



DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 03-047651

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **534** DE

FECHA **28 DE NOVIEMBRE DE 2003** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **25 DE FEBRERO DEL 2004**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

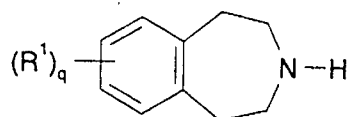
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(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		(74) Agent: GARRETT, Michael; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).	
(72) Inventors; and		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(75) Inventors/Applicants (for US only): HADLEY, Michael, Stewart [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). JOHNSON, Christopher, Norbert [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). MACDONALD, Gregor, James [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). STEMP, Geoffrey [GB/GB]; SmithKline		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: TETRAHYDROBENZAZEPINE DERIVATIVES USEFUL AS MODULATORS OF DOPAMINE D ₃ RECEPTORS (ANTI-PSYCHOTIC AGENTS)			
(I)			
—Ar (a) —Ar¹—Y—Ar² (b) (c) (CH₂)_r—V—(CH₂)_sAr (d)			
(57) Abstract			
Compounds of formula (I), wherein R² represents a hydrogen atom or a C₁₋₄alkyl group; q is 1 or 2; A represents a group of formula (a), (b), (c) or (d), wherein Ar represents an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered aromatic heterocyclic ring; or an optionally substituted bicyclic ring system; Ar¹ and Ar² each independently represent an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered aromatic heterocyclic ring; and Y represents a bond, —NHCO—, —CONH—, —CH₂—, or —(CH₂)_mY¹(CH₂)_n—, wherein Y¹ represents O, S, SO₂, or CO and m and n each represent zero or 1 such that the sum of m+n is zero or 1; providing that when A represents a group of formula (a), any substituent present in Ar <i>ortho</i> to the carboxamide moiety is necessarily a hydrogen or a methoxy group; r and s independently represent an integer from zero to 3 such that the sum of r and s is equal to an integer from 1 to 4; V represents a bond, O or S; and salts thereof. Compounds of formula (I) and their salts have affinity for dopamine receptors, in particular the D₃ receptor, and thus potential in the treatment of conditions wherein modulation of the D₃ receptor is beneficial, e.g. as antipsychotic agents.			

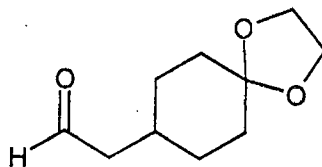
into a corresponding ketone, followed by reductive amination. This may be effected by methods well known in the art for (i) conversion of a ketal to a ketone in the presence of aqueous acid; followed by (ii) reductive amination of the ketone with R^2NH_2 or ammonium acetate in the presence of a reducing agent. Suitable reducing agents which may be employed include sodium borohydride, cyanoborohydride or triacetoxyborohydride under acidic conditions, or catalytic hydrogenation. The reaction may conveniently be effected in a solvent such as methanol, ethanol or dichloroethane.

A compound of formula (VII) may itself be prepared by reacting a compound of formula (VIII):



Formula (VIII)

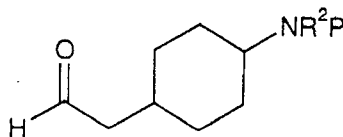
wherein R^1 and q are as hereinbefore defined;
with a compound of formula (IX):



Formula (IX)

in the presence of a reducing agent. Suitable reducing agents which may be employed include sodium borohydride, cyanoborohydride or triacetoxyborohydride under acidic conditions, or catalytic hydrogenation. The reaction may conveniently be effected in a solvent such as ethanol or dichloroethane.

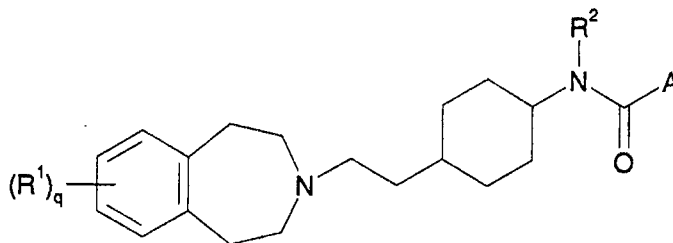
The individual *cis*- and *trans*- isomers of a compound of formula (II) may be prepared starting from *cis*- or *trans*- 4-amino-cyclohexanecarboxylic acid (T.P. Johnson, *et al.*, J. Med. Chem., 1997, (20), 279-290) followed by functional group interchange and/or protection using methods well known in the art, to give the individual *cis*- or *trans*- isomers of a compound of formula (X):



Formula (X)

Claims :

1. A compound of formula (I) :



Formula (I)

wherein:

- R^1 represents a substituent selected from: a hydrogen or halogen atom; a hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-4} alkyl, C_{1-4} alkoxy, aryl C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkoxy C_{1-4} alkyl, C_{3-6} cycloalkyl C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonyloxy, C_{1-4} alkylsulfonyl C_{1-4} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonyl C_{1-4} alkyl, C_{1-4} alkylsulfonylamido, C_{1-4} alkylamido, C_{1-4} alkylsulfonylamido C_{1-4} alkyl, C_{1-4} alkylamido C_{1-4} alkyl, arylsulfonylamido, arylcarboxamido, arylsulfonylamido C_{1-4} alkyl, arylcarboxamido C_{1-4} alkyl, aroyl, aroyl C_{1-4} alkyl, or aryl C_{1-4} alkanoyl group; a group $R^3OCO(CH_2)_p$, $R^3CON(R^4)(CH_2)_p$, $R^3R^4NCO(CH_2)_p$ or $R^3R^4NSO_2(CH_2)_p$ where each of R^3 and R^4 independently represents a hydrogen atom or a C_{1-4} alkyl group or R^3R^4 forms part of a C_{3-6} azacycloalkane or $C_{3-6}(2-oxo)azacycloalkane$ ring and p represents zero or an integer from 1 to 4; or a group Ar^3-Z , wherein Ar^3 represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring and Z represents a bond, O, S, or CH_2 ;

R^2 represents a hydrogen atom or a C_{1-4} alkyl group;

q is 1 or 2;

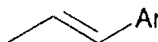
A represents a group of the formula (a), (b) (c) or (d):



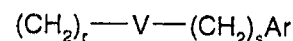
(a)



(b)



(c)



(d)

wherein

- Ar represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; or an optionally substituted bicyclic ring system;

Ar^1 and Ar^2 each independently represent an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; and

- Y represents a bond, $-NHCO-$, $-CONH-$, $-CH_2-$, or $-(CH_2)_mY^1(CH_2)_n-$, wherein Y^1 represents O, S, SO_2 , or CO and m and n each represent zero or 1 such that the sum of

m+n is zero or 1; providing that when A represents a group of formula (a), any substituent present in Ar *ortho* to the carboxamide moiety is necessarily a hydrogen or a methoxy group;

5 r and s independently represent an integer from zero to 3 such that the sum of r and s is equal to an integer from 1 to 4;

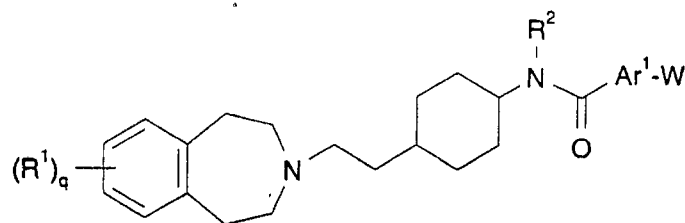
V represents a bond, O or S;
and salts thereof.

10 2. A compound according to claim 1 wherein q represents 1.

3. A compound according to any of the preceding claims wherein rings Ar, Ar¹, or Ar² are each independently optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, cyano, methoxy, methylenedioxy, acetyl, acetylamino, methylsulfonyl, methylsulfonyloxy, methylaminosulfonyl,
15 methylsulfonylamino, or methylaminocarbonyl group.

4. A compound of formula (I) which is:

20 *trans*-3-(2-(1-(4-(4-Quinoliny)carboxamido)cyclohexyl)ethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine;
trans-(*E*)-3-(2-(1-(4-(3-(3-Methylsulfonyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine;
trans-(*E*)-3-(2-(1-(4-(3-(4-Fluoro)phenylpropenoyl)amino)cyclohexyl)ethyl)-2,3,4,5-
25 tetrahydro-1*H*-3-benzazepine;
trans-3-(2-(1-(4-(2-Indolyl)carboxamido)cyclohexyl)ethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine;
trans-3-(2-(1-(4-(3-(3-Pyridyl)phenyl)carboxamido)cyclohexyl)ethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine;
30 *trans*-3-(2-(1-(4-Phenylacetamido)cyclohexyl)ethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine;
trans-3-(2-(1-(4-(3-Indolyl)acetamido)cyclohexyl)ethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine;
trans-3-(2-(1-(4-(4-Quinoliny)acetamido)cyclohexyl)ethyl)-2,3,4,5-tetrahydro-1*H*-3-
35 benzazepine;
trans-(*E*)-3-(2-(1-(4-(3-(4-Fluoro)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine;
trans-6-Methoxy-3-(2-(1-(4-(4-quinoliny)carboxamido)cyclohexyl)ethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine;
40 *trans*-6-Methoxy-3-(2-(1-(4-(3-pyrrolo[2,3-*b*]pyridyl)carboxamido)cyclohexyl)ethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine;
trans-(*E*)-7-Cyano-3-(2-(1-(4-(3-(4-fluoro)phenylpropenoyl)amino)cyclohexyl)ethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine;



Formula (VI)

wherein R^1 , R^2 , q , Ar^1 and W are as hereinbefore defined, with a compound Ar^2-W^1 ,
 5 wherein W^1 is a halogen atom or a trifluoromethylsulfonyloxy group when W is a group M , or W^1 is a group M when W is a halogen atom or a trifluoromethylsulfonyloxy group.

(f) interconversion of one compound of formula (I) to a different compound of
 formula (I) e.g. (i) alkylation of a compound (I) wherein R^2 represents hydrogen, (ii)
 10 conversion of one R^1 from alkoxy (e.g. methoxy) to hydroxy, or (iii) conversion of R^1
 from hydroxy to sulfonyloxy, eg alkylsulfonyloxy or trifluoromethanesulfonyloxy; (iv)
 conversion of a compound wherein Y represents S to a compound wherein Y is SO_2 or
 (v) conversion of Y from CO to CH_2 ;

(g) separation of *cis*- and *trans*- isomers of compounds of formula (I) by
 conventional methods;

15 and optionally thereafter forming a salt of formula (I).

6. A pharmaceutical composition comprising a compound of formula (I) as
 claimed in any of claims 1 to 4 or a physiologically acceptable salt thereof and a
 physiologically acceptable carrier therefor.

7. The use of a compound of formula (I) as claimed in any of claims 1 to 4 or
 a physiologically acceptable salt thereof in the manufacture of a medicament for the
 treatment of a condition which requires modulation of a dopamine receptor.

8. Use according to claim 7 wherein the dopamine receptor is a dopamine D_3
 receptor.

9. Use according to claim 7 or claim 8 wherein a dopamine antagonist is
 required.

10. Use according to any of claims 7 to 9 wherein the condition is a psychotic
 condition.

11. Use according to claim 10 wherein the psychotic condition is
 35 schizophrenia.

12. A method of treating a condition which requires modulation of a dopamine

PCT
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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)



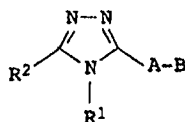
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(51) Internationale Patentklassifikation ⁷ : C07D 401/12, 401/14, A61K 31/41, A61P 25/16, 25/18, 25/24, C07D 413/14, 417/14, 401/06, 409/14	A1	(11) Internationale Veröffentlichungsnummer: WO 00/42036 (43) Internationales Veröffentlichungsdatum: 20. Juli 2000 (20.07.00)
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(21) Internationales Aktenzeichen: PCT/EP00/00177 (22) Internationales Anmeldedatum: 12. Januar 2000 (12.01.00) (30) Prioritätsdaten: 199 00 811.6 12. Januar 1999 (12.01.99) DE (71) Anmelder (für alle Bestimmungsstaaten ausser US): BASF AKTIENGESELLSCHAFT [DE/DE]; D-67056 Ludwigshafen (DE). (72) Erfinder; und (75) Erfinder/Anmelder (nur für US): STARCK, Dorothea [DE/DE]; Kaiser-Wilhelm-Str. 31, D-67059 Ludwigshafen (DE). TREIBER, Hans-Jörg [DE/DE]; Sperberweg 1, D-68782 Brühl (DE). UNGER, Liliane [DE/DE]; Wollstr. 129, D-67065 Ludwigshafen (DE). NEUMANN-SCHULTZ, Barbara [DE/DE]; Rheingastr. 42, D-68526 Ladenburg (DE). BLUMBACH, Kai [DE/DE]; Katharinenberg 26, D-97337 Dettelbach (DE). SCHÖBEL, Dietmar [DE/DE]; Weissbuchenweg 9, D-68167 Mannheim (DE). (74) Anwälte: KINZEBACH, Werner usw.; Ludwigsplatz 4, D-67059 Ludwigshafen (DE).	(81) Bestimmungsstaaten: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Veröffentlicht Mit internationalem Recherchenbericht.
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(54) Title: TRIAZOLE COMPOUNDS WITH DOPAMINE-D₃-RECEPTOR AFFINITY

(54) Bezeichnung: TRIAZOLVERBINDUNGEN MIT DOPAMIN-D₃-REZEPTORAFFINITÄT



(1)

(57) Abstract

The invention relates to triazole compounds of formula (I) in which R¹, R², A and B have the meanings given in the description. The compounds provided for in the invention have a high affinity for the dopamine-D₃-receptor and are therefore suitable for the treatment of diseases which respond to the influence of dopamine-D₃-receptor ligands.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft Triazolverbindungen der Formel (I), worin R¹, R², A und B die in der Beschreibung angegebenen Bedeutungen besitzen. Die erfindungsgemässen Verbindungen besitzen eine hohe Affinität zum Dopamin-D₃-Rezeptor und sind daher zur Behandlung von Erkrankungen brauchbar, die auf die Beeinflussung durch Dopamin-D₃-Liganden ansprechen.

(12) **United States Patent**
Starck et al.

(10) Patent No.: **US 6,602,867 B1**
(45) Date of Patent: **Aug. 5, 2003**

(54) **TRIAZOLE COMPOUNDS WITH
DOPAMINE-D₃-RECEPTOR AFFINITY**

(75) Inventors: **Dorothea Starck**, Ludwigshafen (DE);
Hans-Jörg Treiber, Brühl (DE);
Lilliane Unger, Ludwigshafen (DE);
Barbara Neumann-Schultz, Ladenburg
(DE); **Kai Blumbach**, Dettelbach (DE);
Dietmar Schöbel, Mannheim (DE)

(73) Assignee: **Abbott Laboratories**, Abbott Park, IL
(US)

(*) Notice: Subject to any disclaimer, the term of this
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(21) Appl. No.: **09/889,161**

(22) PCT Filed: **Jan. 12, 2000**

(86) PCT No.: **PCT/EP00/00177**

§ 371 (c)(1),
(2), (4) Date: **Jul. 11, 2001**

(87) PCT Pub. No.: **WO00/42036**

PCT Pub. Date: **Jul. 20, 2000**

(30) **Foreign Application Priority Data**

Jan. 12, 1999 (DE) 199 00 811

(51) Int. Cl.⁷ **C07D 401/12; C07D 401/14;**
C07D 413/14; A61K 31/41; A61P 25/16

(52) U.S. Cl. **514/217.07; 546/142; 546/141;**
546/145; 546/148; 514/309; 514/235.2;
514/307; 514/253.05; 544/125; 544/363;
540/597

(58) Field of Search **546/142, 141,**
546/145, 148; 514/309, 235.2, 307, 253.05,
217.07; 544/125, 363; 540/597

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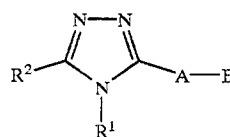
Primary Examiner—Richard L. Raymond

Assistant Examiner—Hong Liu

(74) Attorney, Agent, or Firm—Keil & Weinkauff

(57) **ABSTRACT**

Triazole compounds of the following formula



(I)

where R¹, R², A and B have the meanings given in the description are described. The compounds according to the invention possess a high affinity for the dopamine D₃ receptor and can therefore be used for treating diseases which respond to the influence of dopamine D₃ ligands.

18 Claims, No Drawings

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 D₃ 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 D₃ receptor ligands. U.S. Pat. Nos. 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 endotelin 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.

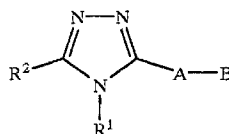
By 1990, two subtypes of dopamine receptor had been clearly defined pharmacologically, namely the D₁ and D₂ receptors.

More recently, a third subtype has been found, namely the D₃ receptor, which appears to mediate some of the effects of the antipsychotic and anti-Parkinson agents (J. C. Schwartz et al., *The Dopamine D₃ 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 D₃ receptors are chiefly expressed in the limbic system, it is assumed that while a selective D₃ ligand would probably have the properties of known antipsychotic agents, it would not have their dopamine D₃ receptor-mediated neurological side-effects (P. Sokoloff et al., *Localization and Function of the D₃ Dopamine Receptor*, *Arzneim. Forsch./Drug Res.* 42(1), 224 (1992); P. Sokoloff et al. *Molecular Cloning and Characterization of a Novel Dopamine Receptor (D₃) 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 D₃ receptor and a low affinity for the D₂ receptor. These compounds are consequently selective D₃ ligands.

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



where

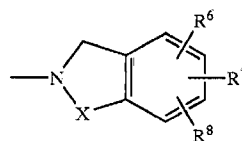
R¹ is H, C₁-C₆-alkyl, which may be substituted by OH, OC₁-C₆-alkyl, halogen or phenyl, C₃-C₆-cycloalkyl or phenyl;

R² is H, C₁-C₆-alkyl, which may be substituted by OH, OC₁-C₆-alkyl, halogen or phenyl, C₁-C₆-alkoxy, C₁-C₆-alkylthio, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, halogen, CN, COOR³, CONR³R⁴, NR³R⁴, SO₂R³, SO₂NR³R⁴, 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 C₁-C₆-alkyl, which may be substituted by OH, OC₁-C₆-alkyl, halogen or phenyl, C₁-C₆-alkoxy, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, halogen, CN, COR³, NR³R⁴, NO₂, SO₂R³, SO₂NR³R⁴ and phenyl which may be substituted by one or two radicals which are selected, independently of each other, from C₁-C₆-alkyl, C₁-C₆-alkoxy, NR³R⁴, CN, CF₃, CHF₂ or halogen;

R³ and R⁴ are, independently of each other, H, C₁-C₆-alkyl, which may be substituted by OH, OC₁-C₆-alkyl, halogen or phenyl, or phenyl;

A is C₄-C₁₀-alkylene or C₃-C₁₀-alkylene which comprises at least one group Z which is selected from O, S, CONR³, COO, CO, C₃-C₆-cycloalkyl and a double or triple bond;

B is a radical of the following formula:



where

X is CH₂ or CH₂CH₂;

R⁶, R⁷ and R⁸ are, independently of each other, selected from H, C₁-C₆-alkyl, which may be substituted by OH, OC₁-C₆-alkyl, which may be substituted by amino, mono- or di-C₁-C₄-alkylamino; C₁-C₆-alkylthio, halogen or phenyl; OH, C₁-C₆-alkoxy, OCF₃, OSO₂CF₃, SH, C₁-C₆-alkylthio, C₂-C₆-alkenyl, C₂-C₆-alkynyl, halogen, CN, NO₂, CO₂R³, SO₂R³, SO₂NR³R⁴, where R³ and R⁴ 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, CONR³R⁴, NHSO₂R³, NR³R⁴, 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

Examples of Pharmaceutical Administration Forms

A) Tablets

Tablets of the following composition were pressed on a tableting 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

D₃ binding test

Cloned human D₃-receptor-expressing CCL 1,3 mouse fibroblasts, obtainable from Res. Biochemicals Internat. One Strathmore Rd., Natick, Mass. 01760-2418 USA, were used for the binding studies.

Cell Preparation

The D₃-expressing cells were multiplied in RPMI-1640 containing 10% fetal calf serum (GIBCO No. 041-32400 N); 100 U of penicillin/ml and 0.2% streptomycin (GIBCO BRL, Gaithersburg, Md., USA). After 48 h, the cells were washed with PBS and incubated for 5 min with 0.05% trypsin-containing PBS. After that, the 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 10⁷ 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 D₃-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 CaCl₂, 2 mM MgCl₂, 10 μM quinolinol, 0.1% ascorbic acid and 0.1% BSA), at a concentration of approx. 10⁶ cells/250 μl of test mixture, and incubated at 30° C. with 0.1 nM ¹²⁵I-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) D₂ binding test

Cell Culture

HEK-293 cells possessing stably expressed human dopamine D_{2A} 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 of penicillin per mol and 100 μg/ml of streptomycin/ml. The cells were maintained at 37° C. in a moist atmosphere containing 5% CO₂.

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 D₂ receptor using ¹²⁵I-spiperone (81 TBq/mmol, Du Pont de Nemours, Dreieich)

The test mixtures (1 ml) consisted of 1×10⁵ cells in incubation buffer (50 mM Tris, 120 mM NaCl, 5 mM KCl, 2 mM MgCl₂ and 2 mM CaCl₂, pH 7.4 with HCl) and 0.1 mM ¹²⁵I-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 GM/B glass 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 IC₅₀ values using the Cheng and Prusoff formula.

In these tests, the compounds according to the invention exhibit very good affinities for the D₃ receptor (<1 μmolar, in particular <100 nmolar) and bond selectively to the D₃ receptor.

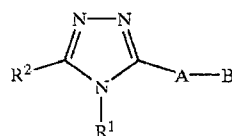
In table 3 pK_i(D₃) values (negative logarithm of the affinity constant for the D₃ receptor) and selectivity versus D₂ receptor (K_i(D₂)/K_i(D₃)) are given for the compounds of the examples 3, 4 and 7.

TABLE 3

Example	pK _i (D ₃)	Selectivity
3	8,02	78
4	7,96	67
7	8,37	81

We claim:

1. A triazole compound of the formula I



where

R¹ is H, C₁–C₆-alkyl, which may be substituted by OH, OC₁–C₆-alkyl, halogen or phenyl, C₃–C₆-cycloalkyl or phenyl;

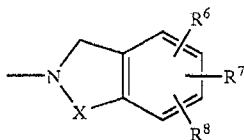
R² is H, C₁–C₆-alkyl, which may be substituted by OH, OC₁–C₆-alkyl, halogen or phenyl, C₁–C₆-alkoxy,

C₁-C₆-alkylthio, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, halogen, CN, COOR³, CONR³R⁴, NR³R⁴, SO₂R³, SO₂NR³R⁴ 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 C₁-C₆-alkyl, which may be substituted by OH, OC₁-C₆-alkyl, halogen or phenyl, C₁-C₆-alkoxy, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, halogen, CN, COR³, NR³R⁴, NO₂, SO₂R³, SO₂NR³R⁴ and phenyl which may be substituted by one or two radicals which are selected, independently of each other, from C₁-C₆-alkyl, C₁-C₆-alkoxy, NR³R⁴, CN, CF₃, CHF₂ or halogen;

R³ and R⁴ are, independently of each other, H, C₁-C₆-alkyl, which may be substituted by OH, OC₁-C₆-alkyl, halogen or phenyl, or phenyl;

A is C₄-C₁₀-alkylene or C₃-C₁₀-alkylene which comprises at least one group Z which is selected from O, S, CONR³, COO, CO, C₃-C₆-cycloalkyl and a double or triple bond;

B is a radical of the following formula:



where

X is CH₂ or CH₂CH₂;

R⁶, R⁷ and R⁸ are, independently of each other, selected from H, C₁-C₆-alkyl, which may be substituted by OH, OC₁-C₆-alkyl, which may be substituted by amino, mono- or di-C₁-C₄-alkylamino; C₁-C₆-alkylthio, halogen or phenyl; OH, C₁-C₆-alkoxy, OCF₃, OSO₂CF₃, SH, C₁-C₆-alkylthio, C₂-C₆-alkenyl, C₂-C₆-alkynyl, halogen, CN, NO₂, C(O)CH₃, CO₂R³, SO₂R³, SO₂NR³R⁴, where R³ and R⁴ 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, CONR³R⁴, NHSO₂R³, NR³R⁴, 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 C₁-C₆-alkyl, phenyl, phenoxy, halogen, C₁-C₆-alkoxy, OH, NO₂, CF₃ and CHF₂, and with two of the substituents R⁶, R⁷ and R⁸ 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 CH₂ groups in the fused ring being replaced by a nitrogen atom, an NH or an N-C₁-C₆ alkyl group; or a salt thereof with a physiologically tolerated acid.

2. A compound as claimed in claim 1 of the formula I, where A is C₄-C₁₀-alkylene or C₃-C₁₀-alkylene which comprises at least one group Z which is selected from O, S, COO, CO, a double bond or triple bond and C₃-C₆-cycloalkyl.

3. A compound as claimed in claim 1 of the formula I, where A is C₄-C₁₀-alkylene or C₃-C₁₀-alkylene which comprises at least one group Z which is selected from O, S, a double bond and cyclohexyl.

4. A compound as claimed in claim 1 of the formula I, where R² is an aromatic radical which is unsubstituted or has one or two substituents which are selected, independently of each other, from C₁-C₆-alkyl, OH, C₁-C₆-alkoxy, phenyl, CN and halogen.

5. A compound as claimed in claim 1 of the formula I, where R² is H, C₁-C₆-alkyl, phenyl, thienyl, furanyl, tetrazolyl, pyrrolyl, pyridyl or pyrazinyl.

6. A compound as claimed in claim 1 of the formula I, where R¹ is H, C₁-C₆-alkyl or C₃-C₆-cycloalkyl.

7. A compound as claimed in claim 1 of the formula I, where R⁶, R⁷ and R⁸ are selected, independently of each other, from H, C₁-C₆-alkyl, OH, C₁-C₆-alkoxy, C₁-C₆-alkylthio, C₁-C₆-alkyl, halogen, CN, C(O)CH₃, NO₂, SO₂R³, SO₂NR³R⁴ and CONR³R⁴.

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

R¹ is H, C₁-C₆-alkyl or phenyl,

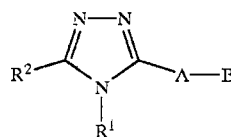
R² is H, C₁-C₆-alkyl, phenyl, thienyl, furanyl, tetrazolyl, pyrrolyl, thiazolyl or pyrazinyl,

A is -SC₃-C₁₀-alkylene which may comprise a double bond, and

R⁶, R⁷ and R⁸ are selected from H, C₁-C₆-alkyl, C₁-C₆-alkoxy, halogen, SO₂NR³R⁴, CN, C(O)CH₃, NO₂, CF₃, CONR³R⁴, CHF₂, OSO₂CF₃, OCF₃ and NHSO₂-C₁-C₆-alkyl.

9. A pharmaceutical which comprises at least one compound as claimed in claim 1, optionally together with physiologically acceptable excipients and/or adjuvants.

10. A triazole compound of formula I



where

R¹ is H, C₁-C₆-alkyl, which may be substituted by OH, OC₁-C₆-alkyl, halogen or phenyl, C₃-C₆-cycloalkyl or phenyl;

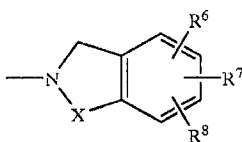
R² is H, C₁-C₆-alkyl, which may be substituted by OH, OC₁-C₆-alkyl, halogen or phenyl, C₁-C₆-alkoxy, C₁-C₆-alkylthio, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, halogen, CN, COOR³, CONR³R⁴, NR³R⁴, SO₂R³, SO₂NR³R⁴ or an aromatic radical which is selected from phenyl, naphthyl and a 5- or 6-membered 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 C₁-C₆-alkyl, which may be substituted by OH, OC₁-C₆-alkyl, halogen or phenyl, C₁-C₆-alkoxy, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, halogen, CN, COR³, NR³R⁴, NO₂, SO₂R³, SO₂NR³R⁴ and phenyl which may be substituted by one or two radicals which are selected, independently of each other, from C₁-C₆-alkyl, C₁-C₆-alkoxy, NR³R⁴, CN, CF₃, CHF₂ or halogen;

R³ and R⁴ are, independently of each other, H, C₁-C₆-alkyl, which may be substituted by OH, OC₁-C₆-alkyl, halogen or phenyl, or phenyl;

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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_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 , $C(O)CH_3$, 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; or a salt thereof with a physiologically tolerated acid.

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11. The compound defined in claim 10, wherein A is C_4-C_{10} -alkylene or C_3-C_{10} -alkylene which comprises at least one group Z selected from the group consisting of O, S, COO, CO, a double bond, a triple bond and C_3-C_6 -cycloalkyl.

12. The compound defined in claim 10, wherein A is C_4-C_{10} -alkylene or C_3-C_{10} -alkylene which comprises at least one group Z selected from the group consisting of O, S, a double bond and cyclohexyl.

13. The compound defined in claim 10, wherein 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.

14. The compound defined in claim 10, wherein R^2 is H, C_1-C_6 -alkyl, phenyl, thienyl, furanyl, tetrazolyl, pyrrolyl, pyridyl or pyrazinyl.

15. The compound defined in claim 10, wherein R^1 is H, C_1-C_6 -alkyl or C_3-C_6 -cycloalkyl.

16. The compound defined in claim 10, wherein 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 -alkylthio- C_1-C_6 -alkyl, halogen, CN, $C(O)CH_3$, NO_2 , SO_2R^3 , $SO_2NR^3R^4$ and $CONR^3R^4$.

17. The compound defined in claim 10, wherein

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, $C(O)CH_3$, NO_2 , CF_3 , $CONR^3R^4$, CHF_2 , OSO_2CF_3 , OCF_3 and $NHSO_2-C_1-C_6$ -alkyl.

18. A pharmaceutical which comprises at least one compound as defined in claim 10, optionally together with physiologically acceptable excipients and/or adjuvants.

* * * * *