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(54) **QUINAZOLINE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

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C07D 413/02 (2006.01)

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(58) **Field of Classification Search** 514/266.24, 514/266.4; 544/293
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,866,572	A	2/1999	Barker et al.
6,127,374	A	10/2000	Bridges
6,153,617	A	11/2000	Bridges
6,251,912	B1	6/2001	Wissner et al.
6,297,258	B1	10/2001	Wissner et al.
6,344,459	B1	2/2002	Bridges et al.
6,362,336	B1	3/2002	Lohmann et al.
6,403,580	B1	6/2002	Himmelsbach et al.
6,617,329	B2	9/2003	Himmelsbach et al.
6,627,634	B2	9/2003	Himmelsbach et al.
6,653,305	B2	11/2003	Himmelsbach et al.
6,656,946	B2	12/2003	Himmelsbach et al.
6,673,803	B2	1/2004	Thomas et al.
6,740,651	B2	5/2004	Himmelsbach et al.
6,924,285	B2	8/2005	Himmelsbach et al.
6,972,288	B1	12/2005	Himmelsbach et al.
7,019,012	B2	3/2006	Himmelsbach et al.
7,084,136	B2	8/2006	Tanimoto et al.
7,119,084	B2	10/2006	Himmelsbach et al.
7,160,889	B2	1/2007	Hennequin et al.
7,196,091	B2	3/2007	Himmelsbach et al.
7,220,750	B2 *	5/2007	Himmelsbach et al. ... 514/266.4
7,223,749	B2	5/2007	Himmelsbach et al.
7,456,189	B2	11/2008	Himmelsbach et al.
7,846,936	B2	12/2010	Hilberg et al.

(Continued)

FOREIGN PATENT DOCUMENTS

DE	199 08 567	2/1999

(Continued)

OTHER PUBLICATIONS

Bell, D.W. et al., "Inherited susceptibility to lung cancer may be associated with the T790M drug resistance mutation in EGFR". Nature Genetics, Dec. 2005, vol. 37, No. 12, p. 1315-1316. Published online Oct. 30, 2005.

(Continued)

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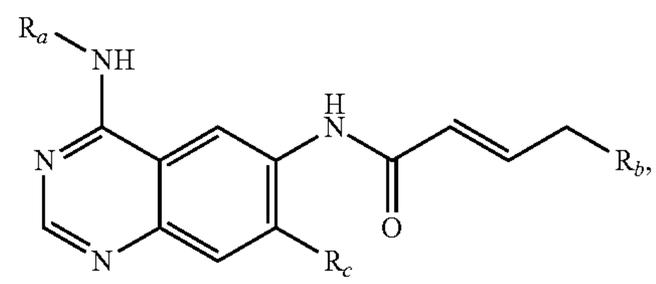
(57) **ABSTRACT**

A compound of general formula I



(I)

wherein:

R_a is a benzyl, 1-phenylethyl, or 3-chloro-4-fluorophenyl group;

R_b is a dimethylamino, N-methyl-N-ethylamino, diethylamino, N-methyl-N-isopropylamino, N-methyl-N-cyclopropylamino, N-methyl-N-(2-methoxyethyl)amino, N-ethyl-N-(2-methoxyethyl)amino, bis(2-methoxyethyl)amino, morpholino, N-methyl-N-(tetrahydrofuran-3-yl)amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino, N-methyl-N-(tetrahydrofuran-3-ylmethyl)amino, N-methyl-N-(tetrahydropyran-4-yl) amino, or N-methyl-N-(tetrahydropyran-4-ylmethyl) amino group; and

R_c is a cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-4-yloxy, or tetrahydropyran-4-ylmethoxy group,

or a tautomer, stereoisomer, or salt thereof,

particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, in particular an inhibitory effect on signal transduction mediated by tyrosine kinases, their use in the treatment of diseases, especially tumoral diseases and diseases of the lungs and airways, and the preparation thereof.

7 Claims, No Drawings

U.S. PATENT DOCUMENTS

2001/0044435	A1	11/2001	Himmelsbach et al.	
2002/0032208	A1	3/2002	Lohmann et al.	
2002/0077330	A1	6/2002	Himmelsbach et al.	
2002/0082270	A1	6/2002	Himmelsbach et al.	
2002/0169180	A1	11/2002	Himmelsbach et al.	
2002/0173509	A1	11/2002	Himmelsbach et al.	
2003/0149062	A1	8/2003	Jung et al.	
2003/0191308	A1	10/2003	Hennequin et al.	
2003/0225079	A1	12/2003	Singer et al.	
2004/0024019	A1	2/2004	Tanimoto et al.	
2004/0158065	A1	8/2004	Barth et al.	
2005/0043233	A1	2/2005	Stefanic et al.	
2005/0085495	A1	4/2005	Soyka et al.	
2005/0215574	A1*	9/2005	Bradbury et al.	514/266.4
2006/0058311	A1	3/2006	Munzert et al.	
2006/0100223	A1	5/2006	Himmelsbach et al.	
2006/0270672	A1	11/2006	Himmelsbach et al.	
2007/0027170	A1	2/2007	Soyka et al.	
2007/0078091	A1	4/2007	Hubler et al.	
2007/0099918	A1	5/2007	Singer et al.	
2007/0185091	A1	8/2007	Himmelsbach et al.	
2008/0103161	A1	5/2008	Himmelsbach et al.	
2008/0254040	A1	10/2008	Stefanic et al.	
2008/0269487	A1*	10/2008	Bradbury et al.	544/283
2009/0036676	A1	2/2009	Himmelsbach et al.	
2009/0203683	A1	8/2009	Himmelsbach et al.	
2009/0238828	A1	9/2009	Munzert et al.	
2009/0306044	A1	12/2009	Solca et al.	
2009/0306072	A1	12/2009	Jung et al.	
2009/0306101	A1	12/2009	Solca et al.	
2009/0306378	A1	12/2009	Schroeder et al.	
2009/0318480	A1	12/2009	Solca	
2010/0010023	A1*	1/2010	Himmelsbach et al.	514/266.24
2010/0069414	A1	3/2010	Himmelsbach et al.	
2010/0144639	A1	6/2010	Singer et al.	
2011/0039863	A1	2/2011	Hilberg et al.	
2011/0046168	A1	2/2011	Himmelsbach et al.	

FOREIGN PATENT DOCUMENTS

DE	199 11 366		3/1999
DE	19825591	A1	12/1999
DE	199 08 567		8/2000
DE	199 11 366		9/2000
DE	10017539	A1	10/2001
DE	10042060	A1	3/2002
DE	10042064	A1	3/2002
EP	0302967	A2	2/1989
EP	566226		10/1993
EP	0799619	A2	10/1997
EP	1123705	A1	8/2001
WO	WO 95/20045		7/1995
WO	9630347	A1	10/1996
WO	WO 96/30347		10/1996
WO	WO 96/33980		10/1996
WO	WO 97/02266		1/1997
WO	WO 97/38983		10/1997
WO	WO 98/43960		10/1998
WO	99-09016	*	2/1999
WO	WO 99/06378		2/1999
WO	WO 99/06396		2/1999
WO	WO 99/09016		2/1999
WO	9933980		7/1999
WO	WO 99/35146		7/1999
WO	9965228		12/1999
WO	9965228	A2	12/1999
WO	WO 00/18740		4/2000
WO	0031048	A1	6/2000
WO	WO 00/31068		6/2000
WO	WO 00/51991		9/2000
WO	WO-00/51991	A1	9/2000
WO	WO 00/55141		9/2000
WO	00/78735	A1 *	12/2000
WO	WO 00/78735		12/2000
WO	WO-00/78735	A1	12/2000
WO	0134574	A1	5/2001
WO	0168186	A2	9/2001
WO	WO 01/77104		10/2001
WO	WO-01/77104	A1	10/2001
WO	0218351	A1	3/2002
WO	0218372	A1	3/2002
WO	0218373	A1	3/2002
WO	0218375	A1	3/2002
WO	0218376	A1	3/2002
WO	0241882	A2	5/2002
WO	0250043	A1	6/2002
WO	03082290	A1	10/2003
WO	03089439	A1	10/2003
WO	03094921	A2	11/2003
WO	2004074263	A1	9/2004
WO	2004096224	A2	11/2004
WO	2004108664	A2	12/2004
WO	2005033096	A1	4/2005
WO	2005037824	A2	4/2005
WO	2006018182	A1	2/2006
WO	2007054550	A1	5/2007
WO	2007054551	A1	5/2007
WO	2007085638	A1	8/2007
WO	2008034776	A1	3/2008
WO	2009147238	A1	12/2009

OTHER PUBLICATIONS

Cancer Genome and Collaborative Group. Nature, Brief Communications, Sep. 2004, vol. 431, p. 525-526.

Harari, P.M. "Epidermal growth factor receptor inhibition strategies in oncology". Endocrine-Related Cancer, 2004, vol. 11. p. 689-708.

Krozely, P. Abstract—Clinical Journal of Oncology Nursing, 2004, vol. 8, No. 2, p. 1092-1095.

Paez, J. G. "EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy". Science, vol. 304, 2004, p. 1497-1500.

Yanase, K. et al., "Gefitinib reverses breast cancer resistance protein-medicated drug resistance". Molecular Cancer Therapeutics, 2004, Vo. 9, No. 9, p. 119-1125.

Abstract in English for DE19911366 in German cited herein, Apr. 16, 2010.

Abstract in English for WO199965228. cited herein, 1999.

Alan, R. "Benign Prostatic Hyperplasia (BPH)". Available at http://healthlibrary.epnet.com/GetContent/asp?token-1baaea3c-d4f5-4e14-8429-e3b3e1add7a7&chunkiid-1203, 2003.

Burris, Ha et al.; "EGF1004: a randomized, multicenter, phase lb study of the safety, biologic activity and clinical efficacy of the dual kinase inhibitor GW572016" Breast Cancer Research and Treatment, V. 82, suppl. 1 (2003), p. S18 #39.

deMiguel, M. et al., "Immunohistochemical comparative analysis of transforming grwoth factor a, epidermal growth factor, and epidermal growth factor receptor in normal, hyperplastic and neoplastic human prostates". Cytokine, 199, p. 722-727, 1998.

Gonzales-Barcena, D. et al., "Responses to the antagonistic analog of LH-RH (SB-75, cetrorelix) in patients with benign prostatic hyperplasia and prostatic cancer". The Prostate, 1994, 24(2), p. 84-92, only abstract provided.

Hofmann, B .B., Chapter 10 Catecholamines, Sympathomimetic Drugs, and Adrenergic Receptor Antagonists. "Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th ed." Hardman JG, Limbird, LE, and Gilman AG, Eds. McGraw-Hill, 2001, p. 215-268, pp. 215, 247 and 248 provided).

International Search Report for PCT/EP01/14569 mailed Mar. 1, 2002.

Lee, M., "Tamsulosin for the Treatment of Benigh Prostatic Hypertrophy". The Annals of Pharmacotherapy, Feb. 2000, 34, p. 188-199.

Rayford, W. et al., "Muscarinic Cholinergic Receptors Promote Growth of Human Prostate Cancer Cells". The Prostate, Feb. 1997, 30(3), p. 160-165.

Duque, J.L. et al., "Heparin-Binding Epidermal Growth Factor-Like Growth Factor is an Autocrine Mediator of Human Prostate Stromal Cell Growth in Vitro". The Journal of Urology, vol. 165, Jan. 2001, p. 284-288.

Barton, J. et al., "Growth Factors and their Receptors: new Targets for Prostate Cancern Therapy". Urology 58 (Supplement 2A), Aug. 2001, p. 114-122.

Herbst, R.S. et al., "Monoclonal Antibodies to Target Epidermal Growth Factor Receptor-Positive Tumors". Cancer, Mar. 1, 2002, vol. 94, No. 5, p. 1593-1611.
Johnson, J, et al. "Relationships between drug activity in NCI preclinical in vitro and in vitro and in vivo models and early clinical trials". British Journal of Cancer, 2001, 84 (10, p. 1424-1431.
Sausville, E. A. et al. "Contributions of Human Tumor Xenografts to Anticancer Drug Development". Cancer Research, 2006, vol. 66 (7), p. 3351-3354.
Laird & Cherrington, "Small Molecule Tyrosine Kinase Inhibitors: Clinical Development of Anticancer Agents," Expert Opinion, Investig. Drugs, Ashley Productions 2003, 12(1) p. 51-64.
Tsou, Hwei-Ru, "6-Substituted-4-(3-bromophenylamino)quinazolines as Putative Irreversible Inhibitors of the Epidermal Growth Factor Receptor (EGFR) and Human Epidermal Growth Factor Receptor (HER-2) Tyrosine Kinases with Enhanced Antitumor Activity", J. Med. Chem., 2001, 2719-2734, vol. 44.
U.S. Appl. No. 12/914,003, filed Oct. 28, 2010, Inventor: Frank Himmelsbach.
U.S. Appl. No. 10/016,280, Himmelsbach et al., filed Dec. 2001.*
Tsou, Hwei-Ru, "6-Substituted-4-(3-bromophenylamino)quinazolines as Putative Irrevesible Inhibitors of the Epidermal Growth Factor Receptor (EGFR) and Human Epidermal Growth Factor Receptor (HER-2) Tyrosine Kinases with Enhanced Antitumor Activity",J. Med. Chem., 2001, 2719-2734, vol. 44.

* cited by examiner

QUINAZOLINE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

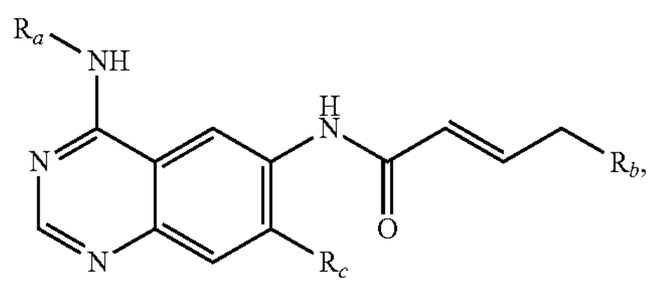
Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

RELATED APPLICATIONS

Benefit under 35 U.S.C. §119(e) of prior provisional application Ser. No. 60/259,201, filed [Dec. 18, 2000] *Dec. 28, 2000*, is hereby claimed*; benefit under 35 U.S.C. §119 of German application 100 63 435.4 filed Dec. 20, 2000 is also claimed.*

SUMMARY OF THE INVENTION

The present invention relates to quinazoline derivatives of general formula



the tautomers, the stereoisomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibitory effect on signal transduction mediated by tyrosine kinases, the use thereof for treating diseases, particularly tumoral diseases, diseases of the lungs and respiratory tract, and the preparation thereof.

In the above general formula I

R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group,

R_b denotes a dimethylamino, N-methyl-N-ethylamino, diethylamino, N-methyl-N-isopropylamino, N-methyl-N-cyclopropylamino, N-methyl-N-(2-methoxyethyl) amino, N-ethyl-N-(2-methoxyethyl)amino, bis(2-methoxyethyl)amino, morpholino, N-methyl-N-(tetrahydrofuran-3-yl)amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino, N-methyl-N-(tetrahydrofuran-3-ylmethyl)amino, N-methyl-N-(tetrahydropyran-4-yl)amino or N-methyl-N-(tetrahydropyran-4-ylmethyl)amino group and

R_c denotes a cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-4-yloxy or tetrahydropyran-4-ylmethoxy group,

with the exception of the compounds

(1) 3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}7-cyclobutyloxyquinazoline,

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}7-cyclopentyloxyquinazoline,

(8) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(9) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(10) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(11) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(12) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(13) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(14) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(15) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-ethyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(17) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,

(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline,

(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydropyran-4-yl)oxy]quinazoline,

(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline and

(21) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline.

Preferred compounds of the above general formula I are those wherein

R_a, R_b, and R_c are as hereinbefore defined, but with the exception of the compounds

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-1-yl]amino}-7-cyclobutyloxyquinazoline,

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}7-cyclopentyloxyquinazoline,

(8) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(9) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(10) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(11) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(12) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(13) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(14) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(15) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-ethyl-N-(2-methoxyethyl)amino]-1oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(17) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,

(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline,

(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-1yl]amino}-7-[(tetrahydropyran-4-yl)oxy]quinazoline,

(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(21) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(22) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(23) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(24) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(25) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(S)-N-methyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(26) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(R)-N-methyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(27) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(28) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(R)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}-amino)-7-cyclobutyloxyquinazoline,

(29) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(S)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}-amino)-7-cyclobutyloxyquinazoline,

(30) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydrofuran-3-yloxy)quinazoline,

(31) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydropyran-4-yloxy)quinazoline,

(32) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydrofuran-2-ylmethoxy)quinazoline and

(33) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

the tautomers, the stereoisomers and the salts thereof.

Particularly preferred compounds of general formula I are those wherein

R_a denotes a 1-phenylethyl or 3-chloro-4-fluorophenyl group,

R_b denotes a dimethylamino, N-methyl-N-ethylamino, diethylamino, N-methyl-N-isopropylamino, N-methyl-N-cyclopropylamino, N-methyl-N-(2-methoxyethyl) amino, N-ethyl-N-(2-methoxyethyl)amino, bis(2-methoxyethyl)amino, morpholino, N-methyl-N-(tetrahydrofuran-3-yl)amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino, N-methyl-N-(tetrahydrofuran-3-ylmethyl)amino, N-methyl-N-(tetrahydropyran-4-yl)amino or N-methyl-N-(tetrahydropyran-4-ylmethyl)amino group and

R_c denotes a cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-4-yloxy or tetrahydropyran-4-ylmethoxy group,

with the exception of the compounds

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}7-cyclobutyloxyquinazoline,

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(8) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(9) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}7-cyclopropylmethoxyquinazoline,

(10) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,
(11) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,
(12) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,
(13) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,
(14) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,
(15) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-ethyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,
(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,
(17) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,
(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline,
(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydropyran-4-yl)oxy]quinazoline,
(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,
(21) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,
(22) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,
(23) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,
(24) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(S)-N-methyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,
(25) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(R)-N-methyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,
(26) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,
(27) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydrofuran-3-yloxy)quinazoline,
(28) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydropyran-4-yloxy)quinazoline,
(29) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydrofuran-2-ylmethoxy)quinazoline,
(30) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,
(31) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,
(32) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(R)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}-amino)-7-cyclobutyloxyquinazoline and
(33) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(S)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}-amino)-7-cyclobutyloxyquinazoline,

the tautomers, the stereoisomers and the salts thereof.

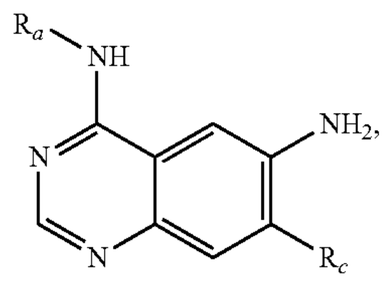
The following particularly preferred compounds of general formula I may be mentioned by way of example:

(a) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline;
(b) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,
(c) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(N,N-bis(2-methoxyethyl)amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,
(d) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(2-methoxyethyl)-N-ethylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,
(e) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,
(f) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,
(g) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(tetrahydrofuran-3-yl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,
(h) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[(tetrahydrofuran-3-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline,
(i) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)quinazoline,
(j) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)quinazoline,
(k) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-(tetrahydropyran-4-yloxy)quinazoline,
(l) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,
(m) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]quinazoline,
(o) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}7-[(tetrahydrofuran-3-yl)methoxy]quinazoline,
(p) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}7-cyclopropylmethoxyquinazoline,
(q) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,
(r) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,
(s) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline; and
(t) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline,

the tautomers, the stereoisomers and the salts thereof.

The compounds of general formula I may be prepared by the following methods, for example:

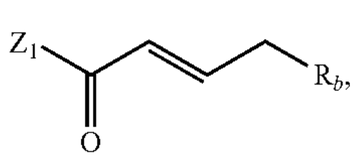
a) reacting a compound of general formula



(II)

wherein:

R_a and R_c are as hereinbefore defined, with a compound of general formula



(III)

wherein:

R_b is as hereinbefore defined; and

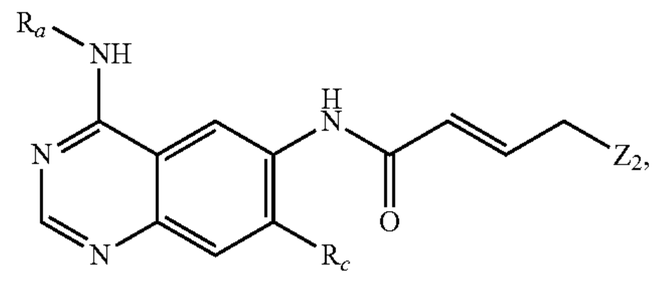
Z_1 denotes a leaving group such as a halogen atom, e.g., a chlorine or bromine atom, or a hydroxy group.

The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of an inorganic or organic base and optionally in the presence of a dehydrating agent, expediently at temperatures between −50° C. and 150° C., preferably at temperatures between −20° C. and 80° C.

With a compound of general formula III wherein Z_1 denotes a leaving group, the reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, conveniently in the presence of a tertiary organic base such as triethylamine, pyridine or 4-dimethylaminopyridine, in the presence of N-ethyldiisopropylamine (Hünig base), whilst these organic bases may simultaneously also act as solvent, or in the presence of an inorganic base such as sodium carbonate, potassium carbonate or sodium hydroxide solution, expediently at temperatures between −50° C. and 150° C., preferably at temperatures between −20° C. and 80° C.

With a compound of general formula III wherein Z_1 denotes a hydroxy group, the reaction is preferably carried out in the presence of a dehydrating agent, e.g., in the presence of isobutyl chloroformate, thionyl chloride, trimethyl chlorosilane, phosphorus trichloride, phosphorus pentoxide, hexamethyldisilazane, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, 1-hydroxybenzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, expediently in a solvent such as methylene chloride, tetrahydrofuran, dioxane, toluene, chlorobenzene, dimethylformamide, dimethylsulfoxide, ethylene glycol diethylether or sulfolane and optionally in the presence of a reaction accelerator such as 4-dimethylaminopyridine at temperatures between −50° C. and 150° C., but preferably at temperatures between −20° C. and 80° C.

b) Reacting a compound of general formula

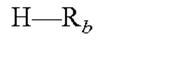


(IV)

wherein:

R_a and R_c are as hereinbefore defined; and

Z_2 denotes a leaving group such as a halogen atom, a substituted hydroxy or sulfonyloxy group such as a chlorine or bromine atom, a methanesulfonyloxy or p-toluenesulfonyloxy group, with a compound of general formula:



(V)

wherein R_b is as hereinbefore defined.

The reaction is expediently carried out in a solvent such as isopropanol, butanol, tetrahydrofuran, dioxane, toluene, chlorobenzene, dimethylformamide, dimethylsulfoxide, methylene chloride, ethylene glycol monomethylether, ethylene glycol diethylether or sulfolane or mixtures thereof, optionally in the presence of an inorganic or tertiary organic base, e.g., sodium carbonate or potassium hydroxide, a tertiary organic base, e.g., triethylamine or N-ethyldiisopropylamine (Hünig base), whilst these organic bases may simultaneously also serve as solvent, and optionally in the presence of a reaction accelerator such as an alkali metal halide at temperatures between −20° C. and 150° C., but preferably at temperatures between −10° C. and 100° C. The reaction may, however, also be carried out without a solvent or in an excess of the compound of general formula V used.

In the reactions described above, the secondary amino group bound to the quinazoline of general formula II or IV may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction. Examples of protecting groups include the formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl, or 2,4-dimethoxybenzyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g., in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulfuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g., in the presence of iodotrimethylsilane, at temperatures between 0° C. and 120° C., preferably at temperatures between 10° C. and 100° C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example hydrogenolytically, e.g., with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0° C. and 100° C., but preferably at ambient temperatures between 20° C. and 60° C., and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert-butyl or tert-butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane, optionally using a solvent such as methylene chloride, dioxane, methanol or diethyl ether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50° C. and 120° C. or by treating with sodium hydroxide solution optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0° C. and 50° C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures obtained may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known per se (cf N. L. Allinger and E. L. Eliel in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known per se, e.g., by chromatography and/or fractional crystallization, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallization from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as, e.g., esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g., on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are, e.g., the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulfonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (−)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (−)-menthyloxycarbonyl.

Furthermore, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, or maleic acid.

The compounds of general formulae II to V used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature.

For example, a starting compound of general formula II is obtained by reacting a 7-fluoro-6-nitro compound correspondingly substituted in the 4 position with a corresponding alkoxide and subsequently reducing the nitro compound thus obtained or

a starting compound of general formula III is obtained, for example, by reacting a suitable bromocrotonic acid derivative with one of the amines of general formula V known from the literature, or

a starting compound of general formula IV is obtained by acylating a compound of general formula II with a suitable crotonic acid derivative.

As already mentioned hereinbefore, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on signal transduction mediated by the Epidermal Growth Factor receptor (EGF-R), whilst this may be achieved for example by inhibiting ligand bonding, receptor dimerization or tyrosine kinase itself. It is also possible to block the transmission of signals to components located further down.

The biological properties of the new compounds were investigated as follows:

The inhibition of human EGF-receptor kinase was determined using the cytoplasmic tyrosine kinase domain (methionine 664 to alamine 1186, based on the sequence published in Nature 309 (1984), 418). To do this, the protein was expressed in Sf9 insect cells as a GST fusion protein using the Baculovirus expression system.

The enzyme activity was measured in the presence or absence of the test compounds in serial dilutions. The polymer pEY (4:1) produced by SIGMA was used as the substrate. Biotinylated pEY (bio-pEY) was added as the tracer substrate. Every 100 μl of reaction solution contained 10 μl of the inhibitor in 50% DMSO, 20 μl of the substrate solution (200 mM HEPES pH 7.4, 50 mM magnesium acetate, 2.5 mg/ml poly(EY), 5 μg/ml bio-pEY) and 20 μl of enzyme preparation. The enzyme reaction was started by the addition of 50 μl of a 100 μM ATP solution in 10 mM magnesium chloride. The dilution of the enzyme preparation was adjusted so that the incorporation of phosphate into the bio-pEY was linear in terms of time and quantity of enzyme. The enzyme preparation was diluted in 20 mM HEPES pH 7.4, 1 mM EDTA, 130 mM common salt, 0.05% Triton X-100, 1 mM DTT and 10% glycerol.

The enzyme assays were carried out at ambient temperature over a period of 30 minutes and were ended by the addition of 50 μl of a stopping solution (250 mM EDTA in 20 mM HEPES pH 7.4). 100 μl were placed on a streptavidin-coated microtiter plate and incubated for 60 minutes at ambient temperature. Then the plate was washed with 200 μl of a washing solution (50 mM Tris, 0.05% Tween 20). After the addition of 100 μl of a HRPO-labelled anti-PY antibody (PY20H Anti-PTyr:HRP produced by Transduction Laboratories, 250 ng/ml), it was incubated for 60 minutes. Then the microtiter plate was washed three times with 200 μl of washing solution. The samples were then combined with 100 μl of a TMB-peroxidase solution (A:B=1:1, Kirkegaard Perry Laboratories). After 10 minutes, the reaction was stopped. The extinction was measured at $OD_{450\ nm}$ with an ELISA reader. All data points were measured three times.

The data were matched by means of an iterative calculation using an analytical program for sigmoidal curves (Graph Pad Prism Version 3.0) with variable Hill pitch. All the iteration data released showed a correlation coefficient of more 0.9 and the upper and lower values of the curves showed a spread of at least a factor of 5. The concentration of active substance which inhibits the activity of EGF-receptor kinase by 50% (IC_{50}) was derived from the curves.

The following results were obtained:

Compound (Example No.)	Inhibition of EGF-Receptor Kinase IC_{50} [nM]
1	0.7
1(2)	0.6
1(3)	4.0
1(5)	3.0
1(10)	0.5
1(22)	1.0
1(32)	0.3
1(33)	0.5
1(34)	0.4

The compounds of general formula I according to the invention thus inhibit signal transduction by tyrosine kinases, as demonstrated by the example of the human EGF receptor, and are therefore useful for treating pathophysiological processes caused by hyperfunction of tyrosine kinases. These are, e.g., benign or malignant tumors, particularly tumors of epithelial and neuroepithelial origin, metastasization and the abnormal proliferation of vascular endothelial cells (neoangiogenesis).

The compounds according to the invention are also useful for preventing and treating diseases of the airways and lungs which are accompanied by increased or altered production of mucus caused by stimulation by tyrosine kinases, e.g., in inflammatory diseases of the airways such as chronic bronchitis, chronic obstructive bronchitis, asthma, bronchiectasis, allergic or non-allergic rhinitis or sinusitis, cystic fibrosis, α1-antitrypsin deficiency, or coughs, pulmonary emphysema, pulmonary fibrosis and hyperreactive airways.

The compounds are also suitable for treating diseases of the gastrointestinal tract and bile duct and gall bladder which are associated with disrupted activity of the tyrosine kinases, such as may be found, e.g., in chronic inflammatory changes such as cholecystitis, Crohn's disease, ulcerative colitis, and ulcers in the gastrointestinal tract or such as may occur in diseases of the gastrointestinal tract which are associated with increased secretions, such as Menetrier's disease, secreting adenomas and protein loss syndrome.

In addition, the compounds of general formula I and the physiologically acceptable salts thereof may be used to treat other diseases caused by abnormal function of tyrosine kinases, such as, e.g., epidermal hyperproliferation (psoriasis), inflammatory processes, diseases of the immune system, hyperproliferation of hematopoietic cells, etc.

By reason of their biological properties the compounds according to the invention may be used on their own or in conjunction with other pharmacologically active compounds, for example in tumour therapy, in monotherapy or in conjunction with other anti-tumour therapeutic agents, for example in combination with topoisomerase inhibitors (e.g., etoposide), mitosis inhibitors (e.g., vinblastine), compounds which interact with nucleic acids (e.g., cis-platin, cyclophosphamide, adriamycin), hormone antagonists (e.g., tamoxifen), inhibitors of metabolic processes (e.g., 5-FU etc.), cytokines (e.g., interferons), antibodies, etc. For treating respiratory tract diseases, these compounds may be used on their own or in conjunction with other therapeutic agents for the airways, such as substances with a secretolytic, broncholytic and/or anti-inflammatory activity. For treating diseases in the region of the gastrointestinal tract, these compounds may also be administered on their own or in conjunction with substances having an effect on motility or secretion. These combinations may be administered either simultaneously or sequentially.

These compounds may be administered either on their own or in conjunction with other active substances by intravenous, subcutaneous, intramuscular, intraperitoneal or intranasal route, by inhalation or transdermally or orally, whilst aerosol formulations are particularly suitable for inhalation.

For pharmaceutical use the compounds according to the invention are generally used for warm-blooded vertebrates, particularly humans, in doses of 0.01-100 mg/kg of body weight, preferably 0.1-15 mg/kg. For administration they are formulated with one or more conventional inert carriers and/or diluents, e.g., with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, stearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, sprays or suppositories.

The following Examples are intended to illustrate the present invention without restricting it.

Preparation of the Starting Compounds

EXAMPLE I

3-methylaminotetrahydrofuran

3.43 g of lithium aluminium hydride are added batchwise to 50 ml of tetrahydrofuran while cooling with an ice bath. Then a solution of 5.00 g of 3-[(benzyloxycarbonyl)-amino] tetrahydrofuran in 20 ml tetrahydrofuran is added dropwise, while the temperature remains below 10° C. After 10 minutes, the cooling bath is removed and the reaction mixture is refluxed for about three hours. For working up, 3.7 ml of water, 3.7 ml of 15% sodium hydroxide solution, and another 3 ml of water are carefully added dropwise to the reaction mixture while cooling with an ice bath. Then some tetrahydrofuran is added and the mixture is stirred for another 15 minutes. The aluminium hydroxide slurry precipitated is suction filtered and washed with a total of 150 ml of tetrahydrofuran. The filtrate is evaporated down using the rotary evaporator. A colorless oil remains, which is reacted without any further purification. Mass spectrum (ESI^+): m/z=102 $[M+H]^+$; R_f value: 0.20 (silica gel, methylene chloride/methanol=9:1).

EXAMPLE II

3-[(benzyloxycarbonyl)amino]tetrahydrofuran

12.36 ml of tetrahydrofuran-3-carboxylic acid and 27.84 ml of diphenylphosphorylazide in 500 ml of dioxane are combined with 41.91 g of benzyl alcohol and 35.81 ml of triethylamine. The reaction mixture is heated to 100° C. for about seven hours. After cooling to ambient temperature, the reaction mixture is evaporated down using the rotary evaporator. The residue is taken up in 500 ml of methylene chloride and washed twice with 100 ml of 1 N sodium hydroxide solution. The organic phase is dried over magnesium sulfate and evaporated down. The crude product is purified by chromatography over a silica gel column with cyclohexane/ethyl acetate (3:1 to 1:2) as eluant. Yield: 15.60 g (55% of theory); mass spectrum (ESI^-): m/z=220 $[M-H]^-$; R_f value: 0.78 (silica gel, methylene chloride/methanol=9:1).

EXAMPLE III

6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-((R)-tetrahydrofuran-3-yloxy)quinazoline

A mixture of 12.80 g of 4-[(3-chloro-4-fluorophenyl) amino]-6-nitro-7-((R)-tetrahydrofuran-3-yloxy)quinazoline, 200 ml of ethanol, 100 ml of water, and 17.20 ml of glacial acetic acid is heated to reflux temperature. Then a total of 7.00 g of iron powder is added in batches. The reaction mixture is

refluxed for about four hours and then cooled to ambient temperature overnight. For working up, the reaction mixture is evaporated using the rotary evaporator. The residue is taken up in methylene chloride/methanol (9:1), mixed with 20 ml of concentrated ammonia solution and filtered through a layer of silica gel. It is washed with copious amounts of methylene chloride/methanol (9:1) and the combined filtrates are evaporated down. The residue is stirred with diethylether and suction filtered. Yield: 8.59 g (73% of theory); mass spectrum (ESI^-): m/z=373, 375 $[M-H]^-$; R_f value: 0.27 (silica gel, ethyl acetate/methanol=9:1).

The following compounds are obtained analogously to Example III:

(1) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-((S)-tetrahydrofuran-3-yloxy)quinazoline
Mass spectrum (ESI^-): m/z=373, 375 $[M-H]^-$; R_f value: 0.27 (silica gel, ethyl acetate/methanol=9:1).

(2) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-(tetrahydropyran-4-yloxy)quinazoline
Mass spectrum (ESI^-): m/z=387, 389 $[M-H]^-$; R_f value: 0.20 (silica gel, ethyl acetate).

(3) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI^-): m/z=387, 389 $[M-H]^-$; R_f value: 0.55 (silica gel, ethyl acetate/methanol=9:1).

(4) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydrofuran-3-yl)methoxy]quinazoline
Mass spectrum (ESI^-): m/z=387, 389 $[M-H]^-$; R_f value: 0.40 (silica gel, ethyl acetate/methanol=9:1).

EXAMPLE IV

4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-((R)-tetrahydrofuran-3-yloxy)quinazoline

13.80 g of potassium tert-butoxide are added batchwise to a solution of 10.80 g of (R)-3-hydroxytetrahydrofuran in 100 ml of N,N-dimethylformamide while cooling with an ice bath. The reaction mixture is stirred for about one hour, then 10.40 g of 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-fluoroquinazoline are added batchwise. The cooling bath is then removed and the deep red reaction mixture is stirred for two hours at ambient temperature. For working up the reaction mixture is poured onto about 500 ml of water and neutralized with 2 N hydrochloric acid. The yellowish precipitate formed is suction filtered and dried at 70° C. in a circulating air drier. Yield: 12.80 g; melting point: 244° C.; mass spectrum (ESI^-): m/z=403, 405 $[M-H]^-$.

The following compounds are obtained analogously to Example IV:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-((S)-tetrahydrofuran-3-yloxy)quinazoline
Mass spectrum (ESI^-): m/z=403, 405 $[M-H]^-$; R_f value: 0.45 (silica gel, ethyl acetate).

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-(tetrahydropyran-4-yloxy)quinazoline
Mass spectrum (ESI^-): m/z=417, 419 $[M-H]^-$; R_f value: 0.42 (silica gel, ethyl acetate).

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI^-): m/z=417, 419 $[M-H]^-$; R_f value: 0.47 (silica gel, ethyl acetate).

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[(tetrahydrofuran-3-yl)methoxy]quinazoline
Mass spectrum (ESI^-): m/z=417, 419 $[M-H]^-$; R_f value: 0.41 (silica gel, ethyl acetate).

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[(tetrahydropyran-4-yl)methoxy]quinazoline
Mass spectrum (ESI^+): m/z=433, 435 $[M+H]^+$; R_f value: 0.79 (silica gel, ethyl acetate/methanol=9:1).

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[(R)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI^+): m/z=419, 421 $[M+H]^+$; R_f value: 0.44 (silica gel, ethyl acetate).

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI^+): m/z=419, 421 $[M+H]^+$; R_f value: 0.44 (silica gel, ethyl acetate).

EXAMPLE V

(R)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamine

21.10 g of (R)-N-[(tetrahydrofuran-2-yl)methyl]-N-benzyl-N-methylamine (crude product from Example VI) are dissolved in 200 ml of methanol and hydrogenated in the presence of 4.00 g of palladium on activated charcoal (10% Pd) at ambient temperature until the uptake of hydrogen has ended. For working up the catalyst is filtered off and the filtrate is evaporated using the rotary evaporator. A thin yellow oil is left, which is further reacted without any more purification. Yield: 8.60 g (73% of theory); mass spectrum (ESI^+): m/z=116 $[M+H]^+$.

The following compounds are obtained analogously to Example V:

(1) (S)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamine
Mass spectrum (ESI^+): m/z=116 $[M+H]^+$.

(2) N-[(tetrahydropyran-4-yl)methyl]-N-methylamine
Mass spectrum (ESI^+): m/z=130 $[M+H]^+$.

EXAMPLE VI

(R)-N-[(tetrahydrofuran-2-yl)methyl]-N-benzyl-N-methylamine

A solution of 24.60 g of (R)-tetrahydrofuran-2-carboxylic acid-N-benzyl-N-methylamide in 90 ml tetrahydrofuran is added dropwise to 17.00 g of lithium aluminium hydride in 150 ml of tetrahydrofuran. The reaction mixture is refluxed for two hours. For working up it is cooled to 0° C. in an ice bath, mixed with 20 ml of water and 10 ml of 15 N sodium hydroxide solution and stirred for another 20 minutes. Then it is filtered through a layer of magnesium sulfate and washed with a total of about 500 ml of tetrahydrofuran. The filtrate is evaporated down in vacuo, leaving a yellowish oil which is further reacted without any more purification. Yield: 21.10 g (92% of theory); mass spectrum (ESI^+): m/z=206 $[M+H]^+$.

The following compounds are obtained analogously to Example VI:

(1) (S)-N-[(tetrahydrofuran-2-yl)methyl]-N-benzyl-N-methylamine
R_f value: 0.20 (silica gel, ethyl acetate/methanol=9:1).

(2) N-[(tetrahydropyran-4-yl)methyl]-N-benzyl-N-methylamine
Mass spectrum (ESI^+): m/z=220 $[M+H]^+$.

EXAMPLE VII

(R)-tetrahydrofuran-2-carboxylic acid-N-benzyl-N-methylamide

25.30 g of N-benzyl-N-methylamine are added to a solution of 20.00 ml of (R)-tetrahydrofuran-2-carboxylic acid in 200 ml tetrahydrofuran. Then a total of 67.10 g of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate are added batchwise while cooling with an ice bath and

the reaction mixture is then stirred for about 48 hours at ambient temperature. The precipitate formed is suction filtered, the filtrate is evaporated, mixed with water and filtered again. The filtrate obtained is made alkaline with sodium hydrogen carbonate solution and extracted with ethyl acetate. The combined ethyl acetate extracts are washed with water and saturated sodium chloride solution, dried over magnesium sulfate, and evaporated down. A yellowish oil remains, which is further reacted without any further purification. Yield: 24.60 g (54% of theory); mass spectrum (ESI^+): m/z=220 $[M+H]^+$; R_f value: 0.62 (silica gel, ethyl acetate).

The following compounds are obtained analogously to Example VII:

(1) (S)-tetrahydrofuran-2-carboxylic acid-N-benzyl-N-methylamide

Mass spectrum (ESI^+): m/z=242 $[M+Na]^+$; R_f value: 0.62 (silica gel, ethyl acetate).

(2) tetrahydropyran-4-carboxylic acid-N-benzyl-N-methylamide

The amide coupling is carried out with 1,1'-carbonyldiimidazole in tetrahydrofuran. Mass spectrum (ESI^+): m/z=256 $[M+Na]^+$; R_f value: 0.45 (silica gel, ethyl acetate).

EXAMPLE VIII

6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydropyran-4-yl)methoxy]quinazoline

22.80 g of 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[(tetrahydropyran-4-yl)methoxy]quinazoline are hydrogenated in 300 ml of tetrahydrofuran in the presence of 3.50 g of platinum dioxide at ambient temperature until the calculated amount of hydrogen has been taken up. The catalyst is filtered off and the filtrate is evaporated to dryness using the rotary evaporator. The residue is stirred with diethylether, suction filtered, washed with diethylether and dried at ambient temperature. Yield: 19.95 g (93% of theory); mass spectrum (ESI^+): m/z=403, 405 $[M+H]^+$; melting point: 221° C.

The following compounds are obtained analogously to Example VIII:

(1) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]quinazoline

Mass spectrum (ESI^+): m/z=389, 391 $[M+H]^+$; R_f value: 0.11 (silica gel, ethyl acetate).

(2) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline

Mass spectrum (ESI^+): m/z=389, 391 $[M+H]^+$; R_f value: 0.33 (silica gel, ethyl acetate/methanol=9:1).

Preparation of the Final Compounds

EXAMPLE 1

4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline

4.70 ml of oxalyl chloride are added dropwise to a solution of 4.50 g of bromocrotonic acid in 60 ml of methylene chloride. Then one drop of N,N-dimethylformamide is added. After about 30 minutes, the development of gas has ended and the reaction mixture is evaporated using the rotary evaporator. The crude bromocrotonic acid chloride is taken up in 30 ml of methylene chloride and, while cooling with an ice bath, added dropwise to a solution of 7.00 g of 4-[(3-chloro-4-fluorophenyl)amino]-6-amino-7-cyclopropylmethoxyquinazoline and 10.20 ml of Hünig base in 150 ml of tetrahydrofuran. The reaction mixture is stirred for about 1.5 hours while cooling with an ice bath and then for another two hours at ambient temperature. Then 5.20 g of N-(2-methoxyethyl)-N-methylamine are added and the reaction mixture is stirred overnight at ambient temperature. For working up, it is diluted with methylene chloride and washed thoroughly with water. The organic phase is dried over magnesium sulfate and evaporated down. The crude product is purified by chromatography over a silica gel column with ethyl acetate followed by ethyl acetate/methanol (19:1) as eluant. Yield: 5.07 g (51% of theory); mass spectrum (ESI^-): m/z=512, 514 $[H-H]^-$; R_f value: 0.25 (silica gel, ethyl acetate/methanol=9:1).

The following compounds are obtained analogously to Example 1:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline

Mass spectrum (ESI^-): m/z=468, 470 $[M-H]^-$; R_f value: 0.09 (silica gel, ethyl acetate/methanol=9:1).

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline

Mass spectrum (ESI^-): m/z=482, 484 $[M-H]^-$; R_f value: 0.11 (silica gel, ethyl acetate/methanol=9:1).

(3) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(N,N-bis(2-methoxyethyl)amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline

Mass spectrum (ESI^-): m/z=532 $[M-H]^-$; R_f value: 0.40 (silica gel, ethyl acetate/methanol=9:1).

(4) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(2-methoxyethyl)-N-ethylamino]-1-oxo-2-buten-1yl}amino)-7-cyclopropylmethoxyquinazoline

Mass spectrum (ESI^-): m/z=502 $[M-H]^-$; R_f value: 0.20 (silica gel, ethyl acetate/methanol=9:1).

(5) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline

Mass spectrum (ESI^-): m/z=488 $[M-H]^-$; R_f value: 0.25 (silica gel, ethyl acetate/methanol=9:1).

(6) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline

Mass spectrum (ESI^-): m/z=514 $[H-H]^-$; R_f value: 0.15 (silica gel, ethyl acetate/methanol=9:1).

(7) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(tetrahydrofuran-3-yl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline

Mass spectrum (ESI^-): m/z=500 $[M-H]^-$; R_f value: 0.18 (silica gel, ethyl acetate/methanol=9:1).

(8) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[(tetrahydrofuran-3-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline

Mass spectrum (ESI^-): m/z=538, 540 $[M-H]^-$; R_f value: 0.27 (silica gel, ethyl acetate/methanol=9:1).

(9) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)quinazoline; mass spectrum (ESI^+): m/z=486, 488 $[M+H]^+$.

(10) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)quinazoline

Mass spectrum (ESI^+): m/z=486, 488 $[M+H]^+$; R_f value: 0.45 (silica gel, methylene chloride/methanol=5:1).

(11) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-(tetrahydropyran-4-yloxy)quinazoline

Mass spectrum (ESI^+): m/z=500, 502 $[M+H]^+$; R_f value: 0.55 (silica gel, methylene chloride/methanol=5:1).

(12) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline

Mass spectrum (ESI^+): m/z=500, 502 $[M+H]^+$; R_f value: 0.60 (silica gel, methylene chloride/methanol=5:1).

(13) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=500, 502 [M+H]+; R_f value: 0.50 (silica gel, methylene chloride/methanol=5:1).
(14) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=528, 530 [M+H]+; R_f value: 0.31 (silica gel, ethyl acetate/methanol=9:1).
(15) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI+): m/z=446 [M+H]+; R_f value: 0.11 (silica gel, ethyl acetate/methanol=9:1).
(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=588, 590 [M+H]+; R_f value: 0.55 (silica gel, methylene chloride/methanol=9:1).
(17) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=542, 544 [M+H]+; R_f value: 0.55 (silica gel, methylene chloride/methanol=9:1).
(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1oxo-2-buten-1-yl}amino)-7-cyclopentyloxyquinazoline
Mass spectrum (ESI+): m/z=528, 530 [M+H]+; R_f value: 0.25 (silica gel, ethyl acetate/methanol=9:1).
(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{(R)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamino}1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI+): m/z=540, 542 [M+H]+; melting point: 149° C.-153° C.
(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{(S)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI+): m/z=540, 542 [M+H]+; R_f value: 0.29 (silica gel, ethyl acetate/methanol=9:1).
(21) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline
Mass spectrum (ESI+): m/z=560 [M+H]+; R_f value: 0.17 (silica gel, ethyl acetate/methanol=9:1).
(22) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline
Mass spectrum (ESI−): m/z=508, 510 [M−H]−; melting point: 140° C.
(23) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI+): m/z=496, 498 [M+H]+; R_f value: 0.42 (silica gel, ethyl acetate/methanol=9:1).
(24) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[(tetrahydropyran-4-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI+): m/z=554, 556 [M+H]+; melting point: 141° C.
(25) 4-[(R)-(1-phenylethyl)amino]-6-[(4-{N-[(tetrahydropyran-4-yl)methyl]-N-methylamino}1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI+): m/z=530 [M+H]+; R_f value: 0.32 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:0.5).
(26) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{(R)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopentyloxyquinazoline
Mass spectrum (ESI+): m/z=554, 556 [M+H]+; melting point: 117° C.-121° C.
(27) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{(S)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopentyloxyquinazoline
Mass spectrum (ESI+): m/z=554, 556 [M+H]+; R_f value: 0.32 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:0.5).
(28) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydropyran-4-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=514, 516 [M+H]+; R_f value: 0.19 (silica gel, methylene chloride/methanol/conc. aqueous ammonia=95:5:0.05).
(29) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}7-[(tetrahydropyran-4-yl)methoxy]quinazoline
Mass spectrum (ESI−): m/z=554, 556 [M−H]−; melting point: 174° C.
(30) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydropyran-4-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=602, 604 [M+H]+; melting point: 100° C.-102° C.
(31) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=500, 502 [M+H]+; melting point: 110° C.-112° C.
(32) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=500, 502 [M+H]+; R_f value: 0.23 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:0.1).
(33) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-ethyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline
Mass spectrum (ESI+): m/z=500, 502 [M+H]+; melting point: 154° C.-157° C.
(34) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-isopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline
Mass spectrum (ESI+): m/z=514, 516 [M+H]+; R_f value: 0.34 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:1).
(35) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline
Mass spectrum (ESI+): m/z=528, 530 [M+H]+; melting point: 184° C.-185° C.
(36) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-isopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline
Mass spectrum (ESI+): m/z=512, 514 [M+H]+; R_f value: 0.53 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:0.5).
(37) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-ethyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI−): m/z=512, 514 [M−H]−; R_f value: 0.15 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:1).
(38) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI−): m/z=526, 528 [M−H]−; R_f value: 0.27 (silica gel, methylene chloride/methanol=9:1).
(39) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-isopropyl-N-methylamino)-1-oxo-2-butene-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=528, 530 [M+H]+; R_f value: 0.31 (silica gel, methylene chloride/methanol=9:1).

The following compounds may also be prepared analogously to the foregoing Examples and other methods known from the literature:

(1) 4-benzylamino-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[(tetrahydropyran-4-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydropyran-4-yl)methoxy]quinazoline

(4) 4-[(R)-(1-phenylethyl)amino]-6-[(4-{N-[(tetrahydrofuran-2-yl)methyl]-N-methylamino}1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline

(5) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline

(6) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N,N-bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline

(7) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline

EXAMPLE 2

Coated tablets containing 75 mg of active substance

1 tablet core contains:

active substance	75.0 mg
calcium phosphate	93.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	1.5 mg
	230.0 mg

Preparation

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape. Weight of core: 230 mg; die: 9 mm, convex. The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax. Weight of coated tablet: 245 mg.

EXAMPLE 3

Tablets containing 100 mg of active substance

Composition:
1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
	220.0 mg

Preparation

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50° C., it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets. Weight of tablet: 220 mg; diameter: 10 mm, biplanar, facetted on both sides and notched on one side.

EXAMPLE 4

Tablets containing 150 mg of active substance

Composition:
1 tablet contains:

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Preparation

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45° C., are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture. Weight of tablet: 300 mg; die: 10 mm, flat.

EXAMPLE 5

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

active substance	50.0 mg
corn starch (dried)	approx. 80.0 mg
lactose (powdered)	approx. 87.0 mg
magnesium stearate	3.0 mg
	approx. 420.0 mg

Preparation

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules. Capsule filling: approx. 320 mg; capsule shell: size 1 hard gelatine capsule.

EXAMPLE 6

Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation

After the suppository mass has been melted, the active substance is homogeneously distributed therein and the melt is poured into chilled molds.

EXAMPLE 7

Suspension containing 50 mg of active substance	
100 ml of suspension contains:	
active substance	1.00 g
carboxymethylcellulose-Na-salt	0.10 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
glucose	10.00 g
glycerol	5.00 g
70% sorbitol solution	20.00 g
flavoring	0.30 g
dist. water	ad 100 ml

Preparation

The distilled water is heated to 70° C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution, and the flavoring have been added and dissolved, the suspension is evacuated with stirring to eliminate air. 5 ml of suspension contains 50 mg of active substance.

EXAMPLE 8

Ampoules containing 10 mg active substance	
Composition:	
active substance	10.0 mg
0.01N hydrochloric acid	q.s.
double-distilled water	ad 2.0 ml

Preparation

The active substance is dissolved in the requisite amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

EXAMPLE 9

Ampoules containing 50 mg of active substance	
Composition:	
active substance	50.0 mg
0.01N hydrochloric acid	q.s.
double-distilled water	ad 10.0 ml

Preparation

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

EXAMPLE 10

Capsules for powder inhalation containing 5 mg of active substance	
1 capsule contains:	
active substance	5.0 mg
lactose for inhalation	15.0 mg
	20.0 mg

Preparation

The active substance is mixed with lactose for inhalation. The mixture is packed into capsules in a capsule-making machine (weight of the empty capsule approx. 50 mg). Weight of capsule: 70.0 mg; size of capsule: 3.

EXAMPLE 11

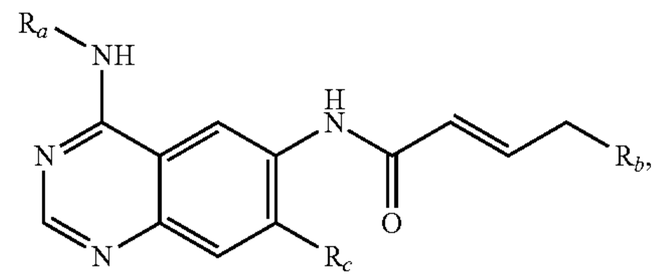
Solution for inhalation for hand-held nebulizers containing 2.5 mg active substance	
1 spray contains:	
active substance	2.500 mg
benzalkonium chloride	0.001 mg
1N hydrochloric acid	q.s.
ethanol/water (50/50)	ad 15.000 mg

Preparation

The active substance and benzalkonium chloride are dissolved in ethanol/water (50/50). The pH of the solution is adjusted with 1N hydrochloric acid. The resulting solution is filtered and transferred into suitable containers for use in hand-held nebulizers (cartridges). Contents of the container: 4.5 g.

We claim:

1. A compound of formula I



(I)

wherein

R_a is a [benzyl, 1-phenylethyl, or] 3-chloro-4-fluorophenyl group;

R_b is a dimethylamino[, N-methyl-N-ethylamino, N-methyl-N-isopropylamino, N-methyl-N-cyclopropylamino, N-methyl-N-(2-methoxyethyl)amino, N-ethyl-N-(2-methoxyethyl)amino, bis(2-methoxyethyl)amino, morpholino, N-methyl-N-(tetrahydrofuran-3-yl)amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino, N-methyl-N-(tetrahydrofuran-3-ylmethyl)amino, N-methyl-N-(tetrahydropyran-4-yl)amino, or N-methyl-N-(tetrahydropyran-4-ylmethyl)amino] group; and

R_c is a [cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy,] tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-4-yloxy, or tetrahydropyran-4-ylmethoxy group,

or a stereoisomer or physiologically acceptable salt thereof.

[**2**. The compound of claim **1**, wherein Rb is a dimethylamino or a stereoisomer or physiologically acceptable salt thereof.]

[**3**. The compound of formula I according to claim **1**, wherein:

R_a is a 1-phenylethyl or 3-chloro-4-fluorophenyl group;

R_b is a dimethylamino, N-methyl-N-ethylamino, N-methyl-N-isopropylamino, N-methyl-N-cyclopropylamino, N-methyl-N-(2-methoxyethyl)amino, N-ethyl-N-(2-methoxyethyl)amino, bis(2-methoxyethyl)amino, morpholino, N-methyl-N-(tetrahydrofuran-3-yl)amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino, N-methyl-N-(tetrahydrofuran-3-ylmethyl)amino, N-methyl-N-(tetrahydropyran-4-yl)amino, or N-methyl-N-(tetrahydropyran-4-ylmethyl)amino group; and

R_c is a cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetradrofuran-3-ylmethoxy, tetrahydropyran-4-yloxy, or tetrahydropyran-4-ylmethoxy group,

or a stereoisomer or physiologically acceptable salt thereof.]

[4. The compounds of claim 3, wherein

R_b is a dimethylamino,

or a stereoisomer or physiologically acceptable salt thereof.]

[5. The compounds of claim 3, wherein

R_a is a 3-chloro-4-fluorohenyl group and

R_b is a dimethylamino group,

or a stereoisomer or physiologically acceptable salt thereof.]

[6. The compound of formula I according to claim 1, wherein:

R_a is a 3-chloro-4-fluorophenyl group;

R_b is a dimethylaminno group; and

R_c is a tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-4-yloxy, or tetrahydropyran-4-ylmethoxy group,

or a steroisomer or physiologically acceptable salt thereof.]

7. The compound of claim 1, wherein:

R_c is a tetrahydrofuran-3-yloxy,

or a steroisomer or physiologically acceptable salt thereof.

8. 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-(tetrahydrofuran-3-yl)oxy)quinazoline.

9. A physiologically acceptable salt comprising the combination of the compound according to claim 8 with an organic or inorganic acid.

10. The salt according to claim 9 wherein the acid is hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, or maleic acid.

11. The salt according to claim 10, wherein the acid is maleic acid.

12. 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-(tetrahydrofuran-3-yl)oxy)quinazoline.

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UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	RE43,431
(45)	ISSUED	:	March 28, 2006 (reissued on May 29, 2012)
(75)	INVENTOR	:	Himmelsbach et al.
(73)	PATENT OWNER	:	Boehringer Ingelheim Pharma GmbH & Co. KG
(95)	PRODUCT	:	GILOTRIF® (afatinib dimaleate)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. RE43,431 based upon the regulatory review of the product GILOTRIF® (afatinib dimaleate) by the Food and Drug Administration. According to United States Patent and Trademark Office records, the original expiration date of the patent as of the date of issuance of this certificate is January 22, 2022. Because it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 1,452 days

subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.

I have caused the seal of the United States Patent and Trademark Office to be affixed this 20th day of July 2020.

Andrei Iancu
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office