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Boehringer Ingelheim International GmbH, and
Boehringer Ingelheim Pharma GmbH & Co. KG*

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

BOEHRINGER INGELHEIM
PHARMACEUTICALS, INC.,
BOEHRINGER INGELHEIM
INTERNATIONAL GMBH, and
BOEHRINGER INGELHEIM
PHARMA GMBH & CO. KG,

Plaintiffs,

v.

FRESENIUS KABI USA, LLC and
FRESENIUS KABI ONCOLOGY LTD.,

Defendants.

Civil Action No. _____

(Filed Electronically)

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Boehringer Ingelheim Pharmaceuticals, Inc., Boehringer Ingelheim International GmbH, and Boehringer Ingelheim Pharma GmbH & Co. KG (collectively, “Plaintiffs” or “Boehringer Ingelheim”) by their undersigned attorneys, bring this action against Fresenius Kabi USA, LLC and Fresenius Kabi Oncology Limited (collectively, “Fresenius Kabi”) and hereby allege as follows:

NATURE OF THE ACTION

1. This action for patent infringement, brought pursuant to the patent laws of the United States, 35 U.S.C. § 1, *et seq.*, and in particular under 35 U.S.C. §§ 271 (a–c, e–g), arises from Fresenius Kabi’s submission of Abbreviated New Drug Application (“ANDA”) No. 209985 (hereinafter, “Fresenius Kabi ANDA”) to the United States Food and Drug Administration (“FDA”). Through the Fresenius Kabi ANDA, Fresenius Kabi seeks approval to market a generic version of the pharmaceutical product GILOTRIF® (afatinib) tablets prior to the expiration of United States Patent Nos. RE43,431 and 8,426,586 (collectively, the “patents-in-suit”). Plaintiffs seek injunctive relief precluding infringement, attorneys’ fees, and any other relief the Court deems just and proper.

2. This is also an action under 28 U.S.C. §§ 2201–02 for a declaratory judgment of patent infringement arising under the patent laws of the United States, 35 U.S.C. § 1, *et seq.*, and in particular under 35 U.S.C. §§ 271(a–c, e–g).

THE PARTIES

3. Plaintiff Boehringer Ingelheim Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 900 Ridgebury Road, Ridgefield, Connecticut 06877.

4. Plaintiff Boehringer Ingelheim International GmbH is a private limited liability company organized and existing under the laws of Germany, having a principal place of business at Binger Strasse 173, 55216 Ingelheim, Germany.

5. Plaintiff Boehringer Ingelheim Pharma GmbH & Co. KG is a limited liability partnership organized and existing under the laws of Germany, having a principal place of business at Binger Strasse 173, 55216 Ingelheim, Germany.

6. On information and belief, Fresenius Kabi USA, LLC is a limited liability company organized and existing under the laws of the State of Delaware, having its principal place of business at Three Corporate Drive, Lake Zurich, Illinois 60047. On information and belief, Fresenius Kabi USA, LLC is in the business of marketing, distributing, and selling, in the State of New Jersey and throughout the United States, pharmaceutical drugs, including generic pharmaceutical drugs manufactured by Fresenius Kabi.

7. On information and belief, Fresenius Kabi USA, LLC, in collaboration with other Fresenius Kabi entities, prepared and submitted the Fresenius Kabi ANDA and continues to collaborate in seeking FDA approval of that application.

8. On information and belief, Fresenius Kabi Oncology Limited is a limited company organized and existing under the laws of India, having its principal place of business at Echelon Institutional Area, Plot No-11, Sector-32, Gurgaon-122001, Haryana, India.

9. On information and belief, Fresenius Kabi USA, LLC and Fresenius Kabi Oncology Limited are related business entities.

10. On information and belief, Fresenius Kabi intends to commercially manufacture, market, offer for sale, and sell the product described in the Fresenius Kabi ANDA (the “ANDA Product”) throughout the United States, including in the State of New Jersey, in the event that the FDA approves the Fresenius Kabi ANDA.

JURISDICTION AND VENUE

11. This civil action for patent infringement arises under the patent laws of the United States, including 35 U.S.C. § 271, and alleges infringement of United States Patent Nos. RE43,431 (“the ’431 patent”) and 8,426,586 (“the ’586 patent”). This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338, and 2201–02.

12. On information and belief, this Court has personal jurisdiction over Fresenius Kabi USA, LLC. On information and belief, (1) Fresenius Kabi USA, LLC is registered to do business in New Jersey under Entity Identification Number 0600313148; (2) Fresenius Kabi USA, LLC is registered with the New Jersey Department of Health as a drug manufacturer under Registration Number 5003710; and (3) Fresenius Kabi USA, LLC has customers in New Jersey.

13. On information and belief, Fresenius Kabi USA, LLC has submitted, caused to be submitted, or aided or abetted in the preparation or submission of the Fresenius Kabi ANDA. On information and belief, in the event that the FDA approves the Fresenius Kabi ANDA, Fresenius Kabi, with the participation of Fresenius Kabi USA, LLC, intends to commercially manufacture, market, offer for sale, and sell the ANDA Product throughout the United States, including in the State of New Jersey.

14. On information and belief, Fresenius Kabi USA, LLC has availed itself of the rights, benefits, and privileges of New Jersey by asserting claims and counterclaims involving pharmaceutical drug patent disputes in this Judicial District in at least the following recent cases: *Fresenius Kabi USA, LLC v. BioQ Pharma Inc.*, Civil Action No. 18-3032; *Fresenius Kabi USA, LLC v. Maia Pharmaceuticals Inc.*, Civil Action No. 16-3315; *Fresenius Kabi USA, LLC v. Dr. Reddys Laboratories Inc., et al.*, Civil Action No. 16-3316; *Helsinn Healthcare S.A., et al. v. Fresenius Kabi USA, LLC, et al.*, Civil Action No. 15-2077 (consolidated); *Merck Sharp & Dohme Corp. v. Fresenius Kabi USA, LLC*, Civil Action No. 14-3917.

15. On information and belief, this Court has personal jurisdiction over Fresenius Kabi Oncology Limited. On information and belief, Fresenius Kabi Oncology Limited has submitted, caused to be submitted, or aided or abetted in the preparation or submission of the Fresenius Kabi ANDA. On information and belief, in the event that the FDA approves the

Fresenius Kabi ANDA, Fresenius Kabi, with the participation of Fresenius Kabi Oncology Limited, intends to commercially manufacture, market, offer for sale, and sell the ANDA Product throughout the United States, including in the State of New Jersey.

16. On information and belief, Fresenius Kabi USA, LLC and Fresenius Kabi Oncology Limited are agents of one another and act in concert together with respect to the Fresenius Kabi ANDA, and both Defendants would benefit from the FDA approval of the Fresenius Kabi ANDA.

17. Further, Fresenius Kabi has committed, or aided, abetted, contributed to and/or participated in the commission of, acts of patent infringement that will lead to foreseeable harm and injury to Plaintiffs, which manufactures GILOTRIF® for sale and use throughout the United States, including in this Judicial District.

18. Venue is proper in this District pursuant to 28 U.S.C. § 1400. Venue is also proper in this District under 28 U.S.C. § 1391(c)(3) because on information and belief, Fresenius Kabi Oncology Limited is a foreign entity and is not resident in the United States. Further, on information and belief, Fresenius Kabi does not object to venue in the District of New Jersey for purposes of this action only.

BOEHRINGER INGELHEIM'S APPROVED GILOTRIF® DRUG PRODUCT AND PATENT

19. Boehringer Ingelheim makes and sells GILOTRIF®, a product used in the first-line treatment of metastatic non-small cell lung cancer (“NSCLC”) where the tumors have epidermal growth factor receptor (“EGFR”) exon 19 deletions or exon 21 (L858R substitution mutations). GILOTRIF® is also used to treat metastatic, squamous NSCLC that progresses after platinum-based chemotherapy. The active ingredient in GILOTRIF® is afatinib. A true and correct copy of the prescribing label for GILOTRIF® is attached as Exhibit A.

20. Boehringer Ingelheim Pharmaceuticals, Inc. is the holder of New Drug Application (“NDA”) No. 201292 for GILOTRIF® and the licensee of the patents-in-suit. The FDA approved NDA No. 201292 for GILOTRIF® in July 2013, and granted GILOTRIF® five years of regulatory exclusivity for a new chemical entity pursuant to 21 C.F.R. § 314.108, which expires on July 12, 2018. The FDA also granted GILOTRIF® orphan drug exclusivity pursuant to 21 C.F.R. § 316.31.

21. Boehringer Ingelheim Pharma GmbH & Co. KG owns the ’431 patent, which is listed in the Approved Drug Products With Therapeutic Equivalence Evaluations (an FDA publication commonly known as the “Orange Book”) for GILOTRIF®. Boehringer Ingelheim International GmbH owns the ’586 patent, which is also listed in the “Orange Book” for GILOTRIF®.

22. The ’431 patent, entitled, “Quinazoline Derivatives and Pharmaceutical Compositions Containing Them,” is a reissue of United States Patent No. 7,019,012. The ’431 patent was duly and lawfully issued by the United States Patent and Trademark Office (“USPTO”) on May 29, 2012. A true and correct copy of the ’431 patent is attached as Exhibit B.

23. The ’586 patent, entitled, “Process for Preparing Amino Crotonyl Compounds,” was duly and lawfully issued by the USPTO on April 23, 2013. A true and correct copy of the ’586 patent is attached as Exhibit C.

FRESENIUS KABI’S ANDA

24. On information and belief, Fresenius Kabi has submitted or caused to be submitted ANDA No. 209985 to the FDA under 21 U.S.C. § 355(j), in order to obtain approval

to engage in the commercial manufacture, use, or sale of afatinib dimaleate tablets, as a purported generic version of GILOTRIF®, prior to the expiration of the patents-in-suit.

25. On information and belief, on or about January 24, 2018, Fresenius Kabi mailed Plaintiffs the Notice Letter. The Notice Letter represented that Fresenius Kabi had submitted to the FDA ANDA No. 209985 and a purported Paragraph IV certification to obtain approval to engage in the commercial manufacture, use, or sale of the product described in the Fresenius Kabi ANDA before the expiration of the patents listed in the Orange Book for GILOTRIF®. Hence, Fresenius Kabi's purpose in submitting the Fresenius Kabi ANDA is to manufacture and market the ANDA Product before the expiration of the patents-in-suit.

26. Fresenius Kabi's Notice Letter stated that the Paragraph IV certification in the Fresenius Kabi ANDA alleges that the '431 patent and the '586 patent are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of the ANDA Product.

27. Fresenius Kabi's Notice Letter contained a purported detailed statement of the factual and legal basis for its opinion that the '431 patent and the '586 patent are invalid, unenforceable, or not infringed by the manufacture, use, or sale of the ANDA Product ("Detailed Statement").

28. On information and belief, Fresenius Kabi has participated in the preparation and submission of the Fresenius Kabi ANDA, has provided material support to the preparation and submission of the Fresenius Kabi ANDA, and intends to support the further prosecution of the Fresenius Kabi ANDA.

29. On information and belief, if the FDA approves the Fresenius Kabi ANDA, Fresenius Kabi will manufacture, offer for sale, or sell the ANDA Product within the United

States, including within New Jersey, or will import the ANDA Product into the United States, including New Jersey.

30. Alternatively, on information and belief, if the FDA approves the Fresenius Kabi ANDA, Fresenius Kabi will actively induce or contribute to the manufacture, use, offer for sale, or sale of the ANDA Product.

31. This action is being brought pursuant to 21 U.S.C. § 355(j)(5)(B)(iii) within forty-five days of Plaintiffs' receipt of the Notice Letter.

COUNT I
INFRINGEMENT OF THE '431 PATENT

32. Plaintiffs incorporate by reference paragraphs 1–31 as if fully set forth herein.

33. On information and belief, Fresenius Kabi has submitted or caused the submission of the Fresenius Kabi ANDA to the FDA and continues to seek FDA approval of the Fresenius Kabi ANDA.

34. Fresenius Kabi has infringed the '431 patent under 35 U.S.C. § 271(e)(2)(A) by submitting the Fresenius Kabi ANDA with a Paragraph IV certification and seeking FDA approval of the Fresenius Kabi ANDA prior to the expiration of the '431 patent.

35. On information and belief, if the Fresenius Kabi ANDA is approved, Fresenius Kabi and its affiliates will make, offer for sale, sell, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, directly infringing the '431 patent.

36. Fresenius Kabi's commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to infringement of the '431 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 209985, Fresenius Kabi will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and

will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the '431 patent.

37. Fresenius Kabi had actual and constructive notice of the '431 patent prior to filing the Fresenius Kabi ANDA and was aware that the filing of the Fresenius Kabi ANDA with the request for FDA approval prior to the expiration of the '431 patent would constitute an act of infringement of the '431 patent. Fresenius Kabi had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not contribute to the infringement of and/or induce the infringement of the '431 patent.

38. Fresenius Kabi's Detailed Statement in the Notice Letter lacks any sufficient contention that the ANDA Product will not infringe, contribute to the infringement of, or induce the infringement of the '431 patent.

39. In addition, Fresenius Kabi filed the Fresenius Kabi ANDA without adequate justification for asserting the '431 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Fresenius Kabi's conduct in certifying invalidity, unenforceability, and/or non-infringement with respect to the '431 patent renders this case "exceptional" under 35 U.S.C. § 285.

40. Plaintiffs will be irreparably harmed if Fresenius Kabi is not enjoined from infringing and from actively inducing or contributing to the infringement of the '431 patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Fresenius Kabi, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT II
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '431 PATENT

41. Plaintiffs incorporate by reference paragraphs 1–40 as if fully set forth herein.

42. Plaintiffs' claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

43. On information and belief, if the Fresenius Kabi ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Fresenius Kabi and its affiliates.

44. On information and belief, Fresenius Kabi knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Fresenius Kabi ANDA and Fresenius Kabi will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the '431 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

45. On information and belief, Fresenius Kabi's infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after the FDA approves the Fresenius Kabi ANDA. Any such conduct before the '431 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '431 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

46. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Fresenius Kabi concerning liability for the infringement of the '431 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

47. Plaintiffs will be substantially and irreparably harmed by Fresenius Kabi's infringing activities unless those activities are enjoined by this Court. Plaintiffs have no adequate remedy at law.

48. This case is exceptional, and Plaintiffs are entitled to an award of attorneys' fees under 35 U.S.C. § 285.

COUNT III
INFRINGEMENT OF THE '586 PATENT

49. Plaintiffs incorporate by reference paragraphs 1–48 as if fully set forth herein.

50. On information and belief, Fresenius Kabi has submitted or caused the submission of the Fresenius Kabi ANDA to the FDA and continues to seek FDA approval of the Fresenius Kabi ANDA.

51. Fresenius Kabi has infringed the '586 patent under 35 U.S.C. § 271(e)(2)(A) by submitting the Fresenius Kabi ANDA with a Paragraph IV certification and seeking FDA approval of the Fresenius Kabi ANDA prior to the expiration of the '586 patent.

52. On information and belief, if the Fresenius Kabi ANDA is approved, Fresenius Kabi and its affiliates will make, offer for sale, sell, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, directly infringing the '586 patent.

53. Fresenius Kabi's commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to infringement of the '586 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 209985, Fresenius Kabi will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the '586 patent.

54. Fresenius Kabi had actual and constructive notice of the '586 patent prior to filing the Fresenius Kabi ANDA and was aware that the filing of the Fresenius Kabi ANDA with the request for FDA approval prior to the expiration of the '586 patent would constitute an act of

infringement of the '586 patent. Fresenius Kabi had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not contribute to the infringement of and/or induce the infringement of the '586 patent.

55. Fresenius Kabi's Detailed Statement in the Notice Letter lacks any sufficient contention that the ANDA Product will not infringe, contribute to the infringement of, or induce the infringement of the '586 patent.

56. In addition, Fresenius Kabi filed the Fresenius Kabi ANDA without adequate justification for asserting the '586 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Fresenius Kabi's conduct in certifying invalidity, unenforceability, and/or non-infringement with respect to the '586 patent renders this case "exceptional" under 35 U.S.C. § 285.

57. Plaintiffs will be irreparably harmed if Fresenius Kabi is not enjoined from infringing and from actively inducing or contributing to the infringement of the '586 patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Fresenius Kabi, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT IV
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '586 PATENT

58. Plaintiffs incorporate by reference paragraphs 1–57 as if fully set forth herein.

59. Plaintiffs' claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

60. On information and belief, if the Fresenius Kabi ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Fresenius Kabi and its affiliates.

61. On information and belief, Fresenius Kabi knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Fresenius Kabi ANDA and Fresenius Kabi will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the '586 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

62. On information and belief, Fresenius Kabi's infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after the FDA approves the Fresenius Kabi ANDA. Any such conduct before the '586 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '586 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

63. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Fresenius Kabi concerning liability for the infringement of the '586 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

64. Plaintiffs will be substantially and irreparably harmed by Fresenius Kabi's infringing activities unless those activities are enjoined by this Court. Plaintiffs have no adequate remedy at law.

65. This case is exceptional, and Plaintiffs are entitled to an award of attorneys' fees under 35 U.S.C. § 285.

REQUEST FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A judgment that Fresenius Kabi infringes the '431 patent and the '586 patent under 35 U.S.C. § 271(e)(2)(A);

B. A declaratory judgment that under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g), Fresenius Kabi's commercial manufacture, use, offer for sale, or sale in, or importation into, the United States of the ANDA Product, or inducing or contributing to such conduct, would constitute infringement of one or more claims of the '431 patent and the '586 patent;

C. A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Fresenius Kabi, its affiliates and subsidiaries, and all persons and entities acting in concert with Fresenius Kabi from commercially manufacturing, using, offering for sale, or selling or importing any product that infringes the '431 patent and the '586 patent, including the ANDA Product described in ANDA No. 209985;

D. The entry of an order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any FDA approval of ANDA No. 209985 shall be no earlier than the expiration date of the '431 patent and the '586 patent, or any later expiration of exclusivity for the '431 patent and the '586 patent, including any extensions or regulatory exclusivities;

E. A declaration under 28 U.S.C. § 2201 that if Fresenius Kabi, its officers, agents, servants, employees, licensees, representatives, and attorneys, and any other persons acting or attempting to act in active concert or participation with them or acting on its behalf, engages in the commercial manufacture, use, offer for sale, sale and/or importation of the product described in ANDA No. 209985, it will constitute an act of direct and/or indirect infringement of the '431 patent and the '586 patent;

F. An award of damages or other relief, pursuant to 35 U.S.C. § 271(e)(4)(C), if Fresenius Kabi engages in the commercial manufacture, use, offer for sale, sale, and/or importation of the ANDA Product, or any product that infringes the '431 patent and the '586 patent, or induces or contributes to such conduct, prior to the expiration of the '431 patent and the '586 patent, or any later expiration of exclusivity for the '431 patent and the '586 patent, including any extensions or regulatory exclusivities;

G. The entry of judgment declaring that Fresenius Kabi's acts render this case an exceptional case and awarding Plaintiffs their attorneys' fees pursuant to 35 U.S.C. §§ 271(e)(4) and 285;

H. An award to Plaintiffs of their costs and expenses in this action; and

I. Such other and further relief as the Court may deem just and proper.

Dated: March 7, 2018

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the following actions are related to the matter in controversy because the matter in controversy involves at least United States Patent No. 8,426,586 and the same drug product:

- *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Aurobindo Pharma USA Inc., et al.*, Civil Action No. 17-7887 (MAS)(LHG)
- *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Hetero USA Inc., et al.*, Civil Action No. 17-7923 (MAS)(LHG)
- *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. MSN Laboratories Private Limited, et al.*, Civil Action No. 17-8399 (MAS)(LHG)
- *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Sun Pharmaceutical Industries Ltd., et al.*, Civil Action No. 17-8819 (MAS)(LHG)
- *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Sandoz Inc.*, Civil Action No. 17-8825 (MAS)(LHG)
- *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Teva Pharmaceuticals USA, Inc., et al.*, Civil Action No. 17-11510 (MAS)(LHG)

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: March 7, 2018

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EXHIBIT A

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GILOTRIF safely and effectively. See full prescribing information for GILOTRIF.

GILOTRIF® (afatinib) tablets, for oral use

Initial U.S. Approval: 2013

RECENT MAJOR CHANGES

Indications and Usage,	
Previously Treated, Metastatic Squamous NSCLC (1.2)	4/2016
Dosage and Administration, Recommended Dose (2.2)	4/2016
Warnings and Precautions (5)	4/2016

INDICATIONS AND USAGE

GILOTRIF is a kinase inhibitor indicated for:

- First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test (1.1)
Limitation of Use: Safety and efficacy of GILOTRIF were not established in patients whose tumors have other EGFR mutations (1.1)
- Treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy (1.2)

DOSAGE AND ADMINISTRATION

- Recommended dose: 40 mg orally, once daily (2.2)
- Renal impairment: 30 mg orally, once daily in patients with severe renal impairment (2.2, 8.6, 12.3)
- Instruct patients to take GILOTRIF at least 1 hour before or 2 hours after a meal (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg, 30 mg, and 20 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Diarrhea:** Diarrhea may result in dehydration and renal failure. Withhold GILOTRIF for severe and prolonged diarrhea not responsive to anti-diarrheal agents. (2.3, 5.1)

- **Bullous and exfoliative skin disorders:** Severe bullous, blistering, and exfoliating lesions occurred in 0.2% of patients. Discontinue for life-threatening cutaneous reactions. Withhold GILOTRIF for severe and prolonged cutaneous reactions. (2.3, 5.2)
- **Interstitial lung disease (ILD):** Occurs in 1.6% of patients. Withhold GILOTRIF for acute onset or worsening of pulmonary symptoms. Discontinue GILOTRIF if ILD is diagnosed. (2.3, 5.3)
- **Hepatic toxicity:** Fatal hepatic impairment occurs in 0.2% of patients. Monitor with periodic liver testing. Withhold or discontinue GILOTRIF for severe or worsening liver tests. (2.3, 5.4)
- **Keratitis:** Occurs in 0.7% of patients. Withhold GILOTRIF for keratitis evaluation. Withhold or discontinue GILOTRIF for confirmed ulcerative keratitis. (2.3, 5.5)
- **Embryo-fetal toxicity:** Can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.6)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 20\%$) were diarrhea, rash/acneiform dermatitis, stomatitis, paronychia, dry skin, decreased appetite, nausea, vomiting, pruritus (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Co-administration of P-gp inhibitors can increase afatinib exposure. Reduce GILOTRIF by 10 mg per day if not tolerated. Co-administration of chronic P-gp inducers orally can decrease afatinib exposure. Increase GILOTRIF by 10 mg per day as tolerated. (2.3, 7)

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer

GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test [see *Clinical Studies (14.1)*].

Limitation of Use: The safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations [see *Clinical Studies (14.1)*].

1.2 Previously Treated, Metastatic Squamous NSCLC

GILOTRIF is indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy [see *Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for EGFR Mutation-Positive Metastatic NSCLC

Select patients for first-line treatment of metastatic NSCLC with GILOTRIF based on the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor specimens [see *Indications and Usage (1.1)* and *Clinical Studies (14.1)*]. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: <http://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dose

The recommended dose of GILOTRIF is 40 mg orally, once daily until disease progression or no longer tolerated by the patient.

Severe Renal Impairment

The recommended dose of GILOTRIF in patients with severe renal impairment (estimated glomerular filtration rate [eGFR*] 15 to 29 mL/min /1.73 m²) is 30 mg orally, once daily [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

*Use the Modification of Diet in Renal Disease [MDRD] formula to estimate eGFR.

Take GILOTRIF at least 1 hour before or 2 hours after a meal.

Do not take a missed dose within 12 hours of the next dose.

2.3 Dose Modifications for Adverse Reactions

Withhold GILOTRIF for any adverse reactions of:

- NCI CTCAE* Grade 3 or higher
- Diarrhea of Grade 2 or higher persisting for 2 or more consecutive days while taking anti-diarrheal medication [see *Warnings and Precautions (5.1)*]
- Cutaneous reactions of Grade 2 that are prolonged (lasting more than 7 days) or intolerable [see *Warnings and Precautions (5.2)*]
- Renal impairment of Grade 2 or higher [see *Warnings and Precautions (5.1)*]

*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v 3.0

Resume treatment when the adverse reaction fully resolves, returns to baseline, or improves to Grade 1. Reinstitution GILOTRIF at a reduced dose, i.e., 10 mg per day less than the dose at which the adverse reaction occurred.

Permanently discontinue GILOTRIF for:

- Life-threatening bullous, blistering, or exfoliative skin lesions [*see Warnings and Precautions (5.2)*]
- Confirmed interstitial lung disease (ILD) [*see Warnings and Precautions (5.3)*]
- Severe drug-induced hepatic impairment [*see Warnings and Precautions (5.4)*]
- Persistent ulcerative keratitis [*see Warnings and Precautions (5.5)*]
- Symptomatic left ventricular dysfunction [*see Adverse Reactions (6.1)*]
- Severe or intolerable adverse reaction occurring at a dose of 20 mg per day

2.4 Dose Modifications for Drug Interactions

P-gp Inhibitors

Reduce GILOTRIF daily dose by 10 mg if not tolerated for patients who require therapy with a P-glycoprotein (P-gp) inhibitor. Resume the previous dose after discontinuation of the P-gp inhibitor as tolerated [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].

P-gp Inducers

Increase GILOTRIF daily dose by 10 mg as tolerated for patients who require chronic therapy with a P-gp inducer. Resume the previous dose 2 to 3 days after discontinuation of the P-gp inducer [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

GILOTRIF is available as:

40 mg tablets: light blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T40” on one side and the Boehringer Ingelheim company symbol on the other side.

30 mg tablets: dark blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T30” on one side and the Boehringer Ingelheim company symbol on the other side.

20 mg tablets: white to slightly yellowish, film-coated, round, biconvex, bevel-edged tablets debossed with “T20” on one side and the Boehringer Ingelheim company symbol on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Diarrhea has resulted in dehydration with or without renal impairment across the clinical experience; some cases were fatal. Grade 3-4 diarrhea occurred in 697 (16%) of the 4257 patients who received GILOTRIF across 44 clinical trials. In Study 1, diarrhea occurred in 96% of patients treated with GILOTRIF (n=229), of which 15% were Grade 3 in severity and occurred within the first 6 weeks. Renal impairment as a consequence of diarrhea occurred in 6% of patients treated with GILOTRIF, of which 1.3% were Grade 3. In Study 2, diarrhea occurred in 75% of patients treated with GILOTRIF (n=392), of which 10% were Grade 3 in severity and 0.8% were Grade 4 in severity. Renal impairment as a consequence of diarrhea occurred in 7% of patients treated with GILOTRIF, of which 2% were Grade 3 [*see Adverse Reactions (6.1)*].

For patients who develop prolonged Grade 2 diarrhea lasting more than 48 hours, or greater than or equal to Grade 3 diarrhea, withhold GILOTRIF until diarrhea resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction [*see Dosage and Administration (2.3)*]. Provide patients with an anti-diarrheal agent (e.g., loperamide) for self-administration at the onset of diarrhea and instruct patients to continue anti-diarrheal therapy until loose bowel movements cease for 12 hours.

5.2 Bullous and Exfoliative Skin Disorders

Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions, occurred in 0.2% of the 4257 patients who received GILOTRIF across clinical trials. In Study 1, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and the incidence of Grade 3 cutaneous reactions was 16%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 7%. In Study 2, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 70%, and the incidence of Grade 3 cutaneous reactions was 7%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 1.5% [see *Adverse Reactions (6.1)*].

Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating lesions. For patients who develop prolonged Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2, or Grade 3 cutaneous reactions, withhold GILOTRIF until the adverse reaction resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction [see *Dosage and Administration (2.3)*].

Postmarketing cases consistent with toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients receiving GILOTRIF. The cases of TEN and SJS bullous skin reactions result from a distinct and separate mechanism of toxicity than the bullous skin lesions secondary to the pharmacologic action of the drug on the epidermal growth factor receptor. Discontinue GILOTRIF if TEN or SJS is suspected [see *Dosage and Administration (2.3)*].

5.3 Interstitial Lung Disease (ILD)

Interstitial lung disease or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in 1.6% of the 4257 patients who received GILOTRIF across clinical trials; of these, 0.4% were fatal. The incidence of ILD appeared to be higher in Asian patients (2.3%; 38/1657) as compared to Whites (1.0%; 23/2241). In Study 1, the incidence of Grade ≥ 3 ILD was 1.3% and resulted in death in 1% of GILOTRIF-treated patients. In Study 2, the incidence of Grade ≥ 3 ILD was 0.9% and resulted in death in 0.8% of GILOTRIF-treated patients.

Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD [see *Dosage and Administration (2.3)*].

5.4 Hepatic Toxicity

In 4257 patients who received GILOTRIF across clinical trials, 9.7% had liver test abnormalities, of which 0.2% were fatal. In Study 1, liver test abnormalities of any grade occurred in 17.5% of the patients treated with GILOTRIF, of which 3.5% had Grade 3-4 liver test abnormalities. In Study 2, liver test abnormalities of any grade occurred in 6% of the patients treated with GILOTRIF, of which 0.2% had Grade 3-4 liver test abnormalities.

Obtain periodic liver testing in patients during treatment with GILOTRIF. Withhold GILOTRIF in patients who develop worsening of liver function [see *Dosage and Administration (2.3)*]. In patients who develop severe hepatic impairment while taking GILOTRIF, treatment should be discontinued.

5.5 Keratitis

Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in 0.7% of patients treated with GILOTRIF among 4257 patients across clinical trials, of which 0.05% of patients experienced Grade 3 keratitis. Keratitis was reported in 2.2% patients in Study 1, with Grade 3 in 0.4%. In Study 2, keratitis was reported in 0.3% patients; there were no patients with \geq Grade 3 keratitis.

Withhold GILOTRIF during evaluation of patients with suspected keratitis, and if diagnosis of ulcerative keratitis is confirmed, treatment with GILOTRIF should be interrupted or discontinued [see *Dosage and*

Administration (2.3)]. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. GILOTRIF should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye [*see Adverse Reactions (6.1)*]. Contact lens use is also a risk factor for keratitis and ulceration.

5.6 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. Administration of afatinib to pregnant rabbits during organogenesis at exposures approximately 0.2 times the exposure in humans at the recommended dose of 40 mg daily resulted in embryotoxicity and, in rabbits showing maternal toxicity, increased abortions at late gestational stages. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 weeks after the last dose of GILOTRIF [*see Use in Specific Populations (8.1 and 8.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Diarrhea [*see Warnings and Precautions (5.1)*]
- Bullous and Exfoliative Skin Disorders [*see Warnings and Precautions (5.2)*]
- Interstitial Lung Disease [*see Warnings and Precautions (5.3)*]
- Hepatic Toxicity [*see Warnings and Precautions (5.4)*]
- Keratitis [*see Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions section reflect exposure to GILOTRIF for clinically significant adverse reactions in 4257 patients enrolled in Studies 1 (n=229) and 2 (n=392), and 3636 patients with cancer enrolled in 42 studies of GILOTRIF administered alone or in combination with other anti-neoplastic drugs at GILOTRIF doses ranging from 10-70 mg daily or at doses 10-160 mg in other regimens. The mean exposure was 5.5 months. The population included patients with various cancers, the most common of which were NSCLC, breast, colorectal, brain, and head and neck.

The data described below reflect exposure to GILOTRIF as a single agent in Study 1, a randomized, active-controlled trial conducted in patients with EGFR mutation-positive, metastatic NSCLC, and in Study 2, a randomized, active-controlled trial in patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

EGFR Mutation-Positive, Metastatic NSCLC

The data in Tables 1 and 2 below reflect the exposure of 229 EGFR-tyrosine kinase inhibitor-naïve, GILOTRIF-treated patients with EGFR mutation-positive, metastatic, non-squamous NSCLC enrolled in a randomized, multicenter, open-label trial (Study 1). Patients received GILOTRIF 40 mg daily until documented disease progression or intolerance to the therapy. A total of 111 patients were treated with pemetrexed/cisplatin. Patients were treated with pemetrexed 500 mg/m² followed after 30 minutes by cisplatin 75 mg/m² every three weeks for a maximum of six treatment courses.

The median exposure was 11 months for patients treated with GILOTRIF and 3.4 months for patients treated with pemetrexed/cisplatin. The overall trial population had a median age of 61 years; 61% of patients in the GILOTRIF arm and 60% of patients in the pemetrexed/cisplatin arm were younger than 65 years. A total of

64% of patients on GILOTRIF and 67% of pemetrexed/cisplatin patients were female. More than two-thirds of patients were from Asia (GILOTRIF 70%; pemetrexed/cisplatin 72%).

Serious adverse reactions were reported in 29% of patients treated with GILOTRIF. The most frequent serious adverse reactions reported in patients treated with GILOTRIF were diarrhea (6.6%); vomiting (4.8%); and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in GILOTRIF-treated patients in Study 1 included pulmonary toxicity/ILD-like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%).

Dose reductions due to adverse reactions were required in 57% of GILOTRIF-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with GILOTRIF were diarrhea (20%), rash/acne (19%), paronychia (14%), and stomatitis (10%).

Discontinuation of therapy in GILOTRIF-treated patients for adverse reactions was 14.0%. The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (1.3%), ILD (0.9%), and paronychia (0.9%).

Clinical trials of GILOTRIF excluded patients with an abnormal left ventricular ejection fraction (LVEF), i.e., below the institutional lower limit of normal. In Study 1, all patients were evaluated for LVEF at screening and every 9 weeks thereafter in the GILOTRIF-treated group and as needed in the pemetrexed/cisplatin group. More GILOTRIF-treated patients (2.2%; n=5) experienced ventricular dysfunction (defined as diastolic dysfunction, left ventricular dysfunction, or ventricular dilation; all < Grade 3) compared to chemotherapy-treated patients (0.9%; n=1).

Tables 1 and 2 summarize common adverse reactions and laboratory abnormalities in Study 1.

Table 1 Adverse Reactions Reported in $\geq 10\%$ of GILOTRIF-Treated Patients in Study 1*

Adverse Reaction	GILOTRIF n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grade 3 [†] (%)	All Grades (%)	Grade 3 [†] (%)
Gastrointestinal disorders				
Diarrhea	96	15	23	2
Stomatitis ¹	71	9	15	1
Cheilitis	12	0	1	0
Skin and subcutaneous tissue disorders				
Rash/acneiform dermatitis ²	90	16	11	0
Pruritus	21	0	1	0
Dry skin	31	0	2	0
Infections				
Paronychia ³	58	11	0	0
Cystitis	13	1	5	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	17	0	2	1
Rhinorrhea	11	0	6	0
Investigations				
Weight decreased	17	1	14	1
General disorders and administration site conditions				
Pyrexia	12	0	6	0
Eye disorders				
Conjunctivitis	11	0	3	0

*NCI CTCAE v 3.0

[†]None of the adverse reactions in this table except stomatitis (one patient on GILOTRIF [0.4%]) were Grade 4 in severity.¹Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration²Includes acne, acne pustular, dermatitis, acneiform dermatitis, dermatosis, drug eruption, erythema, exfoliative rash, folliculitis, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin disorder, skin erosion, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer³Includes paronychia, nail infection, nail bed infection

Other clinically important adverse reactions observed in patients treated with GILOTRIF but that occurred at a higher incidence in pemetrexed/cisplatin-treated patients and not listed elsewhere in section 6 include: decreased appetite (29% Grade 1-4, 4% Grade 3), nausea (25% Grade 1-4, 4% Grade 3), and vomiting (23% Grade 1-4, 4% Grade 3).

Table 2 Laboratory Abnormalities Occurring in $\geq 10\%$ of GILOTRIF Arm and at $\geq 2\%$ Higher Incidence than in Chemotherapy Arm in Study 1*

Laboratory Abnormality	GILOTRIF n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alanine aminotransferase (ALT)	54	2	27	1
Increased alkaline phosphate	51	3	46	1
Decreased creatinine clearance	49	2	47	1
Increased aspartate aminotransferase (AST)	46	3	22	1
Decreased lymphocytes	38	9	32	14
Decreased potassium	30	8	11	3
Increased bilirubin	16	1	8	0

*NCI CTCAE v 3.0

Previously Treated, Metastatic Squamous NSCLC

The safety of GILOTRIF was evaluated in 392 GILOTRIF-treated patients with metastatic squamous NSCLC enrolled in a randomized, multicenter, open-label trial (Study 2). Patients were required to have received at least four cycles of platinum-based chemotherapy, ECOG Performance Status (PS) 0 or 1, and normal left ventricular ejection fraction (LVEF). Patients received GILOTRIF 40 mg once daily (n=392) or erlotinib 150 mg once daily (n=395). Treatment continued until documented disease progression or intolerance to the therapy.

Among the 392 GILOTRIF-treated patients, the median age was 65 years, 53% were 65 years of age or older, 84% were male, 72% were White, 25% were Asian, ECOG PS 0 (32%) or 1 (68%). The median exposure was 2.1 months for patients treated with GILOTRIF, 15% were exposed for at least 6 months, and 5% were exposed for at least 12 months.

Serious adverse reactions occurred in 44% of patients treated with GILOTRIF. The most frequent serious adverse reactions in patients treated with GILOTRIF were pneumonia (6.6%), diarrhea (4.6%), and dehydration and dyspnea (3.1% each). Fatal adverse reactions in GILOTRIF-treated patients included ILD (0.5%), pneumonia (0.3%), respiratory failure (0.3%), acute renal failure (0.3%), and general physical health deterioration (0.3%).

Dose reductions due to adverse reactions were required in 27% of GILOTRIF-treated patients and discontinuation of GILOTRIF for adverse reactions was required for 20%. The most frequent adverse reactions that led to dose reduction in the patients treated with GILOTRIF were diarrhea (15%), rash/acne (5.9%), and stomatitis (3.1%). The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (4.1%) and rash/acne (2.6%). Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities in Study 2.

Table 3 Adverse Reactions Reported in ≥10% of GILOTRIF-Treated Patients in Study 2*

Adverse Reaction	GILOTRIF n=392		Erlotinib n=395	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal disorders				
Diarrhea	75	11	41	3
Stomatitis ¹	30	4	11	1
Nausea	21	2	16	1
Vomiting	13	1	10	1
Skin and subcutaneous tissue disorders				
Rash/acneiform dermatitis ²	70	7	70	11
Pruritus	10	0	13	0
Infections				
Paronychia ³	11	1	5	0
Metabolism and nutrition disorders				
Decreased appetite	25	3	26	2

*NCI CTCAE v 3.0

¹Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

²Includes acne, dermatitis, acneiform dermatitis, eczema, erythema, exfoliative rash, folliculitis, rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer

³Includes paronychia, nail infection, nail bed infection

Table 4 Laboratory Abnormalities Occurring in $\geq 10\%$ of GILOTRIF Arm and at $\geq 2\%$ Higher Incidence than in Erlotinib Arm in Study 2*

Laboratory Abnormality	GILOTRIF n=392		Erlotinib n=395	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alkaline phosphate	34	2	31	0
Decreased white blood cell count	12	1	8	1
Decreased potassium	11	1	8	1

*NCI CTCAE v 3.0

Other clinically important laboratory abnormalities observed in patients treated with GILOTRIF that are not listed in Table 4 are: increased alanine aminotransferase (10% Grade 1-4; 1% Grade 3-4), increased aspartate aminotransferase (7% Grade 1-4; 1% Grade 3-4), and increased bilirubin (3% Grade 1-4; 0 Grade 3-4).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of GILOTRIF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Pancreatitis
- Toxic epidermal necrolysis/Stevens Johnson syndrome

7 DRUG INTERACTIONS

Effect of P-glycoprotein (P-gp) Inhibitors and Inducers

Concomitant taking of P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) with GILOTRIF can increase exposure to afatinib [see *Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

Concomitant taking of P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's wort) with GILOTRIF can decrease exposure to afatinib [see *Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. There are no available data on the use of GILOTRIF in pregnant women. Administration of afatinib to pregnant rabbits during organogenesis at exposures approximately 0.2 times the exposure in humans at the recommended dose of 40 mg daily resulted in embryotoxicity and, in rabbits showing maternal toxicity, increased abortions at late gestational stages [see *Data*]. Advise a pregnant woman of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in rabbits, administration of afatinib to pregnant animals at doses of 5 mg/kg (approximately 0.2 times the exposure by AUC at the recommended human dose of 40 mg daily) or greater during the period of organogenesis caused increased post-implantation loss, and in animals showing maternal toxicity, abortion at late gestational stages. In the same study, at the high dose level of 10 mg/kg (approximately 0.7 times the exposure by AUC at the recommended human dose of 40 mg daily), there were reduced fetal weights, and increases in the incidence of runts, as well as visceral and dermal variations. In an embryo-fetal development study in rats, there were skeletal alterations consisting of incomplete or delayed ossifications and reduced fetal weight at a dose of 16 mg/kg (approximately twice the exposure based on AUC at the recommended human dose of 40 mg daily).

8.2 Lactation

Risk Summary

There are no data on the presence of afatinib in human milk or its effects on the breastfed infant or on milk production. Afatinib was present in the milk of lactating rats [see *Data*]. Because of the potential for serious adverse reactions in nursing infants from GILOTRIF, advise a lactating woman not to breastfeed during treatment with GILOTRIF and for 2 weeks after the final dose.

Data

Afatinib was present in the milk of lactating rats at concentrations 80 and 150 times higher than those found in plasma at 1 and 6 hours after administration.

8.3 Females and Males of Reproductive Potential

Contraception

Females

GILOTRIF can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with GILOTRIF, and for at least 2 weeks after the last dose of GILOTRIF [see *Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)*].

Infertility

Based on results from an animal fertility study, GILOTRIF may reduce fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

Safety and effectiveness of GILOTRIF in pediatric patients have not been established.

8.5 Geriatric Use

Study 1 did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In Study 2, 53% of the 398 patients randomized to receive afatinib were 65 years of age or older and 11% were 75 years or older. In an exploratory subgroup analysis of Study 2, the hazard ratio for overall survival in patients less than 65 years old was 0.68 (95% CI: 0.55, 0.85) and in patients 65 years or older was 0.95 (95% CI: 0.76, 1.19). No overall differences in safety were observed between patients 65 years and older and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment have a higher exposure to afatinib than patients with normal renal function. Administer GILOTRIF at a starting dose of 30 mg once daily in patients with severe renal impairment. Adjustments to the starting dose of GILOTRIF are not necessary in patients with mild or moderate renal impairment. Dosing recommendations for patients with eGFR <15 mL/min/1.73 m² or on dialysis cannot be provided as GILOTRIF has not been studied in these patient populations [see *Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

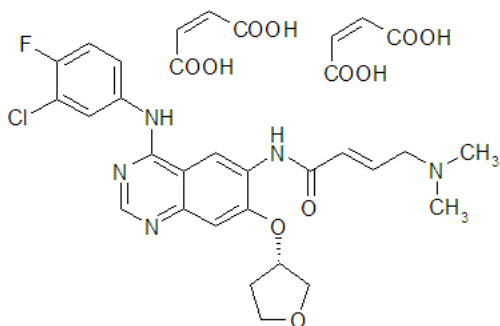
GILOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. Adjustments to the starting dose of GILOTRIF are not necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust GILOTRIF dose if not tolerated [see *Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Overdose was reported in 2 healthy adolescents each of whom ingested 360 mg of GILOTRIF (as part of a mixed-drug ingestion) resulting in nausea, vomiting, asthenia, dizziness, headache, abdominal pain, and elevated amylase [<1.5 times upper limit of normal (ULN)]. Both subjects recovered.

11 DESCRIPTION

GILOTRIF tablets contain afatinib, a tyrosine kinase inhibitor which is a 4-anilinoquinazoline. Afatinib is presented as the dimaleate salt, with the chemical name 2-butenamide, *N*-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[[(3*S*)-tetrahydro-3-furanyl]oxy]-6-quinazoliny]-4-(dimethylamino)-, (2*E*)-, (2*Z*)-2-butenedioate (1:2). Its structural formula is:



Afatinib dimaleate is a white to brownish yellow powder, water soluble and hygroscopic, with an empirical formula of C₃₂H₃₃ClFN₅O₁₁, and a molecular weight of 718.1 g/mol.

GILOTRIF tablets for oral administration are available in 40 mg, 30 mg, or 20 mg of afatinib (equivalent to 59.12 mg, 44.34 mg, or 29.56 mg afatinib dimaleate, respectively). The inactive ingredients of GILOTRIF are the following: Tablet Core: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate and Coating: hypromellose, polyethylene glycol, titanium dioxide, talc, polysorbate 80, FD&C Blue No. 2 (40 mg and 30 mg tablets only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Afatinib covalently binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in downregulation of ErbB signaling.

Afatinib demonstrated inhibition of autophosphorylation and *in vitro* proliferation of cell lines expressing wild-type EGFR or those expressing selected EGFR exon 19 deletion mutations or exon 21 L858R mutations, including some with a secondary T790M mutation, at afatinib concentrations achieved, at least transiently, in patients. In addition, afatinib inhibited *in vitro* proliferation of cell lines overexpressing HER2.

Treatment with afatinib resulted in inhibition of tumor growth in nude mice implanted with tumors either overexpressing wild type EGFR or HER2 or in an EGFR L858R/T790M double mutant model.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of GILOTRIF (50 mg once daily) on the QTc interval was evaluated in an open-label, single-arm study in patients with relapsed or refractory solid tumors. No large changes in the mean QTc interval (i.e., >20 ms) were detected in the study.

12.3 Pharmacokinetics

Absorption and Distribution

Following oral administration of GILOTRIF tablets, time to peak afatinib plasma concentrations (T_{max}) is 2 to 5 hours. Maximum concentration (C_{max}) and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) values increased slightly more than dose proportional in the range of 20 to 50 mg. The geometric mean relative bioavailability of 20 mg GILOTRIF tablets was 92% as compared to an oral solution. *In vitro* binding of afatinib to human plasma proteins is approximately 95%.

A high-fat meal decreased C_{max} by 50% and $AUC_{0-\infty}$ by 39% relative to the fasted condition [see *Dosage and Administration* (2.2)].

Metabolism and Elimination

Covalent adducts to proteins are the major circulating metabolites of afatinib and enzymatic metabolism of afatinib is minimal.

In humans, excretion of afatinib is primarily *via* the feces (85%) with 4% recovered in the urine following a single oral dose of [^{14}C]-labeled afatinib solution. The parent compound accounted for 88% of the recovered dose.

The elimination half-life of afatinib is 37 hours after repeat dosing in cancer patients. Steady-state plasma concentrations are achieved within 8 days of repeat dosing of GILOTRIF resulting in an accumulation of 2.8-fold for AUC and 2.1-fold for C_{max} .

Specific Populations

Renal Impairment: A pharmacokinetic study was conducted in 14 subjects with normal ($eGFR \geq 90$ mL/min/1.73 m²) renal function, 8 subjects with moderate ($eGFR=30$ to 59 mL/min/1.73 m²) and 8 subjects with severe ($eGFR=15$ to 29 mL/min/1.73 m²) renal impairment. All subjects received a single 40 mg oral dose of GILOTRIF. The geometric mean AUC_{inf} for afatinib was 50% higher in subjects with severe renal impairment and was 22% higher in subjects with moderate renal impairment as compared to subjects with normal renal function. Geometric mean C_{max} was 22% higher in subjects with severe renal impairment and was comparable in subjects with moderate renal impairment as compared to subjects with normal renal function [see *Dosage and Administration* (2.2) and *Use in Specific Populations* (8.6)]. GILOTRIF has not been studied in patients with $eGFR < 15$ mL/min/1.73 m² or on dialysis.

Hepatic Impairment: Afatinib is eliminated mainly by biliary/fecal excretion. Mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had no influence on the afatinib exposure following a single dose of

GILOTRIF. Subjects with severe (Child Pugh C) hepatic dysfunction have not been studied [see *Use in Specific Populations* (8.7)].

Body Weight, Gender, Age, and Race: Based on the population pharmacokinetic analysis, weight, gender, age, and race do not have a clinically important effect on exposure of afatinib.

Drug Interactions

Effect of P-gp Inhibitors and Inducers on Afatinib: The effect of ritonavir dosing time relative to a single oral dose of GILOTRIF was evaluated in healthy subjects taking 40 mg of GILOTRIF alone as compared to those after ritonavir (200 mg twice daily for 3 days) co-administration at 6 hours after GILOTRIF administration. The relative bioavailability for $AUC_{0-\infty}$ and C_{max} of afatinib was 119% and 104% when co-administered with ritonavir, and 111% and 105% when ritonavir was administered 6 hours after taking GILOTRIF. In another study, when ritonavir (200 mg twice daily for 3 days) was administered 1 hour before a 20 mg single dose of GILOTRIF, exposure to afatinib increased by 48% for $AUC_{0-\infty}$ and 39% for C_{max} [see *Drug Interactions* (7)].

Pre-treatment with a potent inducer of P-gp, rifampicin (600 mg once daily for 7 days) decreased the plasma exposure to afatinib by 34% ($AUC_{0-\infty}$) and 22% (C_{max}) [see *Drug Interactions* (7)].

P-glycoprotein (P-gp): Based on *in vitro* data, afatinib is a substrate and an inhibitor of P-gp.

Breast Cancer Resistance Protein (BCRP): Based on *in vitro* data, afatinib is a substrate and an inhibitor of the transporter BCRP.

Effect of CYP450 Enzyme Inducers and Inhibitors on Afatinib: *In vitro* data indicated that drug-drug interactions with GILOTRIF due to inhibition or induction of CYP450 enzymes by concomitant medications are unlikely. The metabolites formed by CYP450-dependent reactions were approximately 9% of the total metabolic turnover in sandwich-cultured human hepatocytes. In humans, enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of afatinib. Approximately 2% of the afatinib dose was metabolized by FMO3; the CYP3A4-dependent N-demethylation was not detected.

Effect of Afatinib on CYP450 Enzymes: Afatinib is not an inhibitor or an inducer of CYP450 enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A4) in cultured primary human hepatocytes. Therefore, afatinib is unlikely to affect the metabolism of other drugs that are substrates of CYP450 enzymes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with afatinib.

A marginal response to afatinib was observed in a single tester strain of a bacterial (Ames) mutagenicity assay. No mutagenic or genotoxic potential was identified in an *in vitro* chromosomal aberration test at non-cytotoxic concentrations as well as in the *in vivo* bone marrow micronucleus assay, the *in vivo* Comet assay, and an *in vivo* 4-week oral mutation study in the MutaTM Mouse.

In a dedicated fertility study, male and female rats received afatinib daily by oral administration at doses of 4, 6, or 8 mg/kg. In males at doses of 6 mg/kg (approximately equal to the exposure by AUC in patients at the recommended human dose of 40 mg daily) or greater, there was an increase in the incidence of low or no sperm count, though overall fertility was not affected; decreases in sperm count were supported by findings of increased apoptosis in the testes and atrophy in the seminal vesicles and the prostate in general toxicology studies. In females at the high dose of 8 mg/kg (approximately 0.63 times the exposure by AUC in patients at the recommended human dose of 40 mg daily), there was a mild decrease in the number of corpora lutea along with a mild increase in post-implantation loss due to early resorptions. In a 4-week general toxicology study,

female rats had decreases in ovarian weights at all dose levels; organ weight had not fully recovered by the end of a 2-week recovery period.

14 CLINICAL STUDIES

14.1 EGFR Mutation-Positive Non-Small Cell Lung Cancer

The efficacy and safety of GILOTRIF in the first-line treatment of 345 patients with EGFR mutation-positive, metastatic [Stage IV and Stage IIIb with pleural and/or pericardial effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition)] non-small cell lung cancer (NSCLC) were established in a randomized, multicenter, open-label trial (Study 1). Patients were randomized (2:1) to receive GILOTRIF 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115). Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). Other efficacy outcomes included overall response rate (ORR) and overall survival (OS). EGFR mutation status was prospectively determined for screening and enrollment of patients by a clinical trial assay (CTA). Tumor samples from 264 patients (178 randomized to GILOTRIF and 86 patients randomized to chemotherapy) were tested retrospectively by the companion diagnostic *therascreen*[®] EGFR RGQ PCR Kit, which is FDA-approved for selection of patients for GILOTRIF treatment.

Among the patients randomized, 65% were female, median age was 61 years, baseline ECOG performance status was 0 (39%) or 1 (61%), 26% were Caucasian and 72% were Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations.

A statistically significant improvement in PFS as determined by the IRC was demonstrated for patients randomized to GILOTRIF compared with those randomized to chemotherapy. See Table 5 and Figure 1. There was no statistically significant difference for overall survival between the treatment arms at the final pre-planned analysis.

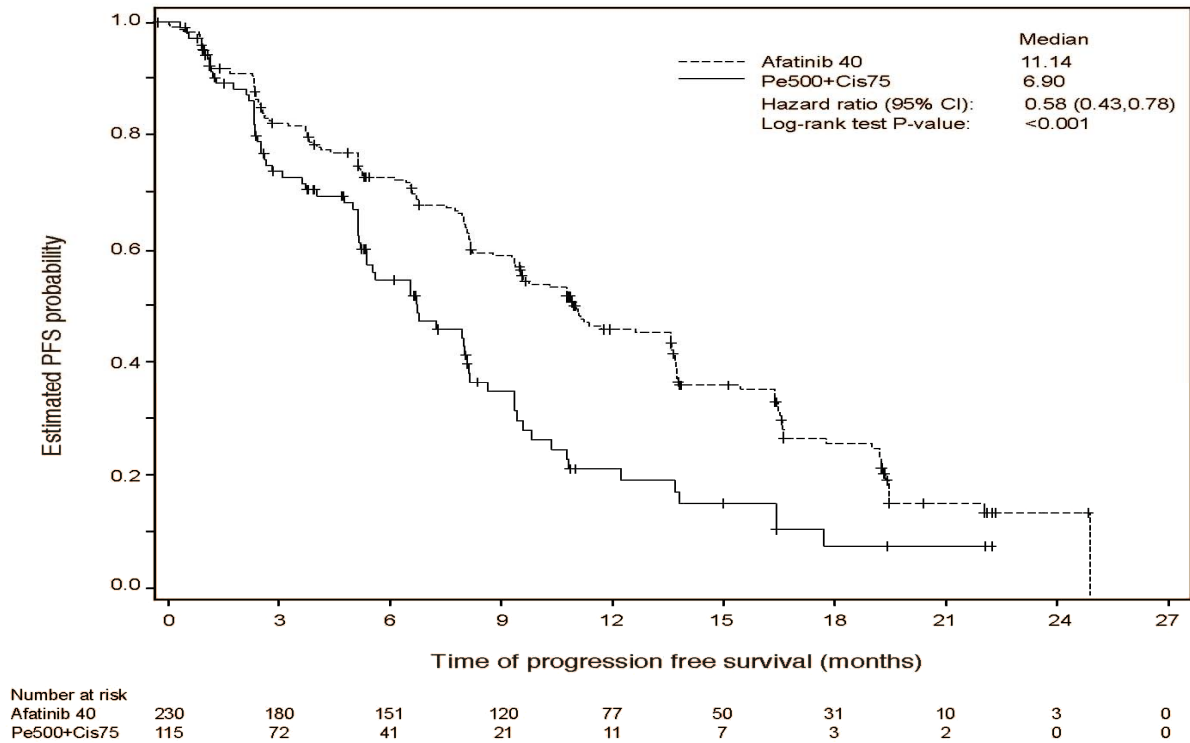
Table 5 Efficacy Results

	GILOTRIF (N=230)	Pemetrexed/Cisplatin (N=115)
Progression-Free Survival by IRC		
Number of Deaths or Progressions, N (%)	152 (66.1%)	69 (60.0%)
Median Progression-Free Survival (months)	11.1	6.9
95% CI	(9.6, 13.6)	(5.4, 8.2)
HR (95% CI)	0.58 (0.43, 0.78)	
Stratified Log-Rank Test p-value*	<0.001	
Overall Survival		
Number of Deaths, N (%)	140 (60.9%)	73 (63.5%)
Median Overall Survival (months)	28.2	28.2
95% CI	(24.6, 33.6)	(20.7, 33.2)
HR (95% CI)	0.88 (0.66, 1.17)	
Stratified Log-Rank Test p-value*	0.39	
Overall Response Rate (CR + PR) by IRC		
N (%)	116 (50.4%)	22 (19.1%)
Response Duration		
Median (months)	12.5	6.7

*Stratified by EGFR mutation status and race.

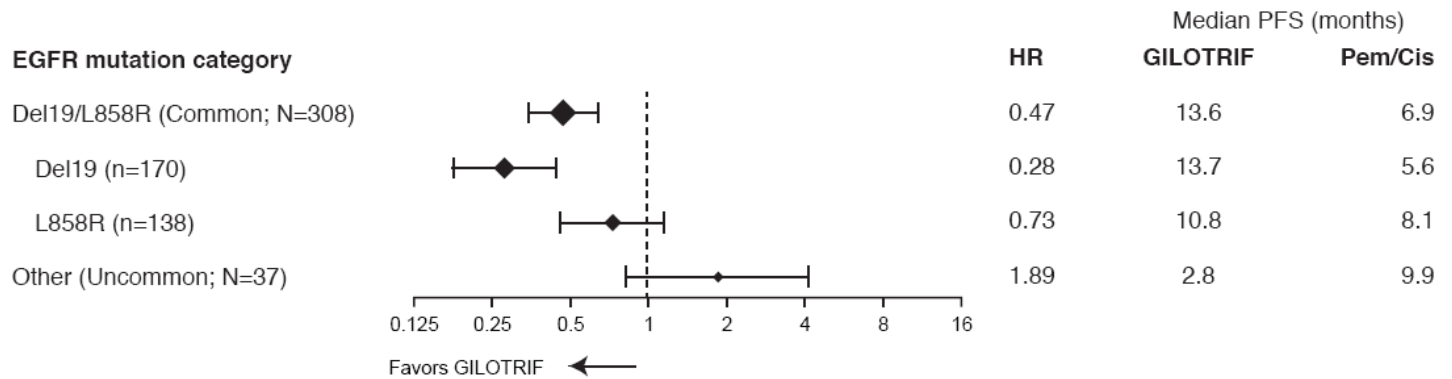
HR=hazard ratio; CR=complete response; PR=partial response

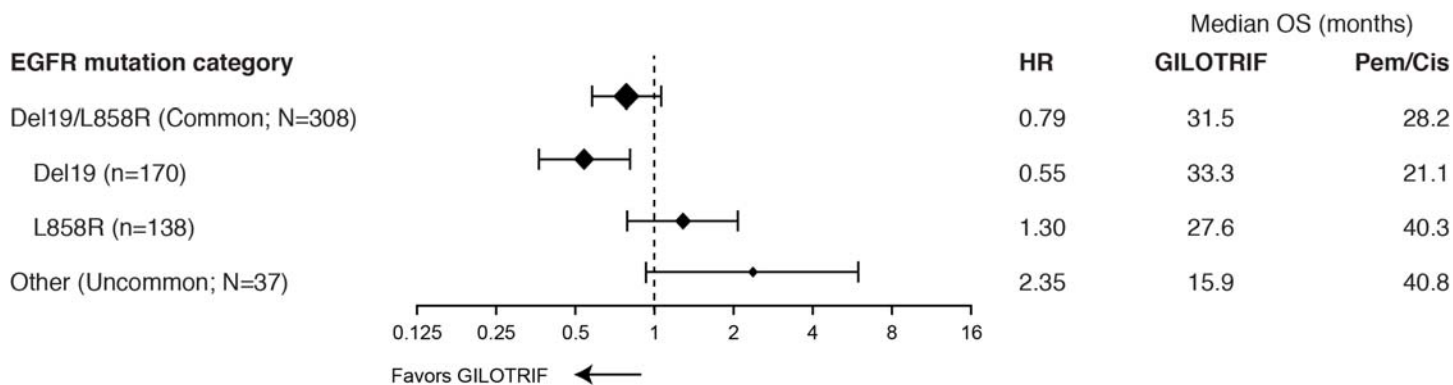
Figure 1 Kaplan-Meier Curve for PFS by Independent Review by Treatment Group



Subgroup analyses were conducted based on the stratification factor of EGFR mutation status (Del19, L858R, other) and mutation category (common [Del19, L858R] vs uncommon [other]). See Figure 2.

Figure 2 Forest Plot of PFS and OS for Common (Del19, L858R) and Uncommon (other) EGFR Mutation Categories





There were 26 GILOTRIF-treated patients in the “other” (uncommon) EGFR mutations subgroup with nine unique mutation patterns. None of these 26 patients achieved a complete response, while four achieved a partial response (see Table 6 below). No responses were seen in GILOTRIF-treated patients with the following mutations: T790M alone (n=2), deletion 19 and T790M (n=3), G719X and T790M (n=1), exon 20 insertion (n=6), and L861Q alone (n=3). There were 11 chemotherapy-treated patients in the “other” uncommon EGFR mutation subgroup; of these, four (36%) achieved a partial response.

Table 6 Objective Tumor Responses in GILOTRIF-Treated Patients Based on Investigator Assessment in the “Other” (Uncommon) EGFR Mutation Subgroup

EGFR Mutations	Number of GILOTRIF-Treated Patients	Number of Patients with Partial Responses	Duration of Response
L858R and T790M	5	1	6.9 months
L858R and S768I	2	1	12.4+ months
S768I	1	1	16.5+ months
G719X	3	1	9.6 months

+ Censored observation

14.2 Previously Treated, Metastatic Squamous NSCLC

The efficacy and safety of GILOTRIF were demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 2). Patients were required to have histologically documented, metastatic squamous NSCLC and have experienced disease progression following an adequate course (≥ 4 cycles) of a platinum-based doublet chemotherapy regimen. Patients were randomized (1:1) to receive GILOTRIF 40 mg or erlotinib 150 mg orally once daily until progression. Randomization was stratified by region (Eastern Asia vs other). The major efficacy outcome measure was PFS as assessed by an independent review committee (IRC) using RECIST v 1.1. Additional efficacy outcome measures were OS and ORR as assessed by IRC.

Baseline patient demographics of the 795 patients were: median age 64 years (range: 35 to 88); 73% White; 24% Asian; 84% male; 33% ECOG performance status (PS) 0 and 67% ECOG PS 1; and 95% current or former smokers. With regard to tumor characteristics, 96% had squamous cell histology and 3.5% had mixed cell histology. All patients received platinum-based doublet therapy.

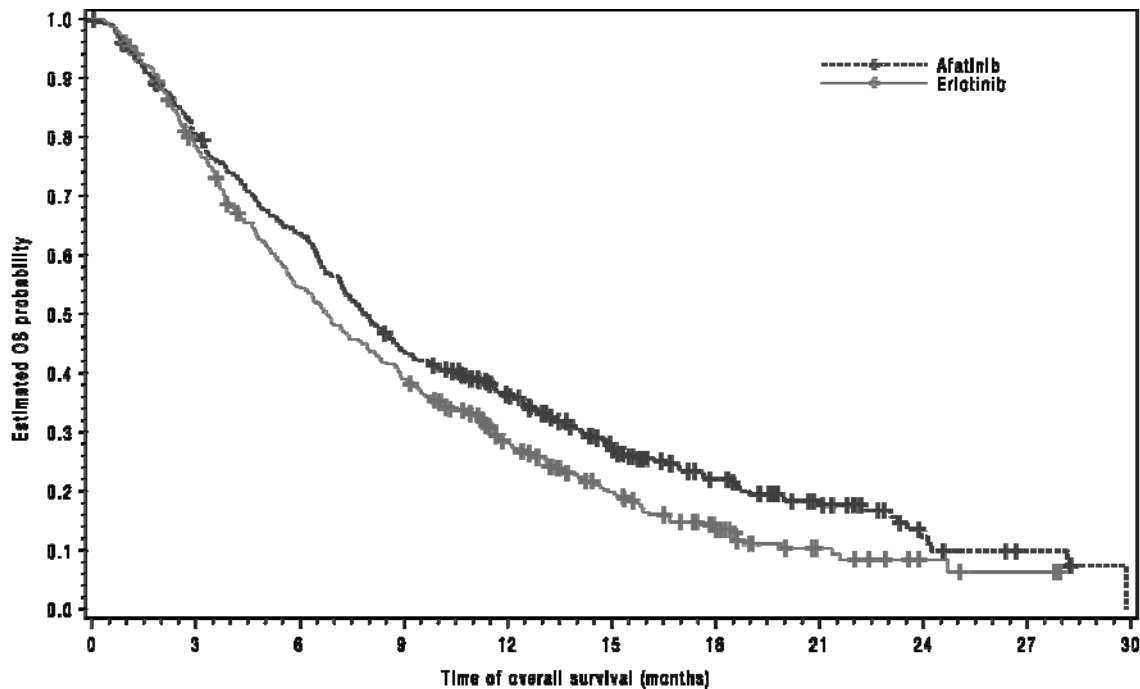
The study demonstrated a statistically significant improvement in PFS and OS for patients randomized to GILOTRIF as compared with erlotinib (see Table 7 and Figure 3).

Table 7 Efficacy Results

	GILOTRIF	Erlotinib
Overall Survival		
	N=398	N=397
Number of Deaths, N (%)	307 (77%)	325 (82%)
Median overall survival (months)	7.9	6.8
95% CI	(7.2, 8.7)	(5.9, 7.8)
HR (95% CI)	0.81 (0.69, 0.95)	
p-value*	0.008	
Progression-Free Survival (PFS) by IRC		
	N=335	N=334
Number of Events, N (%)	202 (60%)	212 (64%)
Median PFS (months)	2.4	1.9
95% CI	(1.9, 2.9)	(1.9, 2.2)
HR (95% CI)	0.82 (0.68, 0.998)	
p-value*	0.0427	
Overall Response Rate (ORR) by IRC		
	N=335	N=334
ORR	3%	2%
(95% CI)	(1.7, 5.8)	(0.8, 4.3)

*Log-rank test stratified by region.
HR=hazard ratio

Figure 3 Kaplan-Meier Curves of Overall Survival



Number at risk		3	6	9	12	15	18	21	24	27	30
Afatinib	398	316	248	170	124	82	47	28	10	4	0
Erlotinib	397	305	210	150	94	54	30	11	4	2	0

16 HOW SUPPLIED/STORAGE AND HANDLING

GILOTRIF tablets are available as follows:

40 mg: light blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T40” on one side and the Boehringer Ingelheim company symbol on the other side.

Unit of use bottles of 30 NDC: 0597-0138-30

30 mg: dark blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T30” on one side and the Boehringer Ingelheim company symbol on the other side.

Unit of use bottles of 30 NDC: 0597-0137-30

20 mg: white to slightly yellowish, film-coated, round, biconvex, bevel-edged tablets debossed with “T20” on one side and the Boehringer Ingelheim company symbol on the other side.

Unit of use bottles of 30 NDC: 0597-0141-30

Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Dispense medication in the original container to protect from exposure to high humidity and light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Diarrhea

Advise patients that diarrhea occurs in nearly all patients who receive GILOTRIF. Inform patients that diarrhea may result in dehydration and renal impairment if not treated. Advise patients to notify their physician if diarrhea develops and to seek medical attention promptly for severe or persistent diarrhea [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

Bullous and Exfoliative Skin Disorders

Advise patients to minimize sun exposure with protective clothing and use of sunscreen while taking GILOTRIF [see *Warnings and Precautions (5.2)*].

Interstitial Lung Disease

Advise patients to immediately report any new or worsening lung symptoms, or any combination of the following symptoms: trouble breathing or shortness of breath, cough, fever [see *Warnings and Precautions (5.3)*].

Hepatic Toxicity

Advise patients that they will need to undergo liver function monitoring periodically. Advise patients to immediately report any symptoms of a liver problem [e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleeds or bruises more easily than normal, lethargy] [see *Warnings and Precautions (5.4)*].

Keratitis

Advise patients to immediately report eye problems (e.g., eye pain, swelling, redness, blurred vision, or other vision changes) [see *Warnings and Precautions (5.5)*].

Left Ventricular Dysfunction

Advise patients to contact a healthcare professional immediately for any of the following: new onset or worsening shortness of breath or exercise intolerance, cough, fatigue, swelling of the ankles/legs, palpitations, or sudden weight gain [*see Dosage and Administration (2.3) and Adverse Reactions (6.1)*].

Instructions for Taking GILOTRIF

Advise patients to take GILOTRIF on an empty stomach at least 1 hour before or 2 hours after eating [*see Dosage and Administration (2.2)*]. Advise patients not to take a missed dose within 12 hours of the next dose.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that GILOTRIF can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with GILOTRIF and for at least 2 weeks after the last dose of GILOTRIF [*see Use in Specific Populations (8.1, 8.3)*].

Lactation

Advise women not to breastfeed during treatment with GILOTRIF and for 2 weeks after the last dose of GILOTRIF [*see Use in Specific Populations (8.2)*].

Infertility

Advise females and males of reproductive potential of the potential for reduced fertility from GILOTRIF [*see Use in Specific Populations (8.3)*].

Distributed by:

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IT5562PJ042016

Patient Information
GILOTRIF® (JEE-loh-trif)
(afatinib) tablets

What is GILOTRIF?

GILOTRIF is a prescription medicine used to treat non-small cell lung cancer (NSCLC):

- that has certain types of abnormal epidermal growth factor receptor (EGFR) genes. Your doctor will perform a test to check for certain types of abnormal EGFR genes, and make sure that GILOTRIF is right for you. GILOTRIF may be used when you have not had previous treatment for cancer that has spread to other parts of your body. It is not known if GILOTRIF is safe and effective in treating lung cancer with other abnormal EGFR genes.

or

- that is squamous type and has spread to other parts of the body after you have tried chemotherapy that contains platinum.

It is not known if GILOTRIF is safe and effective in children.

Before you take GILOTRIF, tell your doctor about all of your medical conditions, including if you:

- have kidney or liver problems
- have lung or breathing problems other than lung cancer
- have a history of severe dry eye or any other eye problems. Tell your doctor if you wear contact lenses.
- have heart problems
- are pregnant or plan to become pregnant. GILOTRIF can harm your unborn baby. You should not become pregnant while taking GILOTRIF.
 - Women who are able to become pregnant should use effective birth control during treatment with GILOTRIF and for at least 2 weeks after your last dose of GILOTRIF. Talk to your doctor about birth control methods that may be right for you.
 - Tell your doctor right away if you become pregnant or think you are pregnant while taking GILOTRIF.
- are breastfeeding or plan to breastfeed. It is not known if GILOTRIF passes into your breast milk. Do not breastfeed while taking GILOTRIF and for 2 weeks after your last dose of GILOTRIF. Talk to your doctor about the best way to feed your baby if you take GILOTRIF.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. GILOTRIF may affect the way other medicines work, and other medicines may affect the way GILOTRIF works.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take GILOTRIF?

- Take GILOTRIF exactly as your doctor tells you to take it.
- Your doctor will tell you how many GILOTRIF tablets to take and when to take them. Do not change your dose or stop GILOTRIF unless your doctor tells you to.
- Take GILOTRIF on an empty stomach at least 1 hour before a meal or 2 hours after a meal.
- If you miss a dose of GILOTRIF, take it as soon as you remember. If it is within 12 hours of your next dose, skip the dose and just take your next dose at your regular time. Do not take 2 doses of GILOTRIF at the same time.
- If you take too much GILOTRIF, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking GILOTRIF?

Limit your time in the sun. GILOTRIF can make your skin sensitive to the sun. You could get or have worsening rash or acne. You could get a severe sunburn. Use sunscreen and wear a hat and clothes that cover your skin while you are taking GILOTRIF if you have to be in sunlight.

What are the possible side effects of GILOTRIF?

GILOTRIF may cause serious side effects, including:

- **diarrhea.** Diarrhea is common with GILOTRIF and may sometimes be severe. Severe diarrhea can cause loss of too much body fluid (dehydration) and kidney problems that can sometimes lead to death. During your treatment with GILOTRIF, your doctor should prescribe medicines to treat diarrhea. Take this medicine exactly as your doctor tells you to. Tell your doctor if you have diarrhea. Get medical attention right away if your diarrhea does not go away or becomes severe.
- **skin reactions.** GILOTRIF can cause redness, rash, and acne. It is important to get treatment for skin reactions as soon as you notice them. Take medicines to help skin reactions exactly as your doctor tells you to. Get medical attention right away if you develop severe skin reactions such as peeling or blistering of the skin, or blisters in your mouth.

- **lung or breathing problems.** GILOTRIF may cause inflammation of the lung that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your doctor right away if you have any new or worsening lung problems, or any combination of the following symptoms: trouble breathing or shortness of breath, cough, or fever.
- **liver problems.** GILOTRIF can cause liver problems that can sometimes lead to death. Tell your doctor right away if you have any symptoms of a liver problem which may include:
 - yellowing of your skin or the white part of your eyes (jaundice)
 - dark or brown (tea colored) urine
 - pain on the upper right side of your stomach area (abdomen)
 - bleeding or bruising more easily than normal
 - feeling very tired
 Your doctor will do blood tests to check your liver function during your treatment with GILOTRIF.
- **eye problems.** Tell your doctor right away if you have symptoms of eye problems which may include:
 - eye pain, swelling, redness, or tearing
 - sensitivity to light
 - blurred vision
 - other changes in your vision
- **heart problems.** Tell your doctor right away if you have symptoms of a heart problem which may include:
 - new or worsening shortness of breath while at rest or with activity
 - swelling of your ankles, feet, or legs
 - cough
 - feeling that your heart is pounding or racing (palpitations)
 - tiredness
 - sudden weight gain

The most common side effects of GILOTRIF include:

- diarrhea
- rash
- mouth sores
- nail inflammation
- dry skin
- acne
- decreased appetite
- nausea
- vomiting
- itching

GILOTRIF may cause decreased fertility in females and males. Talk to your doctor if you have concerns about fertility.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of GILOTRIF. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store GILOTRIF?

- Store GILOTRIF at room temperature 68°F to 77°F (20°C to 25°C).
- Keep GILOTRIF in the original container and keep the container tightly closed.
- Keep GILOTRIF away from moisture and light.
- Safely throw away (discard) any GILOTRIF that is out of date or no longer needed.

Keep GILOTRIF and all medicines out of the reach of children.

General information about GILOTRIF

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use GILOTRIF for a condition for which it was not prescribed. Do not give GILOTRIF to other people, even if they have the same symptoms you have. It may harm them. You can ask your doctor or pharmacist for information about GILOTRIF that is written for health professionals.

What are the ingredients in GILOTRIF?

Active ingredient: afatinib

Inactive ingredients: Tablet Core: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate. **Tablet Coating:** hypromellose, polyethylene glycol, titanium dioxide, talc, polysorbate 80, FD&C Blue No. 2 (40 mg and 30 mg tablets only).

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For more information, go to www.gilotrif.com or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257

or (TTY) 1-800-459-9906, or scan the code to go to www.gilotrif.com.



This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: October 2016

EXHIBIT B

(19) **United States**
 (12) **Reissued Patent**
Himmelsbach et al.

(10) **Patent Number:** **US RE43,431 E**
 (45) **Date of Reissued Patent:** **May 29, 2012**

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

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(Continued)

(73) Assignee: **Boehringer Ingelheim Pharma GmbH & Co. KG**, Ingelheim am Rhein (DE)

(21) Appl. No.: **12/542,929**

(22) Filed: **Aug. 18, 2009**

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 Filed: **Dec. 17, 2001**

U.S. Applications:

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(30) **Foreign Application Priority Data**

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C07D 413/02 (2006.01)

(52) **U.S. Cl.** **514/266.22**; 514/266.4; 514/266.24; 514/217.06; 514/313; 514/314; 544/293; 544/122; 544/283; 544/284

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

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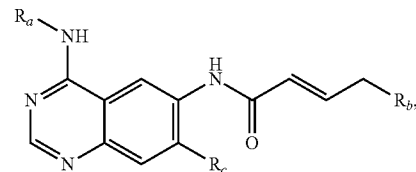
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(57) **ABSTRACT**

A compound of general formula 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, cyclobutylloxy, cyclopentylloxy, 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

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**QUINAZOLINE DERIVATIVES AND
PHARMACEUTICAL COMPOSITIONS
CONTAINING THEM**

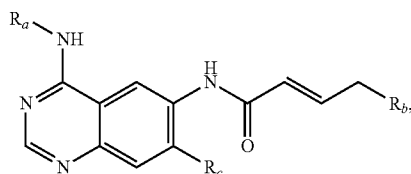
Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

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, cyclobutylloxy, cyclopentylloxy, 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-fluorophenylamino]-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,

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- (4) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutylloxyquinazoline,
 - (5) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentylloxyquinazoline,
 - (6) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutylloxyquinazoline,
 - (7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentylloxyquinazoline,
 - (8) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutylloxyquinazoline,
 - (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-cyclopentylloxyquinazoline,
 - (11) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutylloxyquinazoline,
 - (12) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentylloxyquinazoline,
 - (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-(tetrahydrofuran-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-yl)methyl]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-cyclobutylloxyquinazoline,

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- (5) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-cyclopentyllox-
yquinazoline,
- (6) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(diethylamino)-1-oxo-2-buten-1-yl}amino}-7-cyclobutyllox-
yquinazoline,
- (7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(diethylamino)-1-oxo-2-buten-1-yl}amino}-7-cyclopentyllox-
yquinazoline,
- (8) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-cyclobutyllox-
yquinazoline,
- (9) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-cyclopropylmethox-
yquinazoline,
- (10) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-cyclopentyllox-
yquinazoline,
- (11) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(diethylamino)-1-oxo-2-buten-1-yl}amino}-7-cyclobutyllox-
yquinazoline,
- (12) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(diethylamino)-1-oxo-2-buten-1-yl}amino}-7-cyclopentyllox-
yquinazoline,
- (13) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(diethylamino)-1-oxo-2-buten-1-yl}amino}-7-cyclopropylmethox-
yquinazoline,
- (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-(tetrahydrofuran-2-ylmethyl)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-[(tetrahydrofuran-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-cyclobutyllox-
yquinazoline,
- (24) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl]amino}-7-cyclobutyllox-
yquinazoline,
- (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-cyclobutyllox-
yquinazoline,
- (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-cyclobutyllox-
yquinazoline,

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- (27) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[[N-methyl-N-(tetrahydrofuran-4-yl)amino]-1-oxo-2-buten-1-yl]amino}-7-cyclobutyllox-
yquinazoline,
- (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-cyclobutyllox-
yquinazoline,
- (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-cyclobutyllox-
yquinazoline,
- (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-(tetrahydrofuran-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-(tetrahydrofuran-4-yl)amino or N-methyl-N-(tetrahydrofuran-4-ylmethyl)amino group and
- R_c denotes a cyclopropylmethoxy, cyclobutyllox, cyclopentyllox, tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydrofuran-4-yloxy or tetrahydrofuran-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-cyclobutyllox-
yquinazoline,
- (5) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[[morpholin-4-yl]-1-oxo-2-buten-1-yl]amino}-7-cyclopentyllox-
yquinazoline,
- (6) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[[diethylamino]-1-oxo-2-buten-1-yl]amino}-7-cyclobutyllox-
yquinazoline,
- (7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[[diethylamino]-1-oxo-2-buten-1-yl]amino}-7-cyclopentyllox-
yquinazoline,
- (8) 4-[(R)-(1-phenylethyl)amino]-6-{{4-[[morpholin-4-yl]-1-oxo-2-buten-1-yl]amino}-7-cyclobutyllox-
yquinazoline,
- (9) 4-[(R)-(1-phenylethyl)amino]-6-{{4-[[morpholin-4-yl]-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

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- (10) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-cyclopentylmethoxyquinazoline,
- (11) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(diethylamino)-1-oxo-2-buten-1-yl}amino}-7-cyclobutylmethoxyquinazoline,
- (12) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(diethylamino)-1-oxo-2-buten-1-yl}amino}-7-cyclopentylmethoxyquinazoline,
- (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-cyclobutylmethoxyquinazoline,
- (23) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl]amino}-7-cyclobutylmethoxyquinazoline,
- (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-cyclobutylmethoxyquinazoline,
- (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-cyclobutylmethoxyquinazoline,
- (26) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[N-methyl-N-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-yl]amino}-7-cyclobutylmethoxyquinazoline,
- (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,

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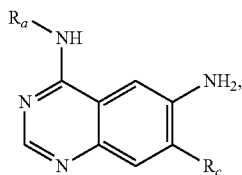
- (32) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[(R)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl]amino}-7-cyclobutylmethoxyquinazoline and
- (33) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[(S)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl]amino}-7-cyclobutylmethoxyquinazoline, 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-cyclobutylmethoxyquinazoline;
- (b) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentylmethoxyquinazoline,
- (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,
- (n) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]quinazoline,
- (o) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,
- (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-cyclopentylmethoxyquinazoline; 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.

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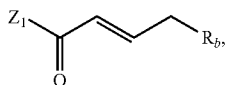
The compounds of general formula I may be prepared by the following methods, for example:

a) reacting a compound of general formula



wherein:

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



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.

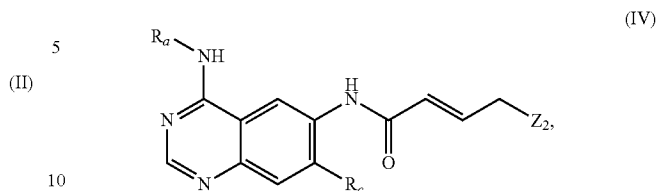
The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of an inorganic or organic base and optionally in the presence of 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-ethyl-diisopropylamine (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 .

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b) Reacting a compound of general formula



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:



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-ethyl-diisopropylamine (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.

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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

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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

5 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:

10 The inhibition of human EGF-receptor kinase was determined using the cytoplasmic tyrosine kinase domain (methionine 664 to alanine 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.

25 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.

35 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 HRP-labelled anti-PY antibody (PY20H Anti-PYr: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.

40 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% (IC₅₀) was derived from the curves.

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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 (neangiogenesis).

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, α 1-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,

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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

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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).

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(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

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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

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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-cyclopentylloxyquinazoline

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-1-yl}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).

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- (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-dimethylamino)-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]-1-oxo-2-buten-1-yl]amino]-7-cyclopentylmethoxyquinazoline
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-cyclopentylmethoxyquinazoline
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-cyclopentylmethoxyquinazoline
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-[(R)-N-[(tetrahydrofuran-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-[(S)-N-[(tetrahydrofuran-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-cyclopentylmethoxyquinazoline
Mass spectrum (ESI⁺): m/z=554, 556 [M+H]⁺; melting point: 117° C.-121° C.

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- (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-cyclopentylmethoxyquinazoline
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-[(tetrahydrofuran-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-[(tetrahydrofuran-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-[(tetrahydrofuran-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-cyclopentylmethoxyquinazoline
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-dimethylamino)-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-buten-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).

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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-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

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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, faceted 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.

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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

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machine (weight of the empty capsule approx. 50 mg). Weight of capsule: 70.0 mg; size of capsule: 3.

EXAMPLE 11

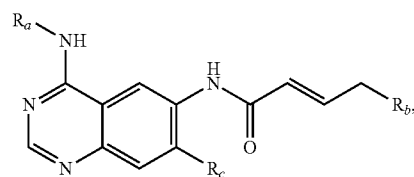
Solution for inhalation for hand-held nebulizers containing 2.5 mg active substance	
1 spray contains:	
active substance	2.500 mg
benzalkonium chloride	0.001 mg
1N hydrochloric acid	q.s.
ethanol/water (50/50)	ad 15.000 mg

15 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



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35 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, cyclobutyl, cyclopentyl, 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 R_b 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

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R_c is a cyclopropylmethoxy, cyclobutylloxy, cyclopentylloxy, 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.]

[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-fluorophenyl 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 dimethylamino group; and

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

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or a stereoisomer or physiologically acceptable salt thereof.]

7. The compound of claim 1, wherein:

R_c is a tetrahydrofuran-3-yloxy,

or a stereoisomer 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.

* * * * *

EXHIBIT C

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

(10) **Patent No.:** **US 8,426,586 B2**
 (45) **Date of Patent:** **Apr. 23, 2013**

(54) **PROCESS FOR PREPARING AMINO CROTONYL COMPOUNDS**
 (75) Inventors: **Rainer Soyka**, Biberach (DE); **Werner Rall**, Mittelbiberach (DE); **Juergen Schnaubelt**, Oberhoefen/Warthausen (DE); **Peter Sieger**, Mittelbiberach (DE); **Christian Kulinna**, Attenweiler (DE)
 (73) Assignee: **Boehringer Ingelheim International GmbH**, Ingelheim am Rhein (DE)
 (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1851 days.

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(21) Appl. No.: **11/457,622**

(22) Filed: **Jul. 14, 2006**

(65) **Prior Publication Data**

US 2007/0027170 A1 Feb. 1, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/941,116, filed on Sep. 15, 2004, now abandoned.

(60) Provisional application No. 60/517,777, filed on Nov. 6, 2003.

(30) **Foreign Application Priority Data**

Oct. 17, 2003 (DE) 103 49 113

(51) **Int. Cl.**

C07D 239/84 (2006.01)

C07D 215/44 (2006.01)

(52) **U.S. Cl.**

USPC **544/153**; 546/153

(58) **Field of Classification Search** 544/153; 546/153

See application file for complete search history.

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Primary Examiner — Paul V. Ward

(74) Attorney, Agent, or Firm — Michael P. Morris; Anthony P. Bottino

(57) **ABSTRACT**

An improved process for preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline and related aminocrotonyl compounds and the preparation of a suitable salt of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline for use as a pharmaceutically active substance.

11 Claims, 2 Drawing Sheets

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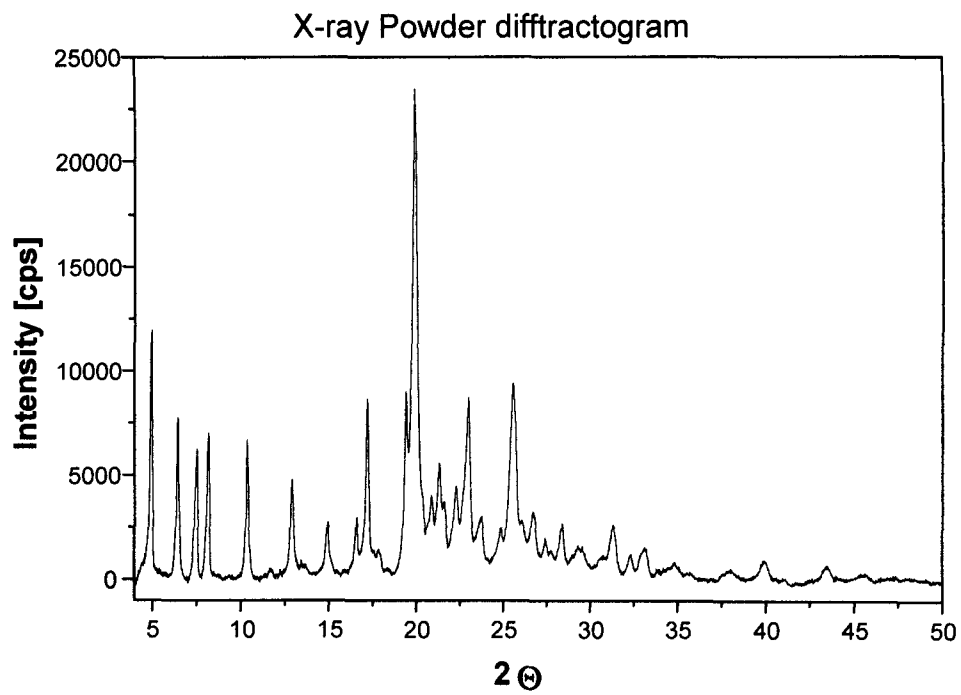


FIG. 1

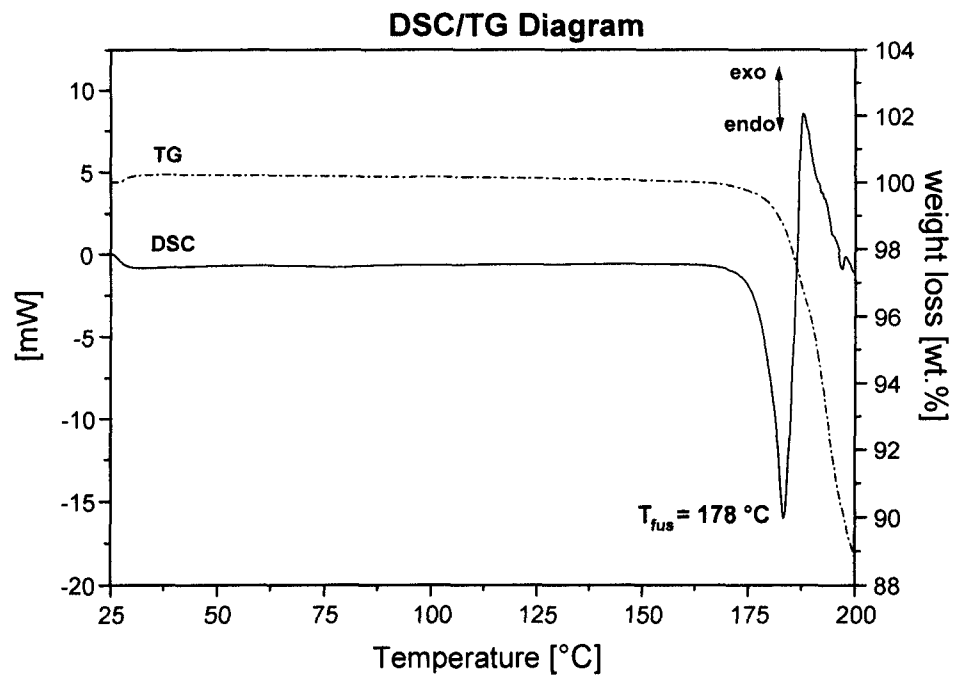


FIG. 2

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PROCESS FOR PREPARING AMINO CROTONYL COMPOUNDS

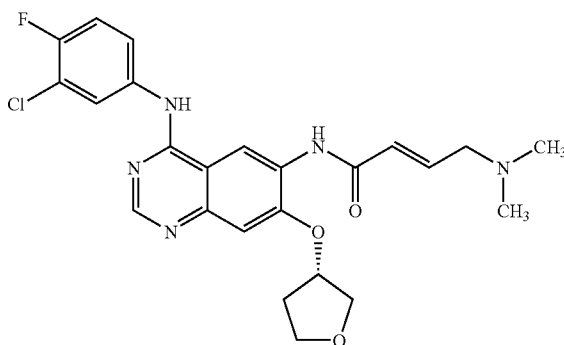
RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 10/941, 116, filed Sep. 15, 2004, which in turn claimed benefit of U.S. Ser. No. 60/517,777, filed Nov. 6, 2003, and priority from German Application No. 103 49 113.9, filed Oct. 17, 2003, each of which related applications is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to an improved process for preparing aminocrotonyl compounds such as for example 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline and the physiologically acceptable salts thereof, particularly 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate, as well as 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate and the use thereof for preparing pharmaceutical compositions.

4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline has the following structure:

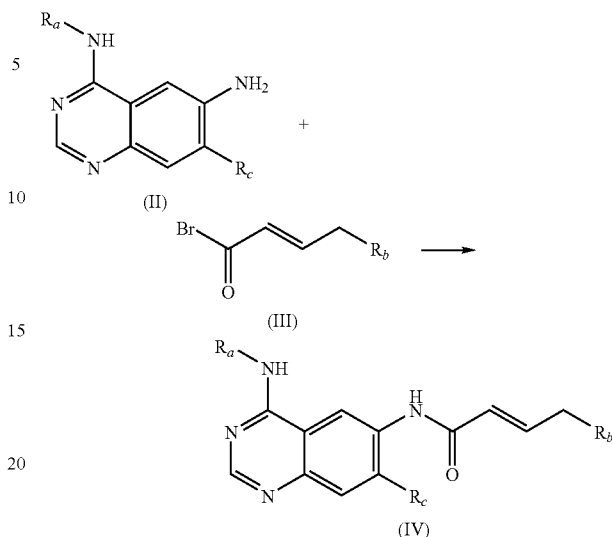


and is already known from WO 02/50043, which describes compounds with valuable pharmacological properties, including in particular an inhibiting effect on signal transduction mediated by tyrosinekinases and an inhibitory effect on signal transduction mediated by the Epidermal Growth Factor receptor (EGF-R). Therefore, compounds of this type are suitable for the treatment of diseases, particularly for the treatment of tumoral diseases, diseases of the lungs and respiratory tract and diseases of the gastrointestinal tract and bile duct and gall bladder.

WO 02/50043 discloses a method of preparation wherein aminocrotonyl compounds (IV) such as for example 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline are prepared in a one-pot reaction from the corresponding aniline component (II), bromocrotonic acid (III), oxalyl chloride and a secondary amine (see Diagram 1).

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Diagram 1:



In this process the yield was at most 50%. In addition, purification was generally carried out by column chromatography. Therefore, the method of preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline was not suitable on an industrial scale. Furthermore, the method had the disadvantage that bromocrotonic acid is not commercially available in large amounts and also the corresponding methyl bromocrotonate is only available in a purity of approx. 80%. These circumstances also militate against the suitability of this process for the industrial production of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline.

In the light of the above disadvantages of the known method of production, the aim of the present invention is to provide a process which allows the production of aminocrotonylarylamides, particularly 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, using highly pure starting materials which are readily available and without any great technical expenditure. This new process should therefore also be suitable for synthesis on an industrial scale and hence for commercial application.

This aim is achieved by the process according to the invention for preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline and other aminocrotonyl compounds. In addition to being industrially practicable with high yields the method of synthesis according to the invention also has the advantages of very good chemical purities and a low cis content of less than 0.1%.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an X-ray powder diffractogram of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate; and

FIG. 2 is a diagram depicting Thermoanalysis of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate.

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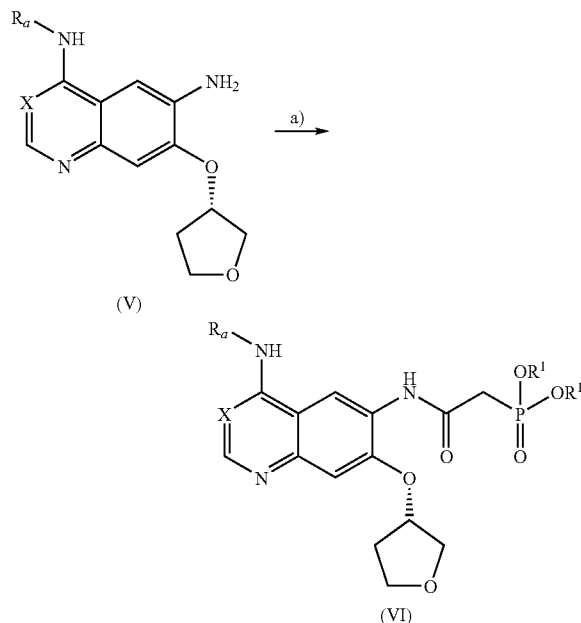
In the process according to the invention the corresponding aminoaryl compound (V) is reacted with a di-(C₁₋₄-alkyl)-phosphonoacetic acid, preferably with diethylphosphonoacetic acid, in suitable solvents, after corresponding activation, preferably with 1,1-carbonyldiimidazole, 1,1-carbonylditriazole or propanephosphonic anhydride, particularly preferably with 1,1-carbonyldiimidazole, according to Diagram 2. The solvent used may be for example tetrahydrofuran (THF), dimethylformamide (DMF) or ethyl acetate.

The activation may be carried out by any possible method of amide linking, i.e. for example with 1,1-carbonyldiimidazole, 1,1-carbonylditriazole, DCC(N,N-dicyclohexylcarbodiimide), EDC (N'-dimethylaminopropyl)-N-ethylcarbodiimide), TBTU (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate), thiazolidine-2-thione or by conversion into the corresponding acid chloride, possibly using thionyl chloride. If desired the activation may be carried out using organic bases such as triethylamine or pyridine, while DMAP (dimethylaminopyridine) may additionally be added. Suitable solvents include DMF, THF, ethyl acetate, toluene, chlorinated hydrocarbons or mixtures thereof.

In the formulae that follow X denotes a methyne group or a nitrogen atom, R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and R¹ denotes a straight-chain or branched C₁₋₄-alkyl group.

The process is preferably used for compounds wherein X denotes a nitrogen atom, R_a denotes a 3-chloro-4-fluorophenyl group and R¹ denotes an ethyl group.

Diagram 2:



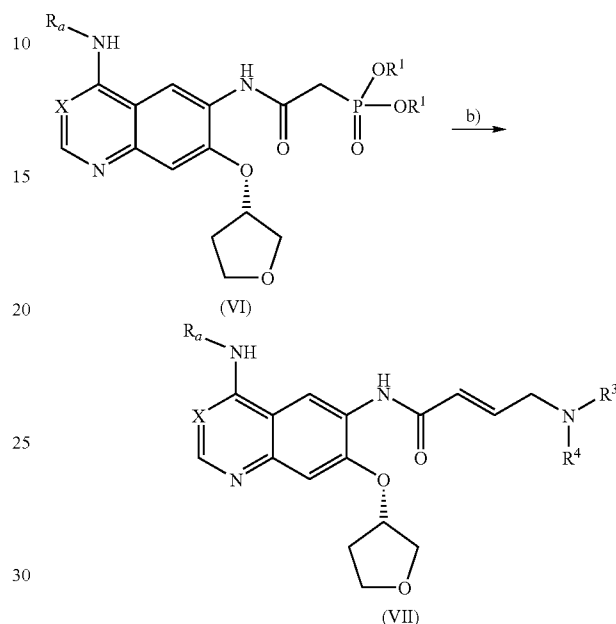
a) di-(C₁₋₄-alkyl)-phosphonoacetic Acid, Activating Agent

The arylamide (VI) thus obtained in a high yield and high purity is reacted with the corresponding 2-aminoacetaldehyde using suitable organic or inorganic bases in the sense of a Wittig-Horner-Emmons reaction (Diagram 3). This reaction may be carried out directly or after isolation of the compound (VI), for example by precipitation by the addition of tert-butylmethyl ether, for example. Suitable bases include for example DBU (1,5-diazabicyclo[4.3.0]non-5-ene), sodium

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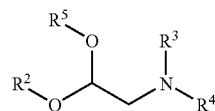
hydroxide and potassium hydroxide, of which sodium hydroxide and potassium hydroxide are preferred and potassium hydroxide is particularly preferred. Instead of the aldehyde a corresponding equivalent, e.g. a hydrate or acetal, may be used, from which the aldehyde is released (beforehand or in situ).

Diagram 3:



b) Aldehyde, Base, THF/Water

The acetals used may be for example compounds of the following general type:



wherein R² to R⁵ in each case represent a straight-chain or branched C₁-C₄-alkyl group, while the groups may be identical or different.

45 Preferably

R³ and R⁴ in each case represent a methyl group and R² and R⁵ in each case represent an ethyl group.

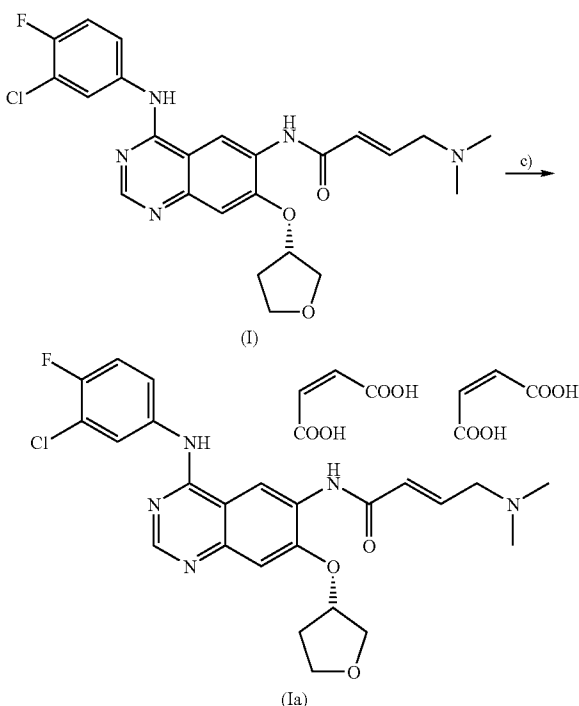
The aminocrotonylarylamide of formula (VII) thus obtained, for example 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline of formula (I), may then be converted into the salts thereof, particularly the physiologically acceptable salts thereof, by methods known per se. Preferably they are converted into fumarates, tartrates or maleates. The dimaleate of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline of structural formula (Ia) and the conversion of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline into its dimaleate as shown in Diagram 4 are particularly preferred. To do this the compound (I) is dissolved in a suitable solvent, such as for example methanol, isopropanol, n-butanol or ethanol, optionally with the addition of water, preferably ethanol, and combined with crystalline maleic acid or a maleic acid solution, with heating. When ethanol is used as solvent the work is preferably done at a

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temperature of between 60 and 75° C. using an ethanolic maleic acid solution. The reaction conditions are preferably selected so that the desired salt crystallises out as quickly as possible. Preferably approx. 2 equivalents of maleic acid are used. After crystallisation has set in the mixture is cooled to ambient temperature, stirred and the crystals consisting of compound (Ia) are separated off.

Diagram 4:



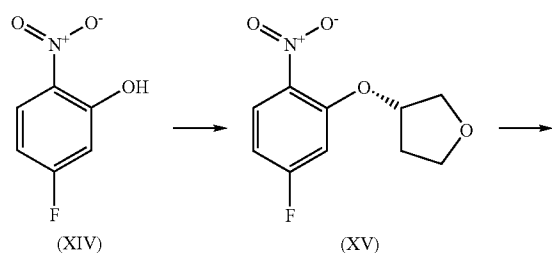
c) Maleic Acid, Ethanol

The starting compound of formula (V) may for example be prepared as follows in accordance with methods known from the literature.

The quinoline components of formula (V), wherein X=CH, may be obtained starting from commercially obtainable 3-fluoro-6-nitrophenol (XIV) by alkylation, exchanging the fluorine atom for an amino group and reacting with ethoxyacrylic acid esters, ethoxymethylene-cyanoacetic acid esters or ethoxymethylene-malonic acid esters (Diagram 5a).

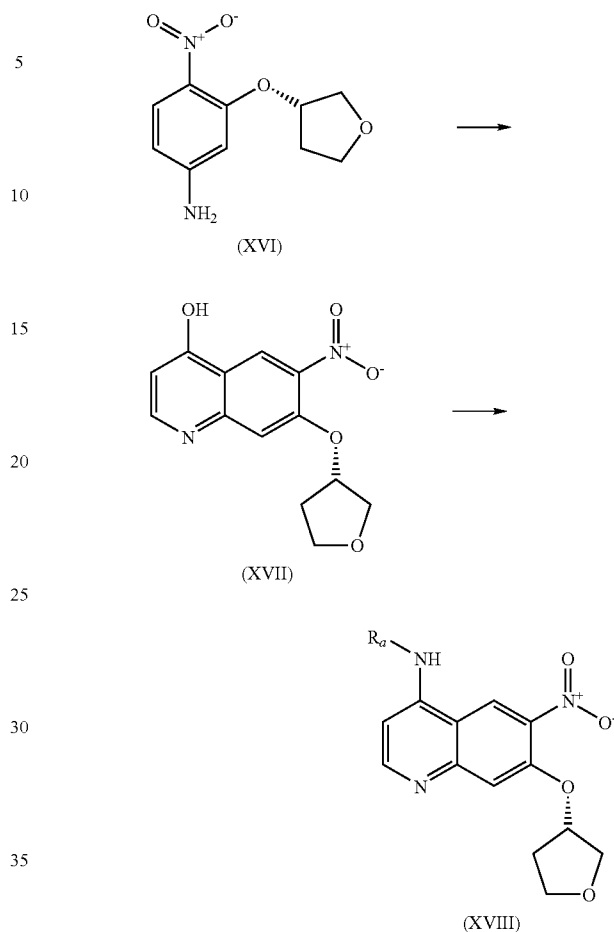
The compound thus obtained (XVII) is then converted into the compound (XVIII) as described in Diagram 6 for the quinazoline analogue

Diagram 5a:



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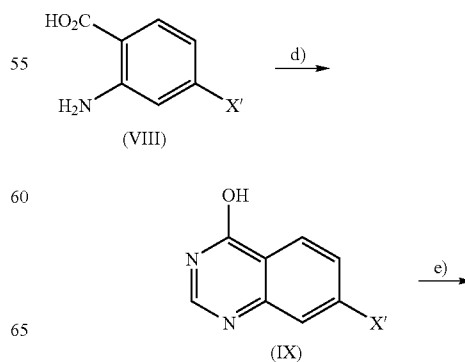
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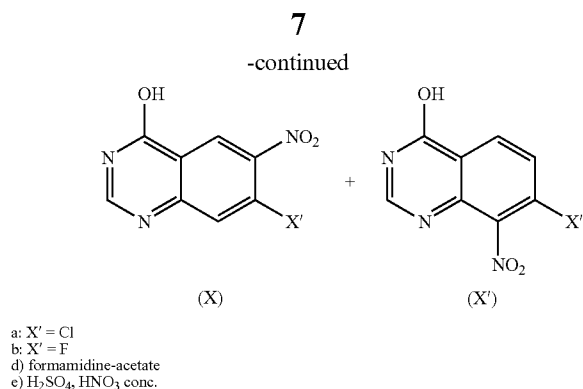
To prepare the compound (V) wherein X=N the following procedure is used:

Starting from commercially obtainable 4-chloro-anthranilic acid (VIII; X'=Cl) the quinazolinone (IX) is obtained by reaction with formamidine-acetate, and is then nitrogenated using sulphuric acid and concentrated nitric acid (Diagram 5b). Alternatively, 4-fluoro-anthranilic acid may also be used as the starting material.

Diagram 5b:

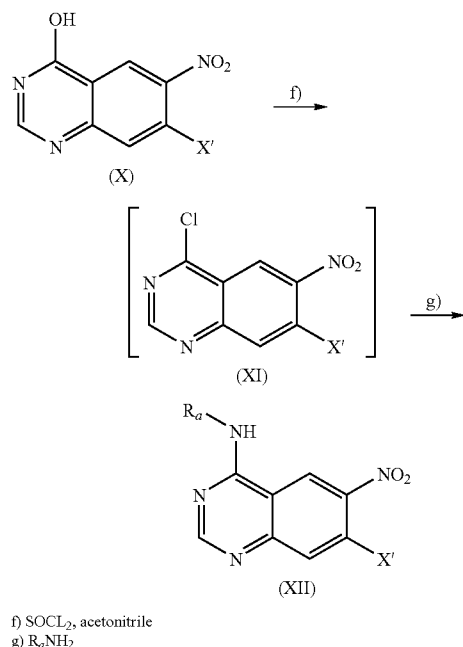


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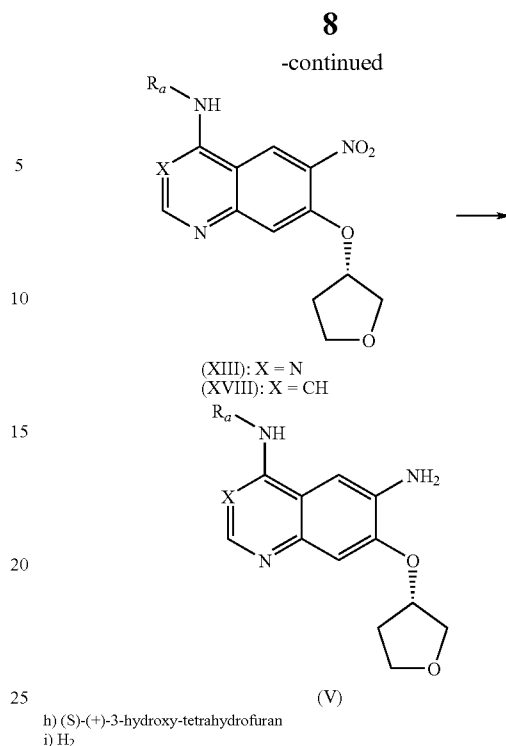
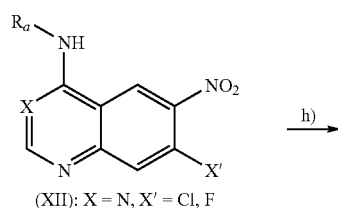
The desired regioisomer (X) of the nitrogenation products thus obtained is then chlorinated, and the chlorination product (XI) is reacted in situ with the corresponding amine (Diagram 6).

Diagram 6:



The compound of formula (XII) thus obtained is reacted with (S)-(+)-3-hydroxytetrahydrofuran to form compound (XIII). Hydrogenation of compound (XIII) or compound (XVIII) from Diagram 5a then yields the starting compound (V) (diagram 7).

Diagram 7:



The invention also relates to 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate. This salt is particularly suitable for pharmaceutical use as it exists in only one crystalline modification, which is moreover anhydrous and very stable.

For pharmaceutical use an active substance not only has to exhibit the desired activity, but must also conform to additional requirements in order to be allowed to be used as a pharmaceutical composition. These parameters are to a large extent connected with the physicochemical nature of the active substance.

Without being restrictive, examples of these parameters are the stability of effect of the starting material under various environmental conditions, stability during production of the pharmaceutical formulation and stability in the final medicament compositions. The pharmaceutically active substance used for preparing the pharmaceutical compositions should therefore have a high stability which must be guaranteed even under various environmental conditions. This is absolutely essential to prevent the use of pharmaceutical compositions which contain, in addition to the actual active substance, breakdown products thereof, for example. In such cases the content of active substance in pharmaceutical formulations might be less than that specified.

The absorption of moisture reduces the content of pharmaceutically active substance on account of the weight gain caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from damp during storage, e.g. by the addition of suitable drying agents or by storing the medicament in a damp-proof environment. In addition, the uptake of moisture can reduce the content of pharmaceutically active substance during manufacture if the medicament is exposed to the environment without being protected from damp in any way. Preferably a pharmaceutically active substance should therefore have only limited hygroscopicity.

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As the crystal modification of an active substance is important to the reproducible active substance content of a preparation, there is a need to clarify as far as possible any existing polymorphism of an active substance present in crystalline form. If there are different polymorphic modifications of an active substance care must be taken to ensure that the crystalline modification of the substance does not change in the pharmaceutical preparation later produced from it. Otherwise, this could have a harmful effect on the reproducible potency of the drug. Against this background, active substances characterised by only slight polymorphism are preferred.

Another criterion which may be of exceptional importance under certain circumstances depending on the choice of formulation or the choice of manufacturing process is the solubility of the active substance. If for example pharmaceutical solutions are prepared (e.g. for infusions) it is essential that the active substance should be sufficiently soluble in physiologically acceptable solvents. It is also very important for drugs which are to be taken orally that the active substance should be sufficiently soluble.

The problem of the present invention is to provide a pharmaceutically active substance which not only is characterised by high pharmacological potency but also satisfies the above-mentioned physicochemical requirements as far as possible. This problem is solved by 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethyl-amino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate.

4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethyl-amino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate has a melting point of 178° C. (cf. the thermoanalysis shown in FIG. 2). The crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate was investigated further by X-ray powder diffraction. The diagram obtained is shown in FIG. 1.

The following Table lists the data obtained in this analysis:

TABLE

X-ray powder reflections and intensities (standardised) of the 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate		
2- Θ [°]	d-value [Å]	intensity I/I _o [%]
4.91	18.0	47
6.42	13.8	33
7.47	11.8	27
8.13	10.9	30
10.37	8.53	30
11.69	7.56	2
12.91	6.85	20
13.46	6.58	3
13.66	6.48	2
14.94	5.93	11
16.58	5.34	12
17.19	5.15	36
17.87	4.96	5
19.43	4.57	38
19.91	4.46	100
20.84	4.26	13
21.33	4.16	21
21.58	4.12	12
22.25	3.992	15
22.94	3.873	32
23.67	3.756	9
24.82	3.584	7

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TABLE-continued

X-ray powder reflections and intensities (standardised) of the 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate		
2- Θ [°]	d-value [Å]	intensity I/I _o [%]
25.56	3.482	37
26.71	3.335	9
27.46	3.245	4
28.37	3.143	8
30.71	2.909	3
29.31	3.045	4
29.57	3.019	4
31.32	2.854	10
32.31	2.769	4
33.10	2.705	5
33.90	2.643	1
34.84	2.573	2
35.71	2.512	1
36.38	2.467	1
36.96	2.430	1
37.99	2.367	2
39.94	2.255	5

In the preceding Table the value “2 Θ [°]” denotes the angle of diffraction in degrees and the value “d_{hkl} [Å]” denotes the specified distances in Å between the lattice planes.

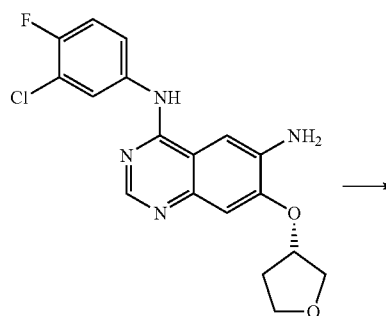
The x-ray powder diagrams were recorded, within the scope of the present invention, using a Bruker D8 Advanced diffractometer fitted with a PSD detector and a Cu anode as the x-ray source (CuK_{α1} radiation, λ=1.5418 Å, 40 kV, 40 mA).

The following Examples are intended to illustrate the invention:

EXAMPLES

Example 1

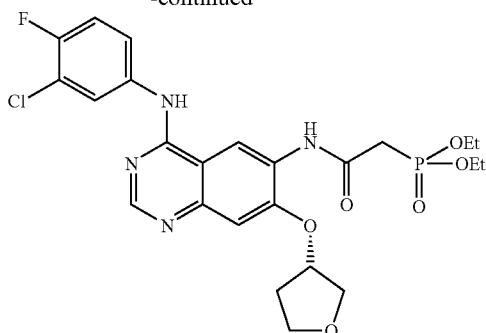
Diethyl {[4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6-ylcarbamoyl]-methyl}-phosphonate



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-continued



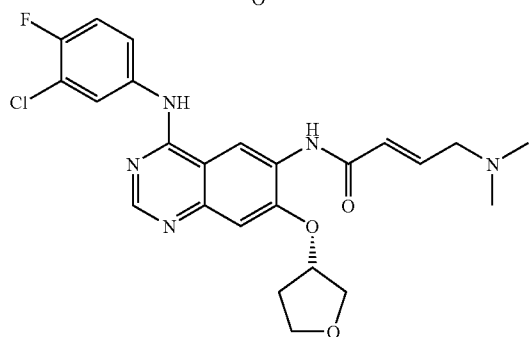
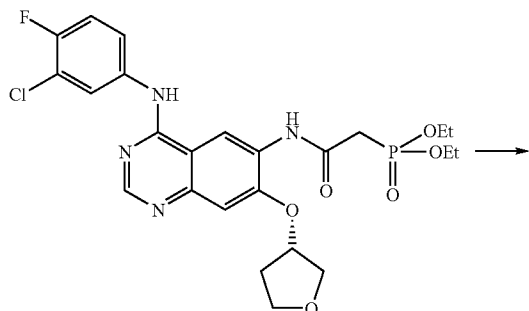
3.58 kg of 1,1-carbonyldiimidazole (22.16 mol) are placed in 12.8 liters of tetrahydrofuran and at 40° C. combined with 4.52 kg (22.16 mol) of diethylphosphonoacetic acid dissolved in 6.5 liters of tetrahydrofuran. The mixture is stirred for 30 minutes at 40° C. The resulting solution is referred to as solution A.

6.39 kg (17.05 mol) of N⁴-(3-chloro-4-fluoro-phenyl)-7-(tetrahydrofuran-3-yloxy)quinazoline-4,6-diamine are placed in 26.5 liters of tetrahydrofuran and at 40° C. combined with solution A and stirred for 2 hours at 30° C. 64 liters of tert.-butylmethylether are added to the suspension and after cooling to 20° C. the precipitate is removed by centrifuging. It is washed with a mixture of 16 liters of tetrahydrofuran and 16 liters of tert.-butylmethylether and then with 32 liters of water and dried at 50° C.

Yield: 6.58 kg (69.8%) of white crystals, content: HPLC 99.1 Fl %

Example 2

(E)-4-dimethylamino-but-2-enoic acid-[4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6yl]-amide



5.6 liters of 30% hydrochloric acid (53.17 mol) are added to 4.4 liters of water. Then 4.28 kg of 95% (dimethylamino)-acetaldehyde-diethylacetal (26.59 mol) are added dropwise

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within 20 minutes at 30° C. The reaction solution is stirred for 8 hours at 35° C. stirred, cooled to 5° C. and stored under argon. This solution is referred to as solution B.

4.55 kg (68.06 mol) of potassium hydroxide are dissolved in 23.5 liters of water and cooled to -5° C. This solution is referred to as solution C.

5.88 kg (10.63 mol) of diethyl ((4-(3-chloro-4-fluoro-phenylamino)-7-(tetrahydrofuran-3-yloxy)-quinazolin-6-yl-carbamoyl)-methyl)-phosphonate and 0.45 kg of lithium chloride (10.63 mol) are placed in 23.5 liters of tetrahydrofuran and cooled to -7° C. The cold solution C is added within 10 minutes. Then solution B is added at -7° C. within 1 hour. After stirring for a further hour at -5° C. the reaction mixture is heated to 20° C. and combined with 15 liters of water. After cooling to 3° C. the suspension is suction filtered, the precipitate is washed with water and dried. Yield: 5.21 kg of crude product, 100%, water content: 6.7%

The crystallisation of the crude product is carried out with butyl acetate/methylcyclohexane

Yield: 78% purity HPLC 99.4 Fl %, water content 5.4%

Example 3

(E)-4-dimethylamino-but-2-enoic acid-(4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6yl)-amide dimaleate

6.0 kg (12.35 mol) of (E)-4-dimethylamino-but-2-enoic acid-(4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6-yl)-amide are placed in 84 litres of ethanol and heated to 70° C. and combined with a solution of 2.94 kg (25.31 mol) of maleic acid in 36 liters of ethanol. After crystallisation has set in, first the mixture is cooled to 20° C. and stirred for 2 hours, then for 3 hours at 0° C. The precipitate is suction filtered, washed with 19 liters of ethanol and dried in vacuo at 40° C.

Yield: 8.11 kg (91.5%)

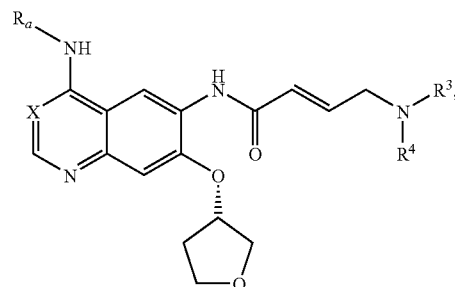
Melting point: 178° C.

¹H-NMR (CD₃OD): δ=2.47+2.27 (m+m, 2H), 2.96 (s, 6H), 4.03 (m, 2H), 4.07+3.92 (m+m, 2H), 4.18+4.03 (m+m, 2H), 5.32 (m, 1H), 6.26 (s, 4H), 6.80 (m, 1H), 6.99 (m, 1H), 7.27(s, 1H), 7.30 (t, 1H), 7.66 (m, 1H), 7.96 (dd, 1H), 8.62 (s, 1H), 9.07 (s, 1H) ppm

What is claimed is:

1. A process for preparing a compound of the formula (VII)

(VII)

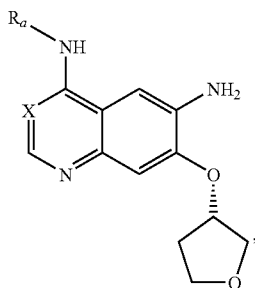


wherein X denotes a methyne group or a nitrogen atom, R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and R³ and R⁴ denote a straight-chain or branched C₁₋₄-alkyl group,

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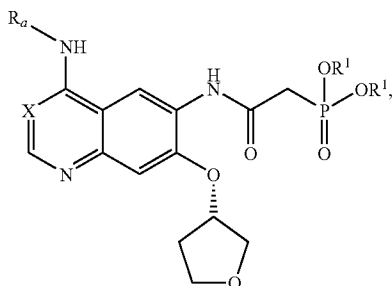
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comprising the following synthesis steps:
a) reacting a compound of the formula (V)

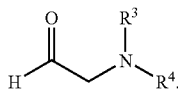


wherein X denotes a methylene group or a nitrogen atom and Ra denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group, in suitable solvents after corresponding activation with di-(C₁₋₄-alkyl)-phosphonoacetic acid and

b) reacting the resulting compound of the formula (VI)



wherein X denotes a methylene group or a nitrogen atom, Ra denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and R¹ denotes a straight-chain or branched C₁₋₄-alkyl group, with the aldehyde of formula



wherein R³ and R⁴ in each case represent a straight-chain or branched C₁-C₄-alkyl group, while the groups may be identical or different, or a corresponding aldehyde equivalent, using suitable organic or inorganic bases.

2. A process for preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, comprising the following synthesis steps:

- a) reacting N⁴-(3-chloro-4-fluoro-phenyl)-7-(tetrahydrofuran-3-yloxy)quinazoline-4,6-diamine in suitable solvents after corresponding activation with di-(C₁₋₄-alkyl)-phos-phonoacetic acid and
- b) reacting the resulting dialkylester {[4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6-ylcarbamoyl]-methyl}-phosphonate with the aldehyde prepared in situ from the corresponding

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(dimethylamino)-acetaldehyde-dialkylacetal using suitable organic or inorganic bases.

3. The process according to claim 2, wherein in step a) diethylphosphonoacetic acid is used as reagent.
4. The process according to claim 1, wherein in step b) DBU (1,5-diaza-bicyclo[4.3.0]non-5-ene), sodium hydroxide or potassium hydroxide is used as base.
5. The process according to claim 4, wherein in step b) potassium hydroxide is used as base.
6. A process for preparing the dimaleates of 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, comprising steps a and b according to claim 1 as well as the following step c):
- c) converting the resulting 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline into the dimaleate by reacting with maleic acid in a suitable solvent, with heating.
7. The process according to claim 6, wherein ethanol or isopropanol is used as solvent, optionally with the addition of water.
8. The process according to claim 6, wherein at least 2 equivalents of maleic acid are used.
9. Crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate, characterized by 2 Θ [°] values obtained by X-ray powder diffraction using CuK _{α 1} radiation, $\lambda=1.5418\text{\AA}$ in the following table:

	2- Θ [°]	intensity I/I ₀ [%]
35	4.91	47
	6.42	33
	7.47	27
	8.13	30
	10.37	30
	17.19	36
	19.43	38
	19.91	100
	21.33	21
	22.94	32
	25.56	37.

10. Crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate, characterized by 2 Θ [°] values obtained by X-ray powder diffraction using CuK _{α 1} radiation, $\lambda=1.5418\text{\AA}$ in the following table:

	2- Θ [°]	intensity I/I ₀ [%]
55	4.91	47
	6.42	33
	7.47	27
	8.13	30
	10.37	30
	12.91	20
	14.94	11
	16.58	12
	17.19	36
	19.43	38
	19.91	100
	20.84	13
	21.33	21

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-continued

2- Θ [°]	intensity I/I _o [%]
21.58	12
22.25	15
22.94	32
25.56	37.

11. Crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-
 {[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-
 ((S))-tetrahydrofuran-3-yloxy)-quinazoline dimaleate, char-
 acterized by 2 Θ [°] values obtained by X-ray powder diffrac-
 tion using CuK $_{\alpha 1}$ radiation, $\lambda=1.5418 \text{ \AA}$ in the following
 table:

2- Θ [°]	d-value [\AA]	intensity I/I _o [%]
4.91	18.0	47
6.42	13.8	33
7.47	11.8	27
8.13	10.9	30
10.37	8.53	30
11.69	7.56	2
12.91	6.85	20
13.46	6.58	3
13.66	6.48	2
14.94	5.93	11
16.58	5.34	12

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-continued

2- Θ [°]	d-value [\AA]	intensity I/I _o [%]
17.19	5.15	36
17.87	4.96	5
19.43	4.57	38
19.91	4.46	100
20.84	4.26	13
21.33	4.16	21
21.58	4.12	12
22.25	3.992	15
22.94	3.873	32
23.67	3.756	9
24.82	3.584	7
25.56	3.482	37
26.71	3.335	9
27.46	3.245	4
28.37	3.143	8
30.71	2.909	3
29.31	3.045	4
29.57	3.019	4
31.32	2.854	10
32.31	2.769	4
33.10	2.705	5
33.90	2.643	1
34.84	2.573	2
35.71	2.512	1
36.38	2.46	71
36.96	2.430	1
37.99	2.367	2
39.94	2.255	5.

* * * * *