
483	Prop	Cyano	S-$(CH_2)_8$-	6-methoxy	7-methoxy	
484	Me	3-Pyrrolyl	S-CH_2-cycHex-CH_2-CH_2-	7-cyano		
485	Me	Methylamino-	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
486	Me	2,5-Dimethylfuranyl-3-	S-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
487	Me	2,5-Dimethylfuranyl-3-	S-$(CH_2)_4$-	7-nitro		
488	iProp	4-Methoxyphenyl	$(CH_2)_4$-	8-ethenyl		
489	Et	Tetrazolyl-	S-$(CH_2)_4$-	7-nitro		
490	Me	Phenyl	COO-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
491	Me	4-Imidazolyl-	S-$(CH_2)_4$-	7-nitro		
492	Me	3-Thienyl	O-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
493	Et	Phenyl	S-CH_2-$C(CH_3)$=CH-CH_2-	8-trifluoromethyl		
494	Me	Pyridin-4-yl-	S-$(CH_2)_6$-	7-nitro		
495	Me	N-Methyl-2-pyrrolyl-	S-$(CH_2)_3$-	7-methanesulfonamide		
496	Et	Phenyl-	S-$(CH_2)_4$-	6-methyl	7-cyano	
497	Prop	4-Methylthiazol-5-yl	S-$(CH_2)_4$-	7-trifluoromethyl		
498	Me	Phenyl	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
499	Me	4-Cyanophenyl	S-CH_2-$C(CH_3)$=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
500	Et	Phenyl	S-$(CH_2)_3$-	7-carboxamide		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
501	Me	N-Propyltetrazolyl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
502	Me	Amino-	S-$(CH_2)_4$-	7-(dimethylaminosulfonyl)		
503	Me	2,4-Dimethoxyphenyl	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
504	Me	3-Benzthienyl-	CO-$(CH_2)_3$-	7-phenylsulfonyl		
505	Me	4-Imidazolyl-	S-$(CH_2)_3$-	7-cyano		
506	Et	Phenyl	S-CH_2-cycHex-CH_2-CH_2-	5-methoxy		
507	Et	3-Pyrrolyl	S-$(CH_2)_6$-	7-cyano		
508	Me	3-Pyrrolyl	S-$(CH_2)_3$-	7-methanesulfonamide		
509	Me	Tetrazolyl-	S-$(CH_2)_2$-	7-(piperidin-1-yl-sulfonyl)		
510	Me	Tetrazolyl-	S-$(CH_2)_3$-	7-methanesulfonamide		
511	Me	3-Thienyl	COO-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
512	Et	2-Me-4-oxazolyl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
513	Me	Pyridin-4-yl-	S-$(CH_2)_3$-	7-methylsulfonyl		
514	Butyl	N-Methyl-2-pyrrolyl-	S-$(CH_2)_8$-	7-cyano		
515	Me	Phenyl-	S-$(CH_2)_3$-	6-$CH(CH_3)CH_2$-NH-7		
516	Me	Pyridin-4-yl-	S-$(CH_2)_3$-	7-cyano		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
517	Me	3-Thienyl	S-CH_2-cycProp-(CH_2)--	7-(3,3-dimethylpiperidin-1-yl-sulfonyl)		
518	Me	2,4-Dimethoxyphenyl	O-$(CH_2)_4$-	7-cyano		
519	Me	4-Methylsulfonylphenyl	O-$(CH_2)_4$-	7-cyano		
520	Me	4-Methylthiazol-5-yl	S-CH_2-C(=CH_2)-CH_2	7-(azepan-1-yl-sulfonyl)		
521	Me	Amino-	S-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
522	Prop	N-Methyl-2-pyrrolyl-	S-$(CH_2)_4$-	7-cyano		
523	Me	5-Methylimidazol-4-yl-	S-$(CH_2)_4$-	7-trifluoromethyl		
524	Me	Cyclohexyl-	S-$(CH_2)_4$-	7-methylsulfonyl		
525	Et	Pyridin-3-yl-	S-CH_2-C(=CH_2)-CH	7-(azepan-1-yl-sulfonyl)		
526	Prop	Phenyl	S-$(CH_2)_3$-	8-ethenyl		
527	Me	5-Methylimidazol-4-yl-	S-CH_2-C(CH_3)=CH-CH_2-	7-(pyrrolidin-1-yl-sulfonyl)		
528	Me	Tetrazolyl-	S-CH_2-cycProp-CH -	6-methoxy		
529	Me	Phenyl-	S-CH_2-C(=CH_2)-CH_2	7-(azepan-1-yl-sulfonyl)		
530	Me	6-Chlorobiphenyl-2-	S-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
531	Et	Phenyl-	S-$(CH_2)_2$-	6-methyl	7-(pyrrolidin-1-yl-sulfonyl)	
532	Me	Pyridin-3-yl-	S-$(CH_2)_4$-	7-methanesulfonamide		
533	Me	2-Pyrazinyl-	S-CH_2-C(=CH_2)-CH_2	7-(piperidin-1-yl-sulfonyl)		
534	Et	3-Iodophenyl	O-$(CH_2)_3$-	7-cyano		
535	Me	3-Benzthienyl-	S-$(CH_2)_4$-	6-methoxy		
536	Me	Oxadiazol-2-yl	S-$(CH_2)_4$-	7-methoxy		
537	Me	6-Chlorobiphenyl-2-	S-CH_2-C(CH_3)=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
538	cycProp	4-Methylthiazol-5-yl	S-CH_2-C(=CH_2)-CH_2	7-(azepan-1-yl-sulfonyl)		
539	Me	Pyridin-3-yl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
540	Et	4-Methylthiazol-5-yl	S-$(CH_2)_4$-	7-trifluoromethyl		
541	Me	3-Pyrrolyl	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
542	Me	3-Pyridyl	COO-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
543	Prop	Carboxamido	S-$(CH_2)_3$-	7-cyano		
544	Me	4-Iodophenyl	COO-$(CH_2)_3$-	7-cyano		
545	Hexyl	Phenyl-	$(CH_2)_4$-	7-(3,3-dimethylpiperidin-1-yl-sulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
546	Me	2-Me-4-oxazolyl-	$S-(CH_2)_3-$	7-trifluoromethyl		
547	Et	Phenyl-	$S-(CH_2)_3-$	7-(piperidin-1-yl-sulfonyl)	8-chloro	
548	Prop	Phenyl	$S-(CH_2)_4-$	7-(pyrrolidin-1-yl-sulfonyl)		
549	Me	N-Propyltetrazolyl-	$S-(CH_2)_3-$	7-methoxy		
550	Me	2-Pyrazinyl-	$S-(CH_2)_4-$	7-methylsulfonyl		
551	Me	Phenyl	$S-CH_2-C(CH_3)=CH-CH_2-$	8-trifluoromethyl		
552	Butyl	tert-butyl	$CO-(CH_2)_3-$	6-methoxy		
553	Prop	5-Methylimidazol-4-yl-	$S-(CH_2)_{10}-$	7-(piperidin-1-yl-sulfonyl)		
554	Me	4-Iodophenyl	$S-(CH_2)_3-$	7-cyano		
555	Me	5-Methylimidazol-4-yl-	$S-(CH_2)_3-$	7-(dimethylaminosulfonyl)		
556	Me	3-Benzthienyl-	$(CH_2)_4-$	7-phenylsulfonyl		
557	Me	Pyridin-3-yl-	$O-(CH_2)_3-$	7-cyano		
558	Me	Tetrazolyl-	$S-(CH_2)_3-$	7-nitro		
559	Me	3-Benzthienyl-	$S-(CH_2)_4-$	7-(pyrrolidin-1-yl-sulfonyl)		
560	cycProp	Phenyl	$S-(CH_2)_3-$	7-acetyl		
561	iProp	Phenyl	$S-(CH_2)_4-$	7-(pyrrolidin-1-yl-sulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
562	Me	Phenyl-	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
563	Me	2-Me-4-Oxazolyl-	O-$(CH_2)_4$-	7-cyano		
564	Me	5-Methylimidazol-4-yl-	O-$(CH_2)_4$-	7-methoxy		
565	Prop	Phenyl-	S-$(CH_2)_3$-	6-$CH(CH_3)CH_2$-$N(CH_3)$-7		
566	Me	N-Propyltetrazolyl-	S-$(CH_2)_4$-	7-trifluoromethyl		
567	Me	2,5-Dimethylfuranyl-3-	S-$(CH_2)_3$-	7-trifluoromethyl		
568	Me	Phenyl	O-$(CH_2)_4$-	7-cyano		
569	Me	4-Iodophenyl	S-$(CH_2)_3$-	7-nitro		
570	Me	N-Methyl-2-pyrrolyl-	S-$(CH_2)_3$-	7-cyano		
571	Prop	3-Pyridyl	S-$(CH_2)_4$-	6-methyl	7-cyano	
572	Me	2,5-Dimethylfuranyl-3-	S-$(CH_2)_4$-	7-cyano		
573	Me	2-Pyrazinyl-	S-$(CH_2)_4$-	7-methanesulfonamide		
574	Me	2-Me-4-oxazolyl-	S-$(CH_2)_4$-	7-cyano		
575	Et	Phenyl	O-$(CH_2)_4$-	7-cyano		
576	Me	Methylamino-	S-$(CH_2)_3$-	7-methanesulfonamide		
577	Me	3-Thienyl	S-$(CH_2)_4$-	7-cyano		
578	Me	4-Chlorophenyl	$(CH_2)_4$-	7-trifluoromethoxy		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
579	Butyl	3-Pyrrolyl	S-CH_2-CH=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
580	cycProp	3-Cyanophenyl	S-$(CH_2)_4$-	7-methanesulfonamide		
581	Me	N-Propyltetrazolyl-	S-$(CH_2)_4$-	7-(dimethylaminosulfonyl)		
582	Me	4-Methylphenyl	COO-$(CH_2)_4$-	7-trifluoromethyl		
583	Me	5-Methylimidazol-4-yl-	S-$(CH_2)_4$-	7-methylsulfonyl		
584	Me	3-Br-pyridin-5-yl-	S-$(CH_2)_4$-	7-methoxy		
585	Me	3-Thienyl	S-CH_2-cycHex-CH_2-	7-trifluoromethoxy		
586	Me	Pyridin-3-yl-	S-$(CH_2)_4$-	7-nitro		
587	Et	3-Thienyl	COO-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
588	Prop	3-Thienyl	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		
589	Butyl	3-Br-pyridin-5-yl-	S-$(CH_2)_3$-	7-cyano		
590	Me	Pyridin-3-yl-	S-$(CH_2)_3$-	7-cyano		
591	Et	3-Cyanophenyl	S-$(CH_2)_4$-	7-nitro		
592	Prop	Phenyl	S-$(CH_2)_{10}$-	7-carboxamide		
593	Et	3-Furanyl	S-CH_2-cycHex-CH_2-CH_2-	7-phenylsulfonyl		
594	Me	N-Methyl-2-pyrrolyl-	S-$(CH_2)_3$-	7-methoxy		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
595	Me	3-Cyanophenyl	S-CH_2-cycHex-CH-CH_2-	6-methyl		
596	Me	4-Methylsulfonyl-phenyl	S-$(CH_2)_3$-	7-methanesulfonamide		
597	Me	2-Aminothiazol-4-yl-	S-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
598	Prop	Phenyl	S-$(CH_2)_3$-	6-bromo		
599	Prop	4-Methylthiazol-5-yl	S-$(CH_2)_3$-	7-methylsulfonyl		
600	Me	2,4-Dimethoxyphenyl	O-$(CH_2)_3$-	7-(piperidin-1-yl-sulfonyl)		
601	Et	Pyridin-4-yl-	S-$(CH_2)_3$-	7-nitro		
602	Me	N-Methyl-2-pyrrolyl-	S-CH_2-C(CH_3)=CH-CH_2-	7-(piperidin-1-yl-sulfonyl)		
603	Me	3-Br-pyridin-5-yl-	S-$(CH_2)_6$-	7-(piperidin-1-yl-sulfonyl)		
604	iProp	Phenyl-	S-$(CH_2)_3$-	6-methyl	7-cyano	
605	Et	2-Pyrazinyl-	CO-$(CH_2)_3$-	7-(morpholin-1-yl-sulfonyl)		
606	Me	Phenyl-	S-$(CH_2)_3$-	6-methyl	7-nitro	
607	Butyl	4-Methylthiazol-5-yl	S-CH_2-C(=CH_2)-CH	7-(azepan-1-yl-sulfonyl)		
608	Me	4-Methoxyphenyl	S-$(CH_2)_3$-	7-(dimethylaminosulfonyl)		

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
609	Me	3-Br-pyridin-5-yl-	S-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
610	Me	Pyridin-4-yl-	S-$(CH_2)_4$-	7-methoxy		
611	cycProp	Pyridin-3-yl-	O-$(CH_2)_4$-	7-(piperidin-1-yl-sulfonyl)		
612	Me	3-Br-pyridin-5-yl-	S-$(CH_2)_4$-	7-trifluoromethyl		
613	Me	2-Me-4-oxazolyl-	S-$(CH_2)_4$-	8-trifluoromethyl		
614	Prop	Phenyl	S-$(CH_2)_3$-	8-trifluoromethyl		
615	Me	3-Benzthienyl-	S-$(CH_2)_4$-	7-trifluoromethyl		
616	Et	Phenyl	S-$(CH_2)_4$-	7-acetyl		
617	Me	Pyridin-3-yl-	S-CH_2-cycProp-CH_2-	7-(pyrrolidin-1-yl-sulfonyl)		
618	Me	Oxadiazol-2-yl	S-$(CH_2)_7$-	7-(piperidin-1-yl-sulfonyl)		
619	Phenyl	3-Thienyl	S-$(CH_2)_4$-	7-cyano		
620	Me	3-Iodophenyl	O-$(CH_2)_4$-	7-cyano		
621	Me	Phenyl	CONH-$(CH_2)_4$-	6-methoxy	8-methyl	
622	Me	3-Thienyl	S-$(CH_2)_4$-	6-$CH(CH_3)CH_2$-NH-7		5-methyl
623	Me	3-Thienyl	S-$(CH_2)_3$-	6-CH=CH-CH_2-CH_2-7		8-bromo
624	Me	4-Pyridyl	S-$(CH_2)_4$-	6-CH_2-CH=CH_2-7		8-ethenyl

09 JUL 2003

Ex.	R^1	R^2	A	R^6	R^7	R^8
625	Me	3-Pyridyl-	S-$(CH_2)_3$-	6-methoxy	7-chloro	8-chloro
626	Me	3-Phenyl-	O-$(CH_2)_3$-	6-chloro	7-chloro	8-methyl

When no meaning is given for them in this table, R^7 and R^8 are hydrogen.

The following abbreviations are used in this table and in the following table:

Me = methyl
Et = ethyl
cycProp = cyclopropyl
Prop = n-propyl
iProp = isopropyl
cycHex = cyclohexyl

09 JUL 2003

The following compounds can in principle be prepared in an analogous manner:

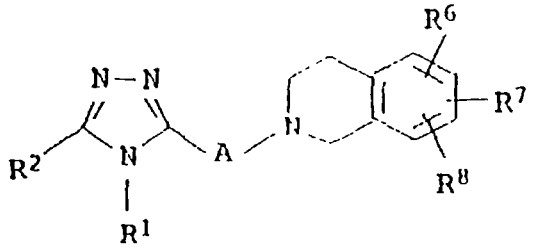


Table 2

Ex.	R^1	R^2	A	R^6
627	Me	Phenyl	CONH-(CH)$_1$-	5-nitro
628	Butyl	Methylamino	S-(CH$_2$)$_3$-	5-fluoro
629	Me	Oxadiazol-2-yl	S-(CH$_2$)$_2$-	5-(piperidin-1-yl-sulfonyl)
630	Me	Tetrazolyl-	S-(CH$_2$)$_2$-	5-(piperidin-1-yl-sulfonyl)
631	Me	3-Cyanophenyl	S-(CH$_2$)$_3$-	5-fluoro
632	Et	3-Thienyl	S-(CH$_2$)$_2$-	5-methoxy
633	Me	Carboxamide	S-CH -C(CH$_3$)=CH-CH -	5-methoxy
634	Butyl	Cyclohexyl-	S-CH -cycProp-(CH) -	5-chloro
635	Me	3-Pyrrolyl	S-(CH$_2$)$_3$-	5-nitro
636	Me	2-Pyrazinyl-	S-(CH$_2$)$_2$-	5-nitro
637	Pentyl	tert-Butyl	CO-(CH$_2$) -	6-methoxy

09 JUL 2003

Ex.	R^1	R^2	A	R^6
638	Me	Pyridin-3-yl-	CO-$(CH_2)_2$-	5-fluoro
639	Me	4-Iodophenyl	S-$(CH_2)_3$-	5-fluoro
640	Me	4-Methylsulfonylphenyl	S-$(CH_2)_8$-	5-(piperidin-1-yl-sulfonyl)
641	iProp	N-Propyltetrazolyl-	S-$(CH_2)_3$-	5-fluoro
642	cycProp	tert-butyl	CO-$(CH_2)_2$-	6-methoxy
643	Me	2-Aminothiazol-4-yl-	S-$(CH_2)_3$-	5-fluoro
644	cycProp	4-Methylsulfonylphenyl	S-$(CH_2)_8$-	5-(piperidin-1-yl-sulfonyl)
645	Me	Pyridin-3-yl-	S-CH_2-CH=CH-CH_2-	5-methoxy
646	Me	N-Propyltetrazolyl-	S-CH_2-CH=CH-CH_2-	5-nitro
647	cycProp	Carboxamide	S-$(CH_2)_4$-	5-fluoro
648	Me	N-Methyl-2-pyrrolyl-	S-$(CH_2)_3$-	5-nitro
649	Me	2-Me-4-oxazolyl-	S-$(CH_2)_4$-	5-nitro
650	Me	Pyridin-4-yl-	S-$(CH_2)_4$-	5-nitro
651	Me	3-Br-pyridin-5-yl-	S-CH_2-CH=CH-CH_2-	5-methoxy
652	Me	Phenyl-	S-$(CH_2)_3$-	5-fluoro
653	Me	4-Iodophenyl	S-$(CH_2)_3$-	5-methoxy
654	Me	3-Pyrrolyl	S-$(CH_2)_4$-	5-methoxy
655	Me	Phenyl-	S-CH_2-CH=CH-CH_2-	5-(piperidin-1-yl-sulfonyl)
656	Me	3-Cyanophenyl	S-$(CH_2)_3$-	5-methoxy
657	Me	N-Methyl-2-pyrrolyl-	S-CH_2-cycProp-$(CH_2)_2$-	5-methoxy
658	Me	Phenyl	O-$(CH_2)_3$-	5-cyano

09 JUL 2003

Ex.	R^1	R^2	A	R^6
659	Pentyl	Cyclohexyl-	S-(CH)$_3$-	5-chloro
660	Me	3-Benzthienyl-	S-CH -cycProp-(CH$_2$)$_2$-	5-fluoro
661	Pentyl	Carboxamido	S-(CH$_2$)$_3$-	5-chloro
662	Et	5-Methylimidazol-4-yl-	S-CH$_2$-CH CH-CH$_2$-	5-methoxy
663	iProp	Cyclohexyl-	S-(CH$_2$)$_3$-	5-fluoro
664	Me	3-Benzthienyl-	S-(CH$_2$)$_3$-	5-nitro
665	Butyl	Cyclohexyl-	S-CH$_2$-cycProp-(CH$_2$)$_2$-	5-methoxy
666	Me	4-Methoxyphenyl	S-(CH$_2$)$_3$-	5-methoxy
667	Prop	N-Propyltetrazolyl-	S-CH$_2$-CH=CH-CH$_2$-	5-fluoro
668	Pentyl	Phenyl	CONH-(CH)$_4$-	5-cyano
669	Me	Phenyl-	CO-(CH$_2$) -	5-methoxy
670	Prop	Cyclohexyl-	S-(CH$_2$)$_2$-	5-fluoro
671	Butyl	Methylamino	S-(CH$_2$)$_3$-	5-methoxy
672	Me	4-Methylthiazol-5-yl	S-(CH$_2$)$_2$-	5-cyano
673	cycProp	N-Propyltetrazolyl-	S-CH$_2$-CH=CH-CH$_2$-	5-nitro
674	cycProp	Propyl	CO-(CH$_2$) -	5-methoxy
675	Me	Oxadiazol-2-yl	S-CH$_2$-CH=CH-CH$_2$-	5-nitro
676	Me	3-Pyridyl	S-(CH$_2$)$_2$-	5-chloro
677	Me	5-Methylimidazol-4-yl-	S-(CH$_2$)$_3$-	5-fluoro
678	Me	5-Methylimidazol-4-yl-	S-CH$_2$-C(CH$_3$)=CH-CH$_2$-	5-(pyrrolidin-1-yl-sulfonyl)
679	Me	3-Pyrrolyl	S-(CH$_2$)$_3$-	5-fluoro

09 JUL 2003

Ex.	R^1	R^2	A	R^6
680	Me	Cyclohexyl-	O-(CH$_2$)$_4$-	5-nitro
681	Me	Methylamino-	S-CH$_2$-C(CH$_3$)=CH-CH$_2$-	5-(piperidin-1-yl-sulfonyl)
682	iProp	6-Chlorobiphenyl-2-	S-(CH$_2$)$_4$-	5-fluoro
683	Me	3-Cyanophenyl	S-(CH$_2$)$_4$-	5-nitro
684	Pentyl	N-Propyltetrazolyl-	S-CH$_2$-CH$_2$-CH=CH$_2$-	5-chloro
685	Me	Phenyl	CONH-(CH$_2$)$_4$-	5-cyano
686	cycProp	Phenyl	COO-(CH$_2$)$_2$-	5-(piperidin-1-yl-sulfonyl)
687	Me	Amino	S-(CH$_2$)$_4$-	5-nitro
688	Me	Phenyl	CONH-(CH$_2$)$_4$-	5-chloro
689	Me	2-Pyrazinyl-	S-(CH$_2$)$_4$-	5-fluoro
690	Me	4-Iodophenyl	S-CH$_2$-CH$_2$-CH-CH$_2$-	5-nitro
691	Me	2-Pyrazinyl-	S-CH$_2$-cycProp-(CH$_2$)$_2$-	5-(pyrolidin-1-yl-sulfonyl)
692	Me	Pyridin-4-yl-	S-(CH$_2$)$_3$-	5-methoxy
693	Pentyl	4-Methylsulfonylphenyl	S-(CH$_2$)$_6$-	5-(piperidin-1-yl-sulfonyl)
694	Pentyl	N-Methyl-2-pyrrolyl-	S-(CH$_2$)$_2$-	5-chloro
695	cycProp	Phenyl	O-(CH$_2$)$_4$-	5-cyano
696	Me	4-Imidazolyl-	S-(CH$_2$)$_2$-	5-nitro
697	Me	3-Pyrrolyl	S-CH$_2$-CH$_2$-CH-CH$_2$-	6-chloro
698	Me	Oxadiazol-2-yl	(CH2)$_2$-CH(CH$_3$)-CH$_2$-CH$_2$-	5-fluoro
699	Me	6-Chlorobiphenyl-2-	S-(CH$_2$)$_4$-	5-nitro
700	Butyl	4-Methoxyphenyl	S-(CH$_2$)$_2$-	5-methoxy

09 JUL 2003

Ex.	R^1	R^2	A	R^6
701	Me	3-Br-pyridin-5-yl-	S-$(CH_2)_2$-	5-nitro
702	Prop	N-Propyltetrazolyl-	S-CH_2-CH=CH-CH_2-	5-chloro
703	Me	5-Methylimidazol-4-yl-	$(CH_2)_2$-$CH(CH_3)$-CH_2-CH_2-	tert-butyl
704	Pentyl	Carboxamido	S-$(CH_2)_2$-	5-fluoro
705	Me	2-Pyrazinyl-	S-$(CH_2)_3$-	5-methoxy
706	Pentyl	Phenyl-	CO-$(CH_2)_3$-	6-methoxy
707	Me	4-Imidazolyl-	S-$(CH_2)_2$-	5-methoxy
708	Me	Phenyl-	CO-$(CH_2)_3$-	6-methoxy
709	Me	Tetrazolyl-	S-CH_2-C(=CH_2)-CH_2	5-nitro
710	cycProp	N-Methyl-2-pyrrolyl-	S-$(CH_2)_2$-	5-chloro
711	cycProp	Cyclohexyl-	S-$(CH_2)_2$-	5-nitro
712	cycProp	Carboxamido	S-$(CH_2)_2$-	5-chloro
713	iProp	2,5-Dimethylfuranyl-3-	S-$(CH_2)_2$-	5-fluoro
714	Me	Amino	S-CH_2-cyclProp-$(CH_2)_2$-	5-fluoro
715	Me	3-Thienyl	$(CH_2)_2$-$CH(CH_3)$-CH_2-CH_2-	5-fluoro
716	Me	3-Thienyl	O-$(CH_2)_3$-	5-nitro
717	Me	tert-butyl	CO-$(CH_2)_3$-	6-methoxy
718	Me	Amino	S-$(CH_2)_3$-	5-methoxy
719	Me	2-Me-4-oxazolyl-	S-$(CH_2)_3$-	5-fluoro
720	Et	Tetrazolyl-	S-CH_2-C(CH_3)=CH-CH_2-	5-methoxy
721	Prop	Carboxamido	S-$(CH_2)_2$-	5-chloro

09 JUL 2003

Ex.	R^1	R^2	A	R^6
722	Et	4-Methylthiazol-5-yl	S-(CH) -	5-methoxy
723	Me	4-Imidazolyl-	S-(CH.) .-	5-fluoro
724	Me	4-Methylthiazol-5-yl	S-(CH.) -	5-fluoro
725	Et	2-Me-4-oxazolyl-	S-(CH.) .-	5-methoxy
726	Butyl	4-Methoxyphenyl	S-(CH.) .-	5-fluoro
727	Me	2,5-Dimethylfuranyl-3-	S-(CH.) .	5-methoxy
728	Me	3-Br-pyridin-5-yl-	S-(CH.) .-	5-fluoro
729	Pentyl	N-Methyl-2-pyrrolyl-	S-(CH.) -	5-fluoro
730	cycProp	N-Methyl-2-pyrrolyl-	S-(CH.) .-	5-nitro
731	Prop	Cyclohexyl-	S-(CH.) .-	5-chloro
732	cycProp	3-Pyridyl	S-(CH) .-	5-chloro
733	cycProp	Cyclohexyl-	S-(CH.) .	5-chloro
734	Me	N-Propyltetrazolyl-	S-(CH.) .-	5-methoxy
735	Me	Methylamino	S-(CH) .	5-nitro
736	Me	Pyridin-3-yl-	S-(CH.) -	5-nitro
737	Me	2-Aminothiazol-4-yl-	S-(CH.) .-	5-nitro
738	Et	Oxadiazol-2-yl	S-(CH.) -	5-methoxy
739	Me	3-Cyanophenyl	S-CH -C(CH)-CH.	5-(piperidin-1-yl-sulfonyl)
740	cycProp	Phenyl-	CO-(CH.) -	6-methoxy
741	Me	2-Me-4-oxazolyl-	(CH) .-CH(CH)-CH.-CH.-	5-(morpholin-1-yl-sulfonyl)
742	Et	2-Aminothiazol-4-yl-	S-CH -CH CH-CH.-	5-methoxy

09 JUL 2003

Ex.	R^1	R^2	A	R^6
743	Me	2,5-Dimethylfuranyl-3-	S-(CH) -	5-nitro
744	Me	Phenyl	COO-(CH) -	5-(piperidin-1-yl-sulfonyl)
745	Me	2-Me-4-oxazolyl-	S-(CH) -	5-fluoro
746	iProp	Pyridin-4-yl-	S-(CH) -	5-fluoro
747	Me	Methylamino	S-CH -cyc Prop-(CH) -	5-methoxy
748	Me	5-Methylimidazol-4-yl-	S-(CH)	5-nitro
749	Me	2-Me-4-oxazolyl-	S-(CH) -	5-cyano
750	cycProp	Carboxamido	S-(CH) -	5-cyano
751	Me	Tetrazolyl-	S-(CH) -	5-fluoro
752	Pentyl	Cyclohexyl-	S-(CH) -	5-fluoro
753	Prop	N-Methyl-2-pyrrolyl-	S-(CH) -	5-chloro
754	Me	N-Methyl-2-pyrrolyl-	S-(CH) -	5-fluoro
755	cycProp	N-Propyltetrazolyl-	S-CH -CH CH-CH -	5,6-dichloro
756	Pentyl	Propyl	CO-(CH) -	5-methoxy
757	Me	4-Methoxyphenyl	S-(CH)	5-nitro
758	Me	Propyl	CO-(CH) -	5-methoxy
759	Me	2-Me-4-oxazolyl-	S-(CH) -	5-methoxy
760	cycProp	Phenyl	CONH-(CH) -	5-cyano
761	Me	Carboxamido	S-(CH)	5-cyano
762	Et	tert-butyl	S-CH -cyc Prop-(CH) -	5-methoxy
763	cycProp	N-Methyl-2-pyrrolyl-	S-(CH) -	5-fluoro

09 JUL 2003

Examples of pharmaceutical administration forms

A) Tablets

Tablets of the following composition were pressed on a tabletting machine in the customary manner

40 mg of the substance from 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 in a submicroscopically fine dispersion)
6.75 mg of potato starch (as a 6% paste)

B) Sugar-coated tablets

20 mg of the substance from Example 3
60 mg of core composition
70 mg of sugar-coating composition

The core composition consists of 9 parts of corn starch, 3 parts of lactose and 1 part of vinylpyrrolidone-vinyl acetate 60:40 copolymer. The sugar-coating composition consists of 5 parts of cane sugar, 2 parts of corn starch, 2 parts of calcium carbonate and 1 part of talc. The sugar-coated tablets which have been prepared in this way are then provided with an enteric coating.

Biological investigations - receptor binding studies

1) D_3 binding test

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

Cell preparation

The D_3-expressing cells were multiplied in RPMI-1640 containing 10% fetal calf serum (GIBCO No. 041-32400 N); 100 U/ml of penicillin and 0.2% streptomycin (GIBO 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 solution was neutralized with medium and the cells were collected by centrifuging at 300 g. In order to lyse the cells, the pellet was washed briefly with lysis buffer (5 mM Tris-HCl, pH 7.4, containing 10% glycerol) and after that 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 $MgCl_2$, 10 µM quinolinol, 0.1% 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 in the presence and absence of the test substance. The nonspecific binding was determined using 10^{-6} M spiperone.

After 60 min, the free radioligand and the bound radioligand were separated by filtering through GF/B glass fiber filters (Whatman, England) on a Skatron cell harvester (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 Glutamix I™ and 25 mM HEPES containing 10% fetal calf serum albumin. All the media contained 100 units per ml of penicillin and 100 µg/ml of streptomycin. The cells were maintained at 37°C in a moist atmosphere containing 5% CO_2.

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

Receptor binding tests

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

The test mixtures (1 ml) consisted 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 additionally 1 µM haloperidol (nonspecific binding) or test substance.

After the test mixtures had been incubated at 25°C for 60 minutes, they were filtered through GF/B glass fiber filters (Whatman, England) on a Skatron cell harvester

(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 results were evaluated as described in a).

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

In these tests, the compounds according to the invention exhibit very good affinities for the D_3 receptor (< 1 µmolar, in particular < 100 nmolar) and bond selectively to the D_3 receptor.

The $pK_i(D_3)$ values (negative decadic logarithm of the binding constant to the D_3 receptor) and the selectivity as compared with the binding to the D_2A receptor ($K_i(D_2)/K_i(D_3)$) for the compounds in Examples 3, 4 and 7 are given in Table 3.

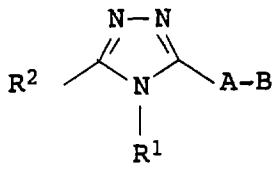
Table 3:

Example	$pK_i(D_3)$	Selectivity
3	8.02	78
4	7.96	67
7	8.37	81

259/iT/ew

We claim:

1. A triazole compound of the formula I



(I)

where

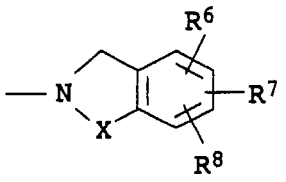
R^1 is H, C_1-C_6-alkyl, which may be substituted by OH, OC_1-C_6-alkyl, halogen or phenyl, C_3-C_6-cycloalkyl or phenyl;

R^2 is H, 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_1-C_6-alkylthio, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_6-cycloalkyl, halogen, CN, $COOR^3$, $CONR^3R^4$, NR^3R^4, SO_2R^3, $SO_2NR^3R^4$ or an aromatic radical which is selected from phenyl, naphthyl and a 5- or 6-membered heterocyclic radical having 1, 2, 3 or 4 heteroatoms which are selected, independently of each other, from O, N and S, with it being possible for the aromatic radical to have one or two 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, COR^3, NR^3R^4, NO_2, SO_2R^3, $SO_2NR^3R^4$ and phenyl which may be substituted by one or two radicals which are selected, independently of each other, from C_1-C_6-alkyl, C_1-C_6-alkoxy, NR^3R^4, CN, CF_3, CHF_2 or halogen;

R^3 and R^4 are, independently of each other, H, C_1-C_6-alkyl, which may be substituted by OH, OC_1-C_6-alkyl, halogen or phenyl, or phenyl;

A is C_4-C_{10}-alkylene or C_3-C_{10}-alkylene which comprises at least one group Z which is selected from O, S, $CONR^3$, COO, CO, C_3-C_6-cycloalkyl and a double or triple bond;

B is a radical of the following formula:



where

X is CH_2 or CH_2CH_2;

R^6, R^7 and R^8 are, independently of each other, selected from H, C_1-C_6-alkyl, which may be substituted by OH, OC_1-C_6-alkyl, which may be substituted by amino, mono- or di-C_1-C_4-alkylamino; C_1-C_6-alkylthio, halogen or phenyl; OH, C_1-C_6-alkoxy, OCF_3, OSO_2CF_3, SH, C_1-C_6-alkylthio, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halogen, CN, NO_2, CO_2R^3, SO_2R^3, $SO_2NR^3R^4$, where R^3 and R^4 have the abovementioned meanings and may also form together with the N atom to which they are bonded a saturated or unsaturated heterocycle with 5 to 7 ring atoms and 1 or 2 N heteroatoms, $CONR^3R^4$, $NHSO_2R^3$, NR^3R^4, a 5- or 6-membered carbocyclic, aromatic or nonaromatic ring and a 5- or 6-membered heterocyclic, aromatic or nonaromatic ring with 1 or 2 heteroatoms which are selected, independently of each other, from O, N and S, with the carbocyclic or heterocyclic ring being able to have one or two substituents which are selected, independently of each other, from C_1-C_6-alkyl, phenyl, phenoxy, halogen, C_1-C_6-alkoxy, OH, NO_2, CF_3 and CHF_2, and with two of the substituents R^6, R^7 and R^8 being able to form, together with the carbon atoms of the phenyl ring to which they are bonded, a phenyl, cyclopentyl or cyclohexyl ring which is fused to the phenyl ring, with the possibility for one or two of the CH or CH_2 groups in the fused ring being replaced by a nitrogen atom, an NH or an N-C_1-C_6 alkyl group;

and the salts thereof with physiologically tolerated acids.

2. A compound as claimed in claim 1 of the formula I, where X is CH_2CH_2.

3. A compound as claimed in claim 1 or 2 of the formula I, where A is C_4-C_{10}-alkylene or C_3-C_{10}-alkylene which comprises at least one group Z which is selected from O, S, COO, CO, a double bond or triple bond and C_3-C_6-cycloalkyl.

4. A compound as claimed in one of the preceding claims of the formula I, where A is C_4-C_{10}-alkylene of C_3-C_{10}-alkylene which comprises at least one group Z which is selected from O, S, a double bond and cyclohexyl.

5. A compound as claimed in one of the preceding claims of the formula I, where R^2 is an aromatic radical which is unsubstituted or has one or two substituents which are selected, independently of each other, from C_1-C_6-alkyl, OH, C_1-C_6-alkoxy, phenyl, CN and halogen.

6. A compound as claimed in one of the preceding claims of the formula I, where R^2 is H, C_1-C_6-alkyl, phenyl, thienyl, furanyl, tetrazolyl, pyrrolyl, pyridyl or pyrazinyl.

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

8. A compound as claimed in one of the preceding claims of the formula I, where R^6, R^7 and R^8 are selected, independently of each other, from H, C_1-C_6-alkyl, OH, C_1-C_6-alkoxy, C_1-C_6-akylthio-C_1-C_6-alkyl, halogen, CN, NO_2, SO_2R^3, $SO_2NR^3R^4$ and $CONR^3R^4$.

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

R^1 is H, C_1-C_6-alkyl or phenyl,
R^2 is H, C_1-C_6-alkyl, phenyl, thienyl, furanyl, tetrazolyl, pyrrolyl, thiazolyl or pyrazinyl,
A is -SC_3-C_{10}-alkylene which may comprise a double bond, and
R^6, R^7 and R^8 are selected from H, C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, $SO_2NR^3R^4$, CN, NO_2, CF_3, $CONR^3R^4$, CHF_2, OSO_2CF_3, OCF_3 and $NHSO_2$-C_1-C_6-alkyl.

10. A compound which is selected from
1-{2-[3-({4-methyl-5-[4-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-yl}sulfanyl)propyl]-1,2,3,4-tetrahydroisochinolin-7-yl}-ethanon;
1-(2-{3-[(4-methyl-5-(3-cyano)phenyl-4H-1,2,4-triazol-3-yl) sufanyl]propyl}-1,2,3,4-tetrahydroisochinolin-7-yl)ethanon;
1-{2-[3-({4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl}sulfanyl)propyl]-1,2,3,4-tetrahydroisochinolin-7-yl}ethanon;
1-{2-[3-({5-(2,4-dinitrophenyl)-4-methyl]-4H-1,2,4-triazol-3-yl}-sulfanyl)propyl]-1,2,3,4-tetrahydroisochinolin-7-yl}-ethanon;
1-(2-{3-[(4-methyl-5-(3-methoxy)phenyl-4H-1,2,4-triazol-

3-yl)-oxy]propyl}-1,2,3,4-tetrahydro-isochinolin-7-yl)ethanon;
1-{2-[3-({4-isopropyl-5-phenyl-4H-1,2,4-triazol-3-yl}sulfanyl)propyl]-1,2,3,4-tetrahydroisochinolin-7-yl}ethanon;
1-{2-[3-({4-butyl-5-phenyl-4H-1,2,4-triazol-3-yl}sulfanyl)propyl]-1,2,3,4-tetrahydroisochinolin-7-yl}ethanon;
1-{2-[3-({5-phenyl-4-propyl-4H-1,2,4-triazol-3-yl}sulfanyl)propyl]-1,2,3,4-tetrahydroisochinolin-7-yl}ethanon;
1-{2-[3-({4-cyclopropyl-5-phenyl-4H-1,2,4-triazol-3-yl}sulfanyl)propyl]-1,2,3,4-tetrahydroisochinolin-7-yl}ethanon; und
1-{2-[3-({4-ethyl-5-phenyl-4H-1,2,4-triazol-3-yl}sulfanyl)propyl]-1,2,3,4-tetrahydroisochinolin-7-yl}ethanon.

11. A pharmaceutical which comprises at least one compound as claimed in one of claims 1 to 9, where appropriate together with physiologically acceptable excipients and/or adjuvants.

12. The use of at least one compound as claimed in one of claims 1 to 9 for preparing a pharmaceutical for treating diseases which respond to the influence of dopamine D_3 receptor antagonists or agonists.