

Charles M. Lizza
William C. Baton
Sarah A. Sullivan
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza
1037 Raymond Blvd., Suite 1520
Newark, NJ 07102-5426
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiffs
Boehringer Ingelheim Pharmaceuticals, Inc.,
Boehringer Ingelheim International GmbH,
and Boehringer Ingelheim Pharma GmbH &
Co. KG

OF COUNSEL:
Christopher N. Sipes
Jeffrey Lerner
Alexander Trzeciak
Daniel W. Cho
Tarek Austin
Daniel Lee
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
(202) 662-6000

Alexa Hansen
COVINGTON & BURLING LLP
Salesforce Tower
415 Mission Street
San Francisco, CA 94105
(415) 591-6000

**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.

**QILU PHARMACEUTICAL CO., LTD.
and QILU PHARMA INC.,**

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 Qilu Pharmaceutical Co., Ltd. and Qilu Pharma Inc. (collectively, “Defendants” or “Qilu”), 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 Qilu’s submission of Abbreviated New Drug Application (“ANDA”) No. 213499 to the United States Food and Drug Administration (“FDA”). Through this ANDA, Qilu seeks approval to market a generic version of the pharmaceutical product GILOTRIF® (afatinib) tablets prior to the expiration of United States Patent No. RE43,431, United States Patent No. 8,426,586, and United States Patent No. 10,004,743 (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 principle place of business at Binger Strasse 173, 55216 Ingelheim, Germany.

6. On information and belief, defendant Qilu Pharmaceutical Co., Ltd. is a corporation organized and existing under the laws of China, having its principal place of business at No. 317, Xinluo Street, Jinan, 250101, China.

7. On information and belief, defendant Qilu Pharma Inc. is a corporation organized and existing under the laws of Pennsylvania, having its principal place of business at 101 Lindenwood Drive, Suite 225, Malvern, PA 19355.

8. On information and belief, Qilu Pharma Inc. is a wholly-owned subsidiary of Qilu Pharmaceutical Co., Ltd.

9. On information and belief, Qilu Pharmaceutical Co., Ltd., in collaboration with Qilu Pharma Inc., prepared and submitted ANDA No. 213499 (the “Qilu ANDA”) and continue to collaborate in seeking FDA approval of that application.

10. On information and belief, Qilu intends to commercially manufacture, market, offer for sale, and sell the product described in the Qilu ANDA (the “ANDA Product”) throughout the United States, including in the State of New Jersey, in the event the FDA approves the Qilu 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 No. RE43,431 (“the ’431 Patent”), United States Patent No. 8,426,586 (“the ’586 Patent”), and United States Patent No. 10,004,743 (“the ’743 Patent”). This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338, and 2201–02.

12. This Court has jurisdiction over Qilu Pharmaceutical Co., Ltd. because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Plaintiffs' claims arise under federal law; (b) Qilu Pharmaceutical Co., Ltd. is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Qilu Pharmaceutical Co., Ltd. has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Qilu Pharmaceutical Co., Ltd. satisfies due process.

13. On information and belief, this Court also has jurisdiction over Qilu Pharmaceutical Co., Ltd. because, *inter alia*, this action arises from actions of Qilu directed toward New Jersey, and because Qilu has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with New Jersey.

14. On information and belief, this Court also has jurisdiction over Qilu Pharma Inc. Qilu Pharma Inc. has an active business entity status registered with the New Jersey Department of Treasury under the business entity identification number 0400704255, and maintains a business address at 104 Carnegie Center, Suite 212, Princeton, NJ 08540 and a corporate agent for service of process at 820 Bear Tavern Road, West Trenton, NJ, 08626.

15. On information and belief, Qilu Pharma Inc. regularly and continuously transacts business within the State of New Jersey, including by selling pharmaceutical products in New Jersey, either on its own or through an affiliate. Upon information and belief, Qilu derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within the State of New Jersey. Further, Qilu 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 manufacture GILOTRIF® for sale and use throughout the United States, including in this Judicial District.

16. On information and belief, Qilu Pharma Inc. has participated or aided and abetted in the preparation or submission of the Qilu ANDA. On information and belief, in the event that the FDA approves the Qilu ANDA, Qilu Pharmaceutical Co., Ltd., with the participation of Qilu Pharma Inc., intends to commercially manufacture, import, market, offer for sell, and sell the ANDA Product throughout the United States and in this Judicial District.

17. Venue is proper in this Judicial District for Qilu Pharmaceutical Co., Ltd. pursuant to 28 U.S.C. § 1391(c)(3).

18. Venue is proper in this Judicial District for Qilu Pharma Inc. On information and belief, Qilu Pharma Inc. maintains a regular and established place of business at 104 Carnegie Center, Suite 212, Princeton, NJ 08540, and on information and belief, based on Qilu Pharma Inc.'s presence in and connections to New Jersey, discoverable information in Qilu Pharma Inc.'s possession, custody, or control regarding the Qilu ANDA will likely show that Qilu Pharma Inc. engaged in activities in New Jersey relevant to the preparation or submission of the Qilu ANDA. In addition, on information and belief, Qilu Pharma Inc. 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 manufacture GILOTRIF® for sale and use throughout the United States. Despite Boehringer Ingelheim's good faith efforts, it was unable to reach an agreement with Qilu under which Boehringer Ingelheim could confidentially access the Qilu ANDA before submitting this complaint.

19. Qilu Pharmaceutical Co., Ltd. and Qilu Pharma Inc. have availed themselves of the rights, benefits, and privileges of New Jersey by asserting claims or counterclaims involving

pharmaceutical drug patent disputes in this Judicial District, including in the following case: *Helsinn Healthcare S.A. v. Qilu Pharmaceutical Co., Ltd.*, No. 2:15-cv-08132 (D.N.J. filed Feb. 16, 2016).

BOEHRINGER INGELHEIM'S APPROVED GILOTRIF® DRUG PRODUCT AND PATENTS

20. 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 non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test. GILOTRIF® is also used to treat metastatic, squamous NSCLC that progresses after platinum-based chemotherapy. A true and correct copy of the prescribing label for GILOTRIF® is attached as Exhibit 1.

21. The active ingredient in GILOTRIF® is afatinib.

22. Boehringer Ingelheim Pharmaceuticals, Inc. is the holder of New Drug Application (“NDA”) No. 201292 for GILOTRIF® and the licensee of the patents-in-suit.

23. 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. The FDA also granted GILOTRIF® orphan drug exclusivity pursuant to 21 C.F.R. § 316.31.

24. Boehringer Ingelheim Pharma GmbH & Co. KG owns the ’431 Patent. Boehringer Ingelheim International GmbH owns the ’586 and ’743 Patents. The ’431, ’586, and ’743 Patents are listed in the Approved Drug Products With Therapeutic Equivalence Evaluations (an FDA publication commonly known as the “Orange Book”) for GILOTRIF®.

25. The '431 Patent is entitled "Quinazoline Derivatives and Pharmaceutical Compositions Containing Them" and was duly and lawfully issued by the USPTO on May 29, 2012. A true and correct copy of the '431 Patent is attached as Exhibit 2.

26. The '586 Patent is entitled "Process for Preparing Amino Crotonyl Compounds" and 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 3.

27. The '743 Patent is entitled "Process for Drying of BIBW2992, of its Salts and of Solid Pharmaceutical Formulations Comprising this Active Ingredient" and was duly and lawfully issued by the USPTO on June 26, 2018. A true and correct copy of the '743 Patent is attached as Exhibit 4.

QILU'S ANDA AND NOTICE OF PARAGRAPH IV CERTIFICATION

28. On information and belief, Qilu has submitted or caused to be submitted ANDA No. 213499 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 Tablets, as a purported generic version of GILOTRIF®, prior to the expiration of the patents-in-suit.

29. On information and belief, on or about December 22, 2020, Qilu mailed Plaintiffs a letter regarding "Notice of Certification Under 21 U.S.C. § 355(j)(2)(B)(ii) (§ 505(j)(2)(B)(i)(ii) of the Federal Food, Drug and Cosmetic Act) and 21 C.F.R. § 314.95" (the "Notice Letter"). The Notice Letter represented that Qilu had submitted to the FDA the Qilu ANDA and a purported Paragraph IV certification to obtain approval to engage in the commercial manufacture, use, or sale of the product described in the Qilu ANDA before the expiration of patents listed in the Orange Book for GILOTRIF®. Hence, Qilu seeks through the Qilu ANDA to manufacture and market the ANDA Product before the expiration of the patents-in-suit.

30. Qilu's Notice Letter stated that the Paragraph IV certification in the Qilu ANDA alleges that the '431, '586, and '743 Patents are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the ANDA Product.

31. Qilu's Notice Letter contained a purported detailed statement of the factual and legal basis for its Paragraph IV certification ("Detailed Statement for ANDA 213499").

32. Qilu's Notice Letter included an Offer of Confidential Access to the Qilu ANDA, subject to stated terms and restrictions. In response to the Letter, which imposed unreasonable restrictions on Boehringer Ingelheim's ability to access the Qilu ANDA, Boehringer Ingelheim sought to negotiate reasonable "restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information." 21 U.S.C. § 355(j)(5)(C)(i)(III). Despite Boehringer Ingelheim's good faith efforts to negotiate reasonable restrictions, it was unable to reach an agreement with Qilu under which Boehringer Ingelheim could confidentially access the Qilu ANDA.

33. On information and belief, Qilu Pharmaceutical Co., Ltd. and Qilu Pharma Inc. have participated in the preparation and submission of the Qilu ANDA, have provided material support to the preparation and submission of the Qilu ANDA, and intend to support the further prosecution of the Qilu ANDA.

34. On information and belief, if the FDA approves the Qilu ANDA, Qilu 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.

35. On information and belief, if the FDA approves the Qilu ANDA, Qilu will actively induce or contribute to the manufacture, use, offer for sale, or sale of the ANDA Product.

36. This action is pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), and was filed on February 2, 2021, which is within forty-five days of Plaintiffs' receipt of the Notice Letter.

COUNT 1
INFRINGEMENT OF THE '431 PATENT

37. Plaintiffs incorporate by reference paragraphs 1–36 as if fully set forth herein.

38. On information and belief, Qilu has submitted or caused the submission of the Qilu ANDA to the FDA and continues to seek FDA approval of the Qilu ANDA.

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

40. On information and belief, if the Qilu ANDA is approved, Qilu 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.

41. Qilu's commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would directly infringe, actively induce infringement, and/or contribute to infringement of the '431 Patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 213499, Qilu 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 directly infringe, induce the infringement of, and/or contribute to the infringement of one or more claims of the '431 Patent.

42. Qilu had actual and constructive notice of the '431 Patent prior to filing the Qilu ANDA and was aware that the request for FDA approval of the Qilu ANDA prior to the expiration of the '431 Patent would constitute an act of infringement of the '431 Patent. Qilu had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the

ANDA Product will not directly infringe, induce the infringement of, and/or contribute to the infringement of the '431 Patent.

43. Qilu's Detailed Statement in the Notice Letter lacks any contention that the ANDA Product will not infringe, contribute to the infringement of, or induce the infringement of any claim of the '431 Patent.

44. In addition, Qilu filed the Qilu 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. Qilu'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.

45. Plaintiffs will be irreparably harmed if Qilu 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 Qilu, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT 2
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '431 PATENT

46. Plaintiffs incorporate by reference paragraphs 1–45 as if fully set forth herein.

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

48. On information and belief, if the Qilu 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 Qilu and its affiliates, which will directly infringe the '431 Patent.

49. On information and belief, Qilu knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Qilu ANDA, and Qilu will therefore induce the infringement and/or contribute to 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).

50. On information and belief, Qilu'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 Qilu 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).

51. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Qilu 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.

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

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

COUNT 3
INFRINGEMENT OF THE '586 PATENT

54. Plaintiffs incorporate by reference paragraphs 1–53 as if fully set forth herein.

55. On information and belief, Qilu has submitted or caused the submission of the Qilu ANDA to the FDA and continues to seek FDA approval of the Qilu ANDA.

56. On information and belief, Qilu has infringed the '586 Patent under 35 U.S.C. § 271(e)(2)(A) by submitting the Qilu ANDA with a Paragraph IV certification and seeking FDA approval of the Qilu ANDA prior to the expiration of the '586 Patent.

57. On information and belief, if the Qilu ANDA is approved, Qilu 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.

58. On information and belief, Qilu's commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would directly infringe, actively induce infringement, and/or contribute to infringement of the '586 Patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 213499, Qilu 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.

59. Qilu had actual and constructive notice of the '586 Patent prior to filing the Qilu ANDA, and was aware that the filing of the Qilu 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. On information and belief, Qilu 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.

60. In addition, on information and belief, Qilu filed the Qilu 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. Qilu'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.

61. Plaintiffs will be irreparably harmed if Qilu 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 Qilu, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT 4
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '586 PATENT

62. Plaintiffs incorporate by reference paragraphs 1–61 as if fully set forth herein.

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

64. On information and belief, if the Qilu 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 Qilu and its affiliates.

65. On information and belief, Qilu knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Qilu ANDA and Qilu 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).

66. On information and belief, Qilu'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 Qilu 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).

67. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Qilu 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.

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

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

COUNT 5
INFRINGEMENT OF THE '743 PATENT

70. Plaintiffs incorporate by reference paragraphs 1–69 as if fully set forth herein.

71. On information and belief, Qilu has submitted or caused the submission of the Qilu ANDA to the FDA and continues to seek FDA approval of the Qilu ANDA.

72. On information and belief, Qilu has infringed the '743 Patent under 35 U.S.C. § 271(e)(2)(A) by submitting the Qilu ANDA with a Paragraph IV certification and seeking FDA approval of the Qilu ANDA prior to the expiration of the '743 Patent.

73. On information and belief, if the Qilu ANDA is approved, Qilu 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 '743 Patent.

74. On information and belief, Qilu's commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would directly infringe, actively induce infringement, and/or contribute to infringement of the '743 Patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 213499, Qilu 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 '743 Patent.

75. Qilu had actual and constructive notice of the '743 Patent prior to filing the Qilu ANDA, and was aware that the filing of the Qilu ANDA with the request for FDA approval prior to the expiration of the '743 Patent would constitute an act of infringement of the '743 Patent. On information and belief, Qilu 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 '743 Patent.

76. Qilu'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 '743 Patent.

77. In addition, on information and belief, Qilu filed the Qilu ANDA without adequate justification for asserting the '743 Patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Qilu's conduct in certifying invalidity, unenforceability, and/or non-infringement with respect to the '743 Patent renders this case "exceptional" under 35 U.S.C. § 285.

78. Plaintiffs will be irreparably harmed if Qilu is not enjoined from infringing and from actively inducing or contributing to the infringement of the '743 Patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Qilu, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT 6

DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '743 PATENT

79. Plaintiffs incorporate by reference paragraphs 1–78 as if fully set forth herein.

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

81. On information and belief, if the Qilu 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 Qilu and its affiliates.

82. On information and belief, Qilu knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Qilu ANDA and Qilu will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the '743 Patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

83. On information and belief, Qilu'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 Qilu ANDA. Any such conduct before the '743 Patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '743 Patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

84. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Qilu concerning liability for the infringement of the '743 Patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

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

86. 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 Qilu infringes the '431, '586, and '743 Patents under 35 U.S.C. § 271(e)(2)(A);

(b) 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. 213499 shall be no earlier than the expiration date of the '431, '586, and '743 Patents, or any later expiration of exclusivity for the '431, '586, and '743 Patents, including any extensions or regulatory exclusivities;

(c) A Declaratory Judgment that under one or more of 35 U.S.C. § 271(a), (b), (c), (f) and (g), Qilu'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, '586, and '743 Patents;

(d) A Permanent Injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Qilu, its affiliates and subsidiaries, and all persons and entities acting in concert with Qilu from commercially manufacturing, using, offering for sale, or selling or importing any product that infringes '431, '586, and '743 Patents, including the ANDA Product described in ANDA No. 213499;

(e) A Declaration under 28 U.S.C. § 2201 that if Qilu, 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 their behalf, engages in the commercial manufacture, use, offer for sale, sale and/or importation of the product described in ANDA No.

213499, it will constitute an act of direct and/or indirect infringement of the '431, '586, and '743 Patents;

(f) An award of damages or other relief, pursuant to 35 U.S.C. § 271(e)(4)(C), if Qilu engages in the commercial manufacture, use, offer for sale, sale, and/or importation of the ANDA Product, or any product that infringes the '431, '586, or '743 Patents, or induces or contributes to such conduct, prior to the expiration of the '431, '586, or '743 Patents, or any later expiration of exclusivity for the '431, '586, and '743 Patents, including any extensions or regulatory exclusivities;

(g) The entry of Judgment declaring that Qilu'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 this Court deems just and proper.

Dated: February 2, 2021

OF COUNSEL:

Christopher N. Sipes
Jeffrey Lerner
Alexander Trzeciak
Daniel W. Cho
Tarek Austin
Daniel Lee
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
(202) 662-6000

Alexa Hansen
COVINGTON & BURLING LLP
Salesforce Tower
415 Mission Street
San Francisco, CA 94105
(415) 591-6000

By: s/ Charles M. Lizza _____

Charles M. Lizza
William C. Baton
Sarah A. Sullivan
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza
1037 Raymond Blvd., Suite 1520
Newark, NJ 07102-5426
(973) 286-6700
clizza@saul.com

*Attorneys for Plaintiffs
Boehringer Ingelheim Pharmaceuticals,
Inc., Boehringer Ingelheim International
GmbH, and Boehringer Ingelheim
Pharma GmbH & Co. KG*

CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matter captioned *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Aurobindo Pharma USA Inc., et al.*, Civil Action No. 17-7887 (MAS)(LHG) (consolidated) is related to the matter in controversy because the matter in controversy involves the same Plaintiffs, some of the same patents-in-suit, and the same drug product.

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: February 2, 2021

OF COUNSEL:

Christopher N. Sipes
Jeffrey Lerner
Alexander Trzeciak
Daniel W. Cho
Tarek Austin
Daniel Lee
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
(202) 662-6000

Alexa Hansen
COVINGTON & BURLING LLP
Salesforce Tower
415 Mission Street
San Francisco, CA 94105
(415) 591-6000

*Attorneys for Plaintiffs
Boehringer Ingelheim Pharmaceuticals, Inc.,
Boehringer Ingelheim International GmbH,
and Boehringer Ingelheim Pharma GmbH &
Co. KG*

By: s/ Charles M. Lizza
Charles M. Lizza
William C. Baton
Sarah A. Sullivan
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5246
(973) 286-6700
clizza@saul.com

*Attorneys for Plaintiffs
Boehringer Ingelheim Pharmaceuticals,
Inc., Boehringer Ingelheim International
GmbH, and Boehringer Ingelheim
Pharma GmbH & Co. KG*

EXHIBIT 1

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**-----

Warnings and Precautions, Gastrointestinal Perforation (5.5) 10/2019

-----**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 non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test (1.1)
Limitations of Use: Safety and efficacy of GILOTRIF were not established in patients whose tumors have resistant EGFR mutations (1.1)
- Treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy (1.2)

-----**DOSAGE AND ADMINISTRATION**-----

- Recommended dosage: 40 mg orally once daily (2.2)
- Renal impairment: 30 mg orally once daily in patients with severe renal impairment (2.4, 8.6, 12.3)
- Instruct patients to take GILOTRIF at least 1 hour before or 2 hours after a meal (2.2)

-----**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)
- Gastrointestinal perforation: Occurs in 0.2% of patients. Permanently discontinue GILOTRIF in patients who develop gastrointestinal perforation. (2.3, 5.5)
- Keratitis: Occurs in 0.7% of patients. Withhold GILOTRIF for keratitis evaluation. Withhold or discontinue GILOTRIF for confirmed ulcerative keratitis. (2.3, 5.6)
- 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. (5.7)

-----**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**-----

- P-glycoprotein (P-gp) Inhibitors: Co-administration of P-gp inhibitors can increase afatinib exposure. Reduce GILOTRIF by 10 mg per day if not tolerated. (2.5, 7)
- P-gp Inducers: Co-administration of chronic P-gp inducers orally can decrease afatinib exposure. Increase GILOTRIF by 10 mg per day as tolerated. (2.5, 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: 10/2019

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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 non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test [see *Dosage and Administration (2.1)*, *Clinical Pharmacology (12.1)*, *Clinical Studies (14.1)*].

Limitations of Use: The safety and efficacy of GILOTRIF have not been established in patients whose tumors have resistant 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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Non-Resistant EGFR Mutation-Positive Metastatic NSCLC

Select patients for first-line treatment of metastatic NSCLC with GILOTRIF based on the presence of non-resistant EGFR mutations in tumor specimens [see *Clinical Pharmacology (12.1)*, *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 Dosage

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

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 Dosage Modifications for Adverse Reactions

Withhold GILOTRIF for:

- Grade* 3 or higher adverse reactions
- Diarrhea of Grade 2 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)*]

*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. Reinststitute 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 exfoliating 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)*]
- Gastrointestinal perforation [see *Warnings and Precautions (5.5)*]
- Persistent ulcerative keratitis [see *Warnings and Precautions (5.6)*]

- 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 Dosage Modification for Pre-Existing Severe Renal Impairment

The recommended dosage of GILOTRIF in patients with pre-existing 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), Clinical Pharmacology (12.3)*].

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

2.5 Dosage Modifications for Drug Interactions

P-glycoprotein 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), Clinical Pharmacology (12.3)*].

P-glycoprotein 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), 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 LUX-Lung 3, 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 LUX-Lung 8, 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 skin lesions, occurred in 0.2% of the 4257 patients who received GILOTRIF across clinical trials. In LUX-Lung 3, 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 LUX-Lung 8, 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 skin lesions. For patients who develop prolonged Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2 cutaneous reactions, 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

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 LUX-Lung 3, the incidence of Grade ≥ 3 ILD was 1.3% and resulted in death in 1% of GILOTRIF-treated patients. In LUX-Lung 8, 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 LUX-Lung 3, 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 LUX-Lung 8, 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, discontinue treatment.

5.5 Gastrointestinal Perforation

Gastrointestinal perforation, including fatal cases, has occurred with GILOTRIF. Gastrointestinal perforation has been reported in 0.2% of patients treated with GILOTRIF among 3213 patients across 17 randomized controlled clinical trials. Patients receiving concomitant corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) or anti-angiogenic agents, or patients with increasing age or who have an underlying history of gastrointestinal ulceration, underlying diverticular disease or bowel metastases may be at increased risk of perforation.

Permanently discontinue GILOTRIF in patients who develop gastrointestinal perforation [*see Dosage and Administration (2.3)*].

5.6 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 LUX-Lung 3, with Grade 3 in 0.4%. In LUX-Lung 8, 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, interrupt or discontinue GILOTRIF [*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.

5.7 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, 8.3)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in 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)*]
- Gastrointestinal Perforation [*see Warnings and Precautions (5.5)*]
- Keratitis [*see Warnings and Precautions (5.6)*]

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 LUX-Lung 3 (n=229) and LUX-Lung 8 (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 LUX-Lung 3, a randomized, active-controlled trial conducted in patients with EGFR mutation-positive, metastatic NSCLC, and in LUX-Lung 8, a randomized, active-controlled trial in patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

EGFR Mutation-Positive Metastatic NSCLC

The safety of GILOTRIF was evaluated in 229 EGFR-tyrosine kinase inhibitor-naïve patients with EGFR mutation-positive, metastatic non-squamous NSCLC enrolled in a randomized (2:1), multicenter, open-label trial (LUX-Lung 3). Patients received either GILOTRIF 40 mg daily until documented disease progression or intolerance to the therapy or 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 LUX-Lung 3 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 LUX-Lung 3, 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 LUX-Lung 3.

Table 1 Adverse Reactions Reported in $\geq 10\%$ of GILOTRIF-Treated Patients in LUX-Lung 3*

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% Grades 1-4, 4% Grade 3), nausea (25% Grades 1-4, 4% Grade 3), and vomiting (23% Grades 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 LUX-Lung 3*

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 (LUX-Lung 8). 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. 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.

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%).

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%).

The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (4.1%) and rash/acne (2.6%).

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%).

Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities in LUX-Lung 8.

Table 3 Adverse Reactions Reported in $\geq 10\%$ of GILOTRIF-Treated Patients in LUX-Lung 8*

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
Metabolism and nutrition disorders				
Decreased appetite	25	3	26	2
Infections				
Paronychia ³	11	1	5	0

*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 LUX-Lung 8*

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).

Less Common Adverse Reactions

Other adverse reactions reported in patients treated with GILOTRIF in LUX-Lung 3 and LUX-Lung 8 include: *Skin and subcutaneous disorders*: nail disorders occurred in 9.2% and 2.8% of patients, respectively.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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 *Clinical Pharmacology (12.3)*]. Reduce GILOTRIF daily dose as recommended [see *Dosage and Administration (2.5)*].

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 *Clinical Pharmacology (12.3)*]. Increase GILOTRIF daily dose as recommended [see *Dosage and Administration (2.5)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action [see *Clinical Pharmacology (12.1)*], 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 breastfed infants from GILOTRIF, advise women 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), 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

LUX-Lung 3 did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In LUX-Lung 8, 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 LUX-Lung 8, the hazard ratio for overall survival (OS) 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 (eGFR 15 to 29 mL/min /1.73 m² as determined by Modification of Diet in Renal Disease formula) [see *Dosage and Administration (2.4), Clinical Pharmacology (12.3)*]. Adjustments to the starting dose of GILOTRIF are not necessary in patients with mild or moderate renal impairment (eGFR 30 to 89 mL/min /1.73 m²). GILOTRIF has not been studied in patients with eGFR <15 mL/min/1.73 m² or on dialysis.

8.7 Hepatic Impairment

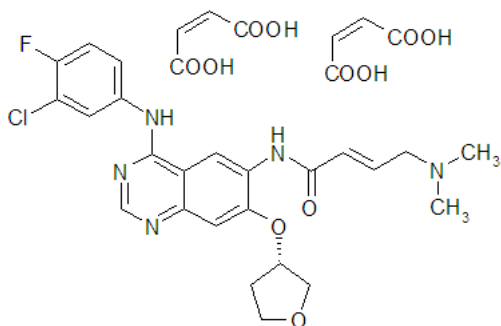
GILOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. Adjustments to the starting dose of GILOTRIF are not necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment [see *Clinical Pharmacology (12.3)*]. Closely monitor patients with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

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 C₃₂H₃₃ClF₂N₅O₁₁, 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. Certain mutations in EGFR, including non-resistant mutations in its kinase domain, can result in increased autophosphorylation of the receptor, leading to receptor activation, sometimes in the absence of ligand binding,

and can support cell proliferation in NSCLC. Non-resistant mutations are defined as those occurring in exons constituting the kinase domain of EGFR that lead to increased receptor activation and where efficacy is predicted by 1) clinically meaningful tumor shrinkage with the recommended dose of afatinib and/or 2) inhibition of cellular proliferation or EGFR tyrosine kinase phosphorylation at concentrations of afatinib sustainable at the recommended dosage according to validated methods. The most commonly found of these mutations are exon 21 L858R substitutions and exon 19 deletions.

Afatinib demonstrated inhibition of autophosphorylation and/or *in vitro* proliferation of cell lines expressing wild-type EGFR and in those expressing selected EGFR exon 19 deletion mutations, exon 21 L858R mutations, or other less common non-resistant mutations, at afatinib concentrations achieved 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

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 ($AUC_{0-∞}$) 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. 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} .

Effect of Food

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

Distribution

In vitro binding of afatinib to human plasma proteins is approximately 95%.

Elimination

The elimination half-life of afatinib is 37 hours after repeat dosing in cancer patients.

Metabolism

Covalent adducts to proteins are the major circulating metabolites of afatinib and enzymatic metabolism of afatinib is minimal. The metabolites formed by CYP450-dependent reactions were approximately 9% of the total metabolic turnover in sandwich-cultured human hepatocytes. Approximately 2% of the afatinib dose was metabolized by FMO3; the CYP3A4-dependent N-demethylation was not detected.

Excretion

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.

Specific Populations

Based on the population pharmacokinetic analysis, weight, gender, age, and race do not have a clinically important effect on exposure of afatinib.

Patients with Renal Impairment

A pharmacokinetic study was conducted in 14 subjects with normal (eGFR ≥ 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 to subjects with normal renal function [see *Dosage and Administration* (2.4), *Use in Specific Populations* (8.6)]. GILOTRIF has not been studied in patients with eGFR <15 mL/min/1.73 m² or on dialysis.

Patients with Hepatic Impairment

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 impairment have not been studied [see *Use in Specific Populations* (8.7)].

Drug Interactions Studies

Clinical Studies

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-INF} 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-INF} 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-INF}) and 22% (C_{max}) [see *Drug Interactions* (7)].

In Vitro Studies

Effect of Afatinib on P-gp: Based on *in vitro* data, afatinib is an inhibitor of P-gp.

Interaction of Afatinib with BCRP: Based on *in vitro* data, afatinib is a substrate and an inhibitor of the transporter BCRP.

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.

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, Metastatic NSCLC

The efficacy of GILOTRIF for the first-line treatment of 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)] NSCLC was established in a randomized, multicenter, open-label trial (LUX-Lung 3 [NCT00949650]). Patients were randomized (2:1) to receive GILOTRIF 40 mg orally once daily (n=230) or intravenous pemetrexed (500 mg/m²) plus cisplatin (75 mg/m²) once every 21 days for up to 6 cycles (n=115). Randomization was stratified according to EGFR mutation category (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 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 (PS) was 0 (39%) or 1 (61%), 26% were White 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.

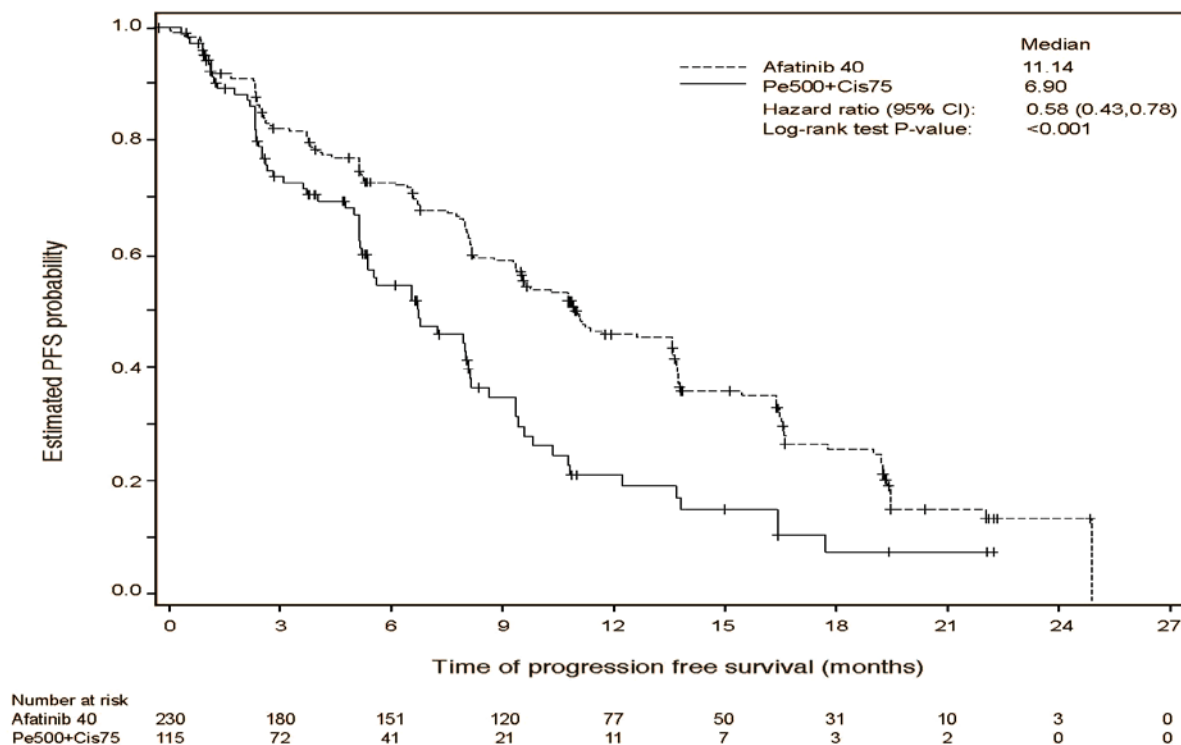
A statistically significant improvement in PFS as determined by the IRC was demonstrated for patients randomized to GILOTRIF compared with those randomized to chemotherapy. See Table 5 and Figure 1. There was no statistically significant difference for OS between the treatment arms at the final pre-planned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

Table 5 Efficacy Results in LUX-Lung 3

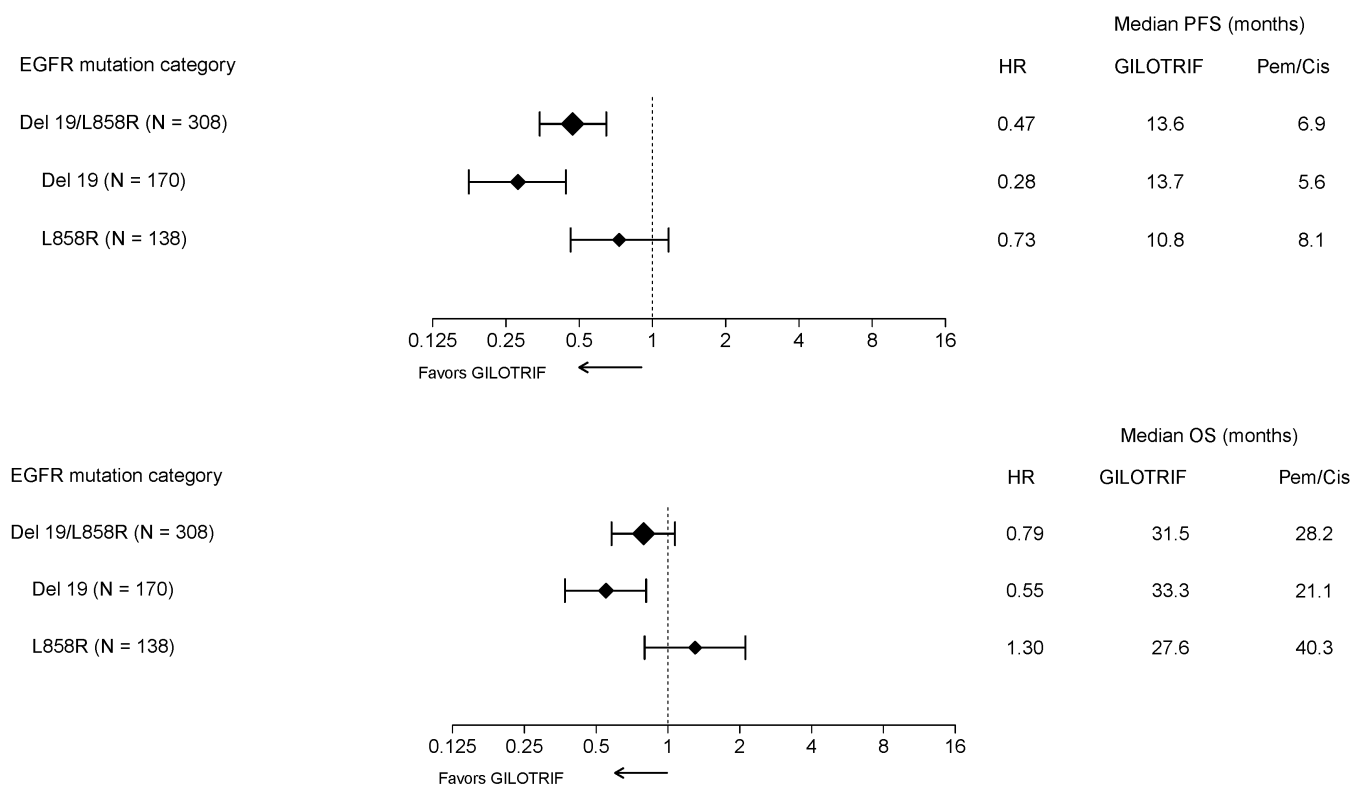
	GILOTRIF (N=230)	Pemetrexed/Cisplatin (N=115)
Progression-Free Survival by IRC		
Number of Deaths or Progressions, N (%)	152 (66.1%)	69 (60.0%)
Median Progression-Free Survival (months)	11.1	6.9
95% CI	(9.6, 13.6)	(5.4, 8.2)
HR (95% CI)	0.58 (0.43, 0.78)	
Stratified Log-Rank Test p-value*	<0.001	
Overall 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 in LUX-Lung 3

Pre-specified exploratory subgroup analyses were conducted according to the stratification factor of EGFR mutation category. See Figure 2 and text below Figure 2.

Figure 2 Forest Plots of PFS and OS by EGFR Mutation Subgroups in LUX-Lung 3

Overall Response Rate in Other EGFR Mutations

The efficacy of GILOTRIF in patients with NSCLC harboring non-resistant EGFR mutations (S768I, L861Q, and G719X) other than exon 19 deletions or exon 21 L858R substitutions was evaluated in a pooled analysis of such patients enrolled in one of three clinical trials (LUX-Lung 2 [NCT00525148], LUX-Lung 3 [NCT00949650], and LUX-Lung 6 [NCT01121393]).

- LUX-Lung 2 was a single arm, multicenter study of afatinib 40 or 50 mg orally once daily until disease progression or intolerable side effects. EGFR status was determined by bi-directional Sanger sequencing of tumor tissue.
- LUX-Lung 3 was a randomized, multicenter study comparing treatment with afatinib 40 mg orally once daily to intravenous cisplatin 75 mg/m² plus pemetrexed 500 mg/m² every 21 days for up to 6 cycles. EGFR status was determined by the *therascreen*[®] EGFR RGQ PCR Kit.
- LUX-Lung 6 was a randomized, multicenter study comparing treatment with afatinib 40 mg to intravenous gemcitabine 1000 mg/m² on day 1 and day 8 plus cisplatin 75 mg/m² on day 1 of a 3-week schedule for up to 6 cycles. EGFR status was determined by the *therascreen*[®] EGFR RGQ PCR Kit.

Among the 75 GILOTRIF-treated patients with uncommon EGFR mutations, 32 patients had a non-resistant EGFR mutation. Among the 32 patients with a confirmed non-resistant EGFR mutation, the median age was 60.5 years (range 32-79), 66% were female, 97% were Asian, 3% were other races, 38% had an ECOG PS of 0, 63% had an ECOG PS 1, 66% were never smokers, 28% were former smokers, and 6% were current smokers. Baseline disease characteristics were 97% Stage IV disease, 3% Stage IIIb disease, and 88% had received no prior systemic therapy for advanced or metastatic disease.

The number of patients, the number of responders, and durations of response in subgroups defined by identified mutation(s) are summarized in Table 6.

Table 6 IRC-Assessed Responses in Patients with NSCLC Harboring EGFR Mutations G719X, L861Q, and/or S768I from LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6

EGFR Mutation	Number of GILOTRIF Treated Patients (N=32)	Number of Confirmed Responses (N=21)	Duration of Response (months) (N=21)
S768I	1	1	37.3
S768I and G719X	5	4	4.1, 13.2, 15.2, 29.5+
S768I and L858R	2	1	34.5+
G719X	8	6	5.7+, 8.1, 9.6, 23.5+, 25.2, 31.8+
G719X and L861Q	3	2	2.8+, 6.8
L861Q	12	7	2.8, 4.0, 4.1, 8.3+, 12.9, 15.2, 20.6
L861Q and Del 19	1	0	NA

+ response ongoing at time of censoring

14.2 Previously Treated, Metastatic Squamous NSCLC

The efficacy and safety of GILOTRIF were demonstrated in a randomized, multicenter, open-label, active-controlled study (LUX-Lung 8 [NCT01523587]). 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 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 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.

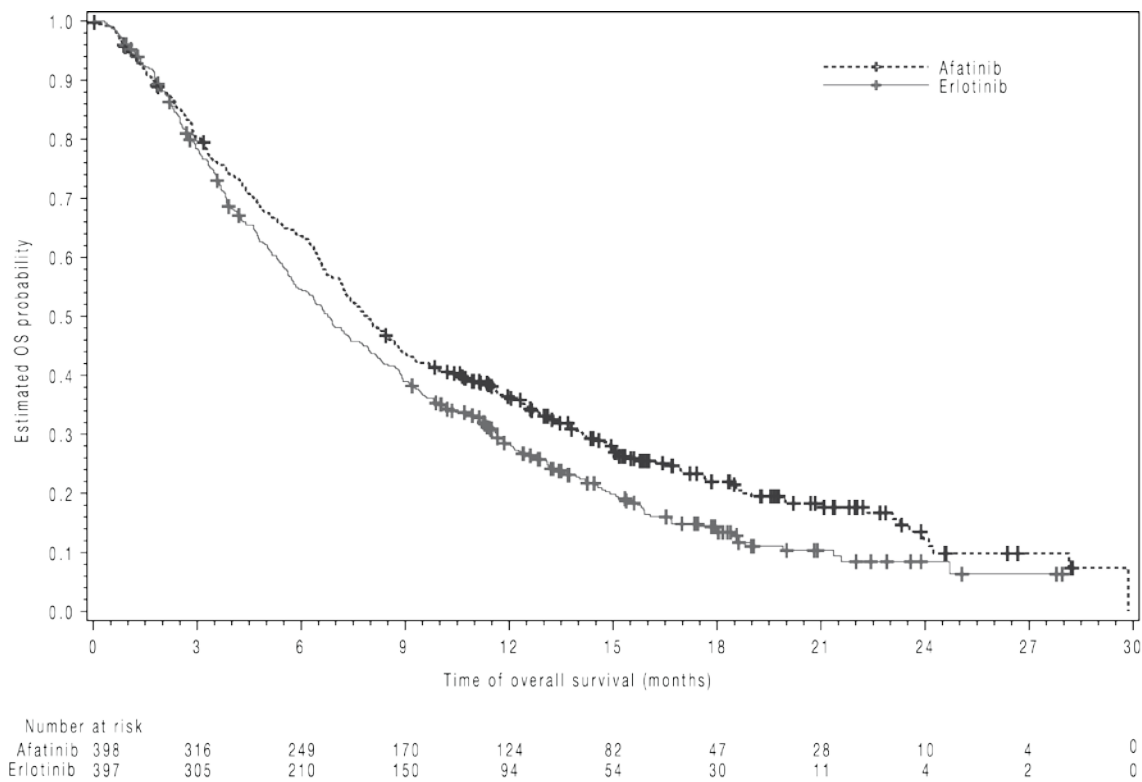
The study demonstrated a statistically significant improvement in PFS and OS for patients randomized to GILOTRIF as compared with erlotinib (see Table 7 and Figure 3).

Table 7 Efficacy Results in LUX-Lung 8

	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 in LUX-Lung 8

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)*].

Gastrointestinal Perforation

Advise patients that GILOTRIF can increase the risk of gastrointestinal perforation and to seek immediate medical attention for severe abdominal pain [see *Warnings and Precautions (5.5)*].

Keratitis

Advise patients to immediately report eye problems (e.g., eye pain, swelling, redness, blurred vision, or other vision changes) [see *Warnings and Precautions (5.6)*].

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)*].

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IT5562SJ162019

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

What is GILOTRIF?

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

- has certain (non-resistant) abnormal epidermal growth factor receptor (EGFR) gene(s). Your healthcare provider will perform a test to make sure that GILOTRIF is right for you.
- has spread to other parts of the body (metastatic), and
- has not been previously treated for metastatic lung cancer

It is not known if GILOTRIF is safe and effective in treating people with lung cancer that has resistant abnormal EGFR genes.

or

is used to treat people with squamous cell lung cancer that:

- has spread to other parts of the body, and
- has been previously treated with 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 an ulcer, a tear (perforation) in your stomach or intestine, or diverticular disease (inflammation) in parts of your large intestine. **See “What are the possible side effects of GILOTRIF?”**
- 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.
 - Females 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 during treatment with GILOTRIF.
- are breastfeeding or plan to breastfeed. It is not known if GILOTRIF passes into your breast milk. Do not breastfeed during treatment with 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. Taking certain medicines with GILOTRIF may increase your risk of developing a tear (perforation) in your stomach or intestine. **See “What are the possible side effects of GILOTRIF?”**

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 sunlight. 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 if you have to be in sunlight during treatment with GILOTRIF.

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.

- **tear (perforation) in your stomach or intestine.** Tears in your stomach or intestine can happen with GILOTRIF and can sometimes lead to death. Your risk of developing a tear in your stomach or intestine may be increased if you:
 - take certain medicines with GILOTRIF including: corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and certain other medicines.
 - have a history of stomach or intestinal ulcers, or if you have had diverticular disease (inflammation in parts of the large intestine).

Get medical help right away if you develop severe stomach-area (abdomen) pain during 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
 - blurred vision
 - sensitivity to light
 - 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
 - cough
 - tiredness
 - swelling of your ankles, feet, or legs
 - feeling that your heart is pounding or racing (palpitations)
 - sudden weight gain

Your doctor may change your dose, temporarily stop or permanently stop treatment with GILOTRIF if you have certain side effects.

The most common side effects of GILOTRIF include:

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

GILOTRIF may cause decreased fertility in females and males. This may affect your ability to have a child. Talk to your doctor if this is a concern for you.

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 between 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 2019

EXHIBIT 2



US00RE43431E

(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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(75) Inventors: **Frank Himmelsbach**, Mittelbiberach (DE); **Elke Langkopf**, Biberach an der Riss (DE); **Stefan Blech**, Warthausen (DE); **Birgit Jung**, Laupheim (DE); **Anke Baum**, Vienna (AT); **Flavio Solca**, Vienna (AT)

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

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

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

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **7,019,012**
 Issued: **Mar. 28, 2006**
 Appl. No.: **10/023,099**
 Filed: **Dec. 17, 2001**

U.S. Applications:

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(30) Foreign Application Priority Data

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A61K 31/517 (2006.01)
C07D 239/94 (2006.01)
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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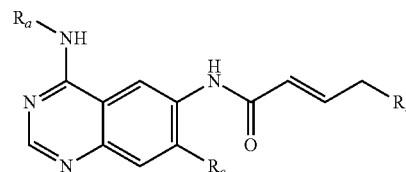
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Primary Examiner — James O Wilson*Assistant Examiner* — Tamthom N Truong(74) *Attorney, Agent, or Firm* — Michael P. Morris; Anthony P. Bottino

(57) ABSTRACT

A compound of general formula I



(I)

wherein:

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

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

R_c is a cyclopropylmethoxy, 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**

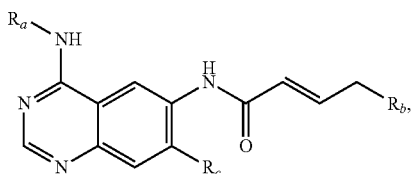
Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

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-ylloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-4-ylloxy 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-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
 - (17) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(diethylamino)-1-oxo-2-buten-1-yl]amino]-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,
 - (18) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(diethylamino)-1-oxo-2-buten-1-yl]amino]-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline,
 - (19) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(diethylamino)-1-oxo-2-buten-1-yl]amino]-7-[(tetrahydropyran-4-yl)oxy]quinazoline,
 - (20) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-[N-methyl-N-(tetrahydrofuran-2-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-(diethyl-
lamino)-1-oxo-2-buten-1-yl}amino}-7-cyclobutyllox-
yquinazoline,
- (7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(diethyl-
lamino)-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-cyclobutylloxquinazoline,
- (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-cyclopentylloxquinazo-
line,
- (11) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(diethylamino)-1-
oxo-2-buten-1-yl}amino}-7-cyclobutylloxquinazoline,
- (12) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(diethylamino)-1-
oxo-2-buten-1-yl}amino}-7-cyclopentylloxquinazoline,
- (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-meth-
oxyethyl)amino]-1-oxo-2-buten-1-yl]amino}-7-cyclopro-
pylmethoxyquinazoline,
- (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-(diethyl-
lamino)-1-oxo-2-buten-1-yl}amino}-7-[(tetrahydrofuran-
2-yl)methoxy]quinazoline,
- (18) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(diethyl-
lamino)-1-oxo-2-buten-1-yl}amino}-7-[(S)-(tetrahydro-
furan-3-yl)oxy]quinazoline,
- (19) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(diethyl-
lamino)-1-oxo-2-buten-1-yl}amino}-7-[(tetrahydropy-
ran-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-meth-
oxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl]amino}-
7-cyclopropylmethoxyquinazoline,
- (23) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[[bis(2-meth-
oxyethyl)amino]-1-oxo-2-buten-1-yl]amino}-7-cyclobu-
tyloxyquinazoline,
- (24) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[N-methyl-
N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl]amino}-
7-cyclobutylloxquinazoline,
- (25) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[(S)-N-me-
thyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-
yl]amino}-7-cyclobutylloxquinazoline,
- (26) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[(R)-N-me-
thyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-
yl]amino}-7-cyclobutylloxquinazoline,

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- (27) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[N-methyl-
N-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-
yl]amino}-7-cyclobutylloxquinazoline,
- (28) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[(R)-N-me-
thyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-
buten-1-yl]-amino}-7-cyclobutylloxquinazoline,
- (29) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[(S)-N-me-
thyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-
buten-1-yl]-amino}-7-cyclobutylloxquinazoline,
- (30) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[N-methyl-
N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl]amino}-
7-(tetrahydrofuran-3-yloxy)quinazoline,
- (31) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[N-methyl-
N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl]amino}-
7-(tetrahydropyran-4-yloxy)quinazoline,
- (32) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[N-methyl-
N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl]amino}-
7-(tetrahydrofuran-2-ylmethoxy)quinazoline and
- (33) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[N-cyclo-
propyl-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-meth-
oxyethyl)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, cyclo-
pentylloxy, tetrahydrofuran-3-yloxy, tetrahydrofuran-2-
ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydro-
pyran-4-yloxy or tetrahydropyran-4-ylmethoxy group,
with the exception of the compounds
- (1) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[N,N-diethyl-
lamino]-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-
methoxyquinazoline,
- (2) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(morpholin-
4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethox-
yquinazoline,
- (3) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(dimethyl-
lamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-
methoxyquinazoline,
- (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-(diethyl-
lamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyllox-
yquinazoline,
- (7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(diethyl-
lamino)-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-cyclobutylloxquinazoline,
- (9) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(morpholin-4-yl)-1-
oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazo-
line,

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

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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-cyclobutyloxyquinazoline and
- (33) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-[(S)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}-amino}-7-cyclobutyloxyquinazoline,

the tautomers, the stereoisomers and the salts thereof.

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

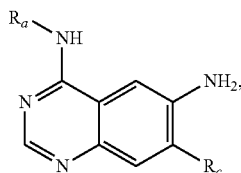
- (a) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl}amino}-7-cyclobutyloxyquinazoline;
- (b) 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl}amino}-7-cyclopentyloxyquinazoline,
- (c) 4-[(R)-(1-phenylethyl)amino]-6-{{4-(N,N-bis(2-methoxyethyl)amino)-1-oxo-2-buten-1-yl}amino}-7-cyclopropylmethoxyqui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

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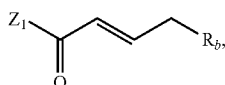
The compounds of general formula I may be prepared by the following methods, for example:

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.

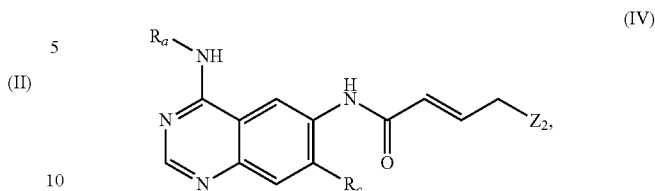
The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of an inorganic or organic base and optionally in the presence of 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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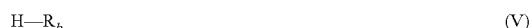
b) Reacting a compound of general formula



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, benzoyloxycarbonyl, 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 benzoyloxycarbonyl 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

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

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

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

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

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

The enzyme assays were carried out at ambient temperature over a period of 30 minutes and were ended by the addition of 50 µl of a stopping solution (250 mM EDTA in 20 mM HEPES pH 7.4). 100 µl were placed on a streptavidin-coated microtiter plate and incubated for 60 minutes at ambient temperature. Then the plate was washed with 200 µl of a washing solution (50 mM Tris, 0.05% Tween 20). After the addition of 100 µl of a HRPO-labelled anti-PY antibody (PY20H Anti-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.

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 (neoangiogenesis).

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

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-cyclobutylmethoxyquinazoline

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-cyclopentylmethoxyquinazoline

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-[N-[(tetrahydropyran-4-yl)methyl]-N-methylamino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI⁺): m/z=554, 556 [M+H]⁺; melting point: 141° C.
- (25) 4-[(R)-(1-phenylethyl)amino]-6-[[4-[N-[(tetrahydropyran-4-yl)methyl]-N-methylamino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI⁺): m/z=530 [M+H]⁺; R_f value: 0.32 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:0.5).
- (26) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-((R)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamino)-1-oxo-2-buten-1-yl]amino]-7-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-[(tetrahydropyran-4-yl)methoxy]quinazoline
Mass spectrum (ESI⁺): m/z=514, 516 [M+H]⁺; R_f value: 0.19 (silica gel, methylene chloride/methanol/conc. aqueous ammonia=95:5:0.05).
- (29) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-[(tetrahydropyran-4-yl)methoxy]quinazoline
Mass spectrum (ESI⁻): m/z=554, 556 [M-H]⁻; melting point: 174° C.
- (30) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-[N,N-bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl]amino]-7-[(tetrahydropyran-4-yl)methoxy]quinazoline
Mass spectrum (ESI⁺): m/z=602, 604 [M+H]⁺; melting point: 100° C.-102° C.
- (31) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI⁺): m/z=500, 502 [M+H]⁺; melting point: 110° C.-112° C.
- (32) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI⁺): m/z=500, 502 [M+H]⁺; R_f value: 0.23 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:0.1).
- (33) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N-ethyl-N-methylamino)-1-oxo-2-buten-1-yl]amino]-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline
Mass spectrum (ESI⁺): m/z=500, 502 [M+H]⁺; melting point: 154° C.-157° C.
- (34) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N-isopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino]-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline
Mass spectrum (ESI⁺): m/z=514, 516 [M+H]⁺; R_f value: 0.34 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:1).
- (35) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline
Mass spectrum (ESI⁺): m/z=528, 530 [M+H]⁺; melting point: 184° C.-185° C.
- (36) 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N-isopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino]-7-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,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

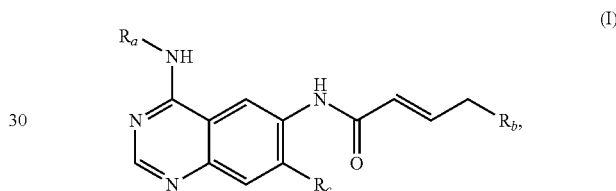
15 Preparation

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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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 3



US008426586B2

(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**

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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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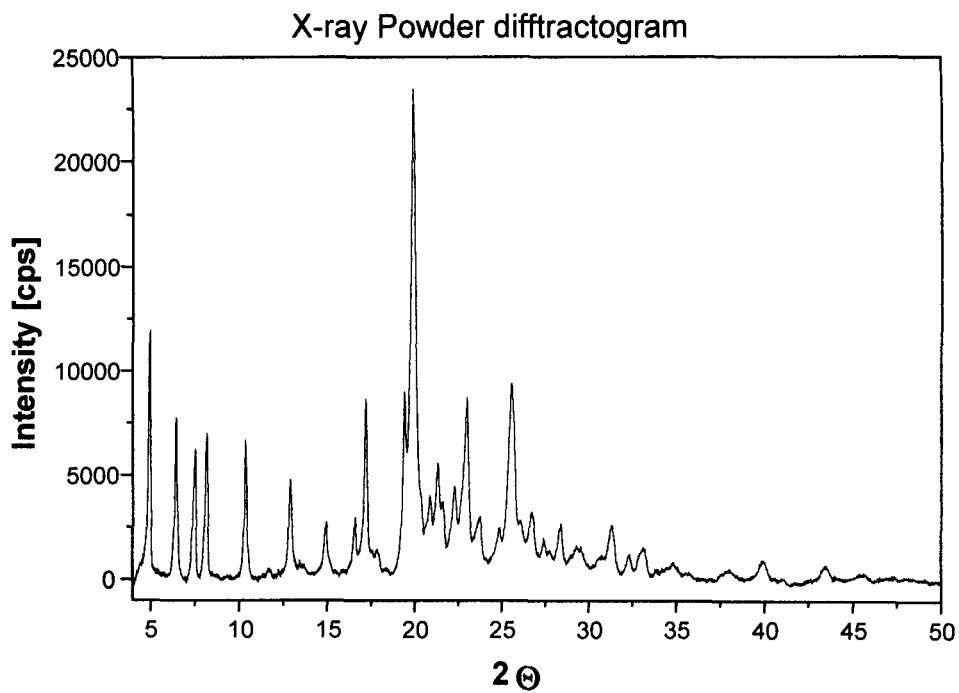


FIG. 1

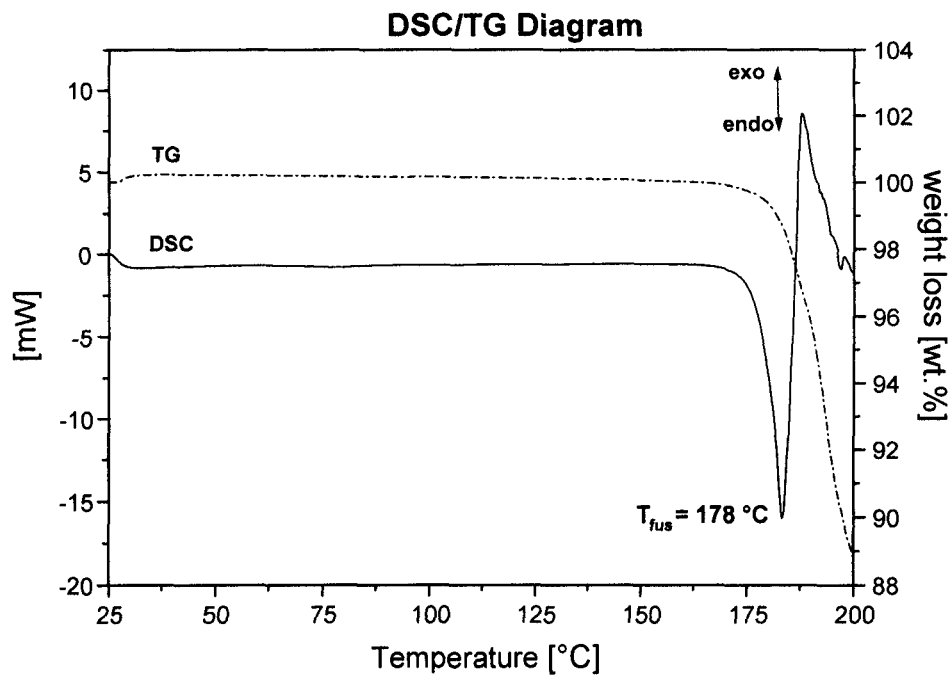


FIG. 2

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PROCESS FOR PREPARING AMINO CROTONYL COMPOUNDS

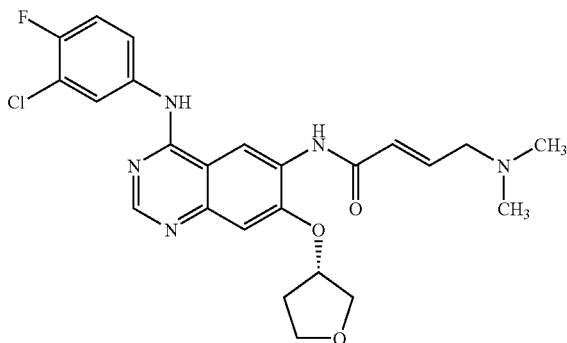
RELATED APPLICATIONS

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:

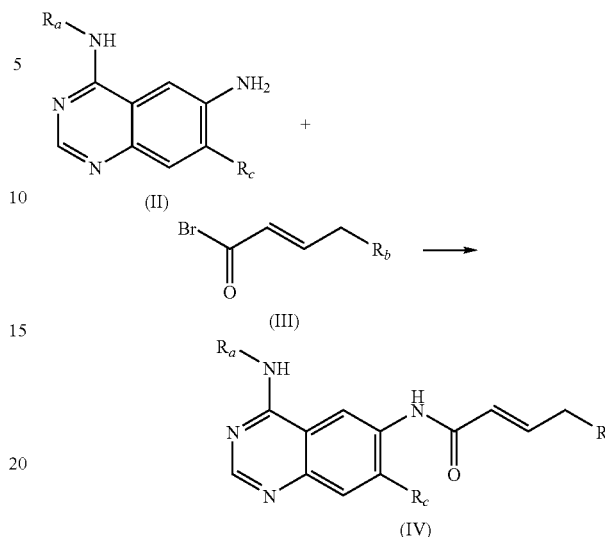


and is already known from WO 02/50043, which describes compounds with valuable pharmacological properties, including in particular an inhibiting effect on signal transduction mediated by tyrosinekinases and an inhibitory effect on signal transduction mediated by the Epidermal Growth Factor receptor (EGF-R). 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'-ethyl-3-(3-dimethylaminopropyl)-carbodiimide), 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 methylene 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.

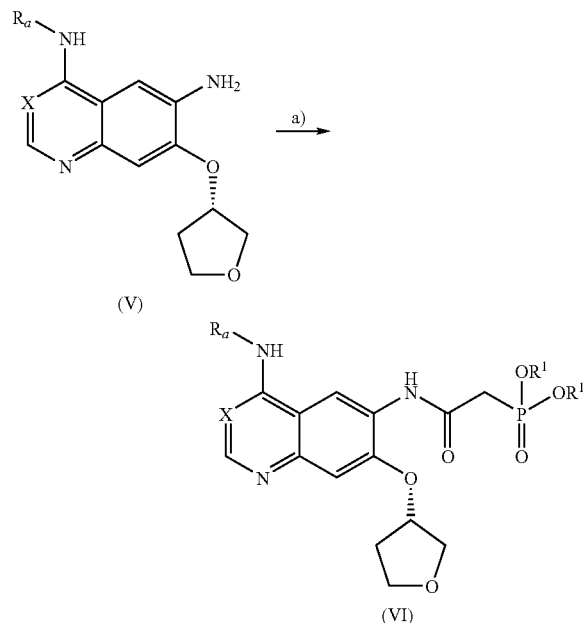
The process is preferably used for compounds wherein

X denotes a nitrogen atom,

R_a denotes a 3-chloro-4-fluorophenyl group and

R¹ denotes an ethyl group.

Diagram 2:



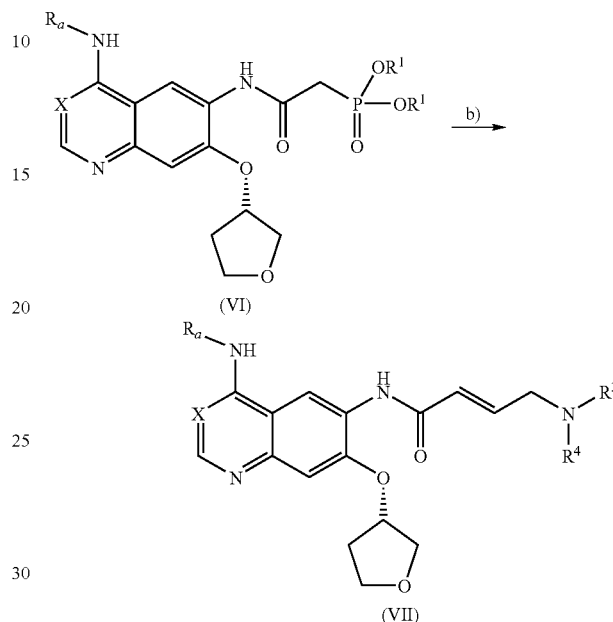
a) di-(C₁₋₄-alkyl)-phosphonoacetic Acid, Activating Agent

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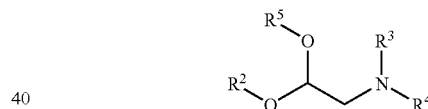
hydroxide and potassium hydroxide, of which sodium hydroxide and potassium hydroxide are preferred and potassium hydroxide is particularly preferred. Instead of the aldehyde a corresponding equivalent, e.g. a hydrate or acetal, may be used, from which the aldehyde is released (beforehand or in situ).

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.

Preferably

R³ and R⁴ in each case represent a methyl group and

R² and R⁵ in each case represent an ethyl group.

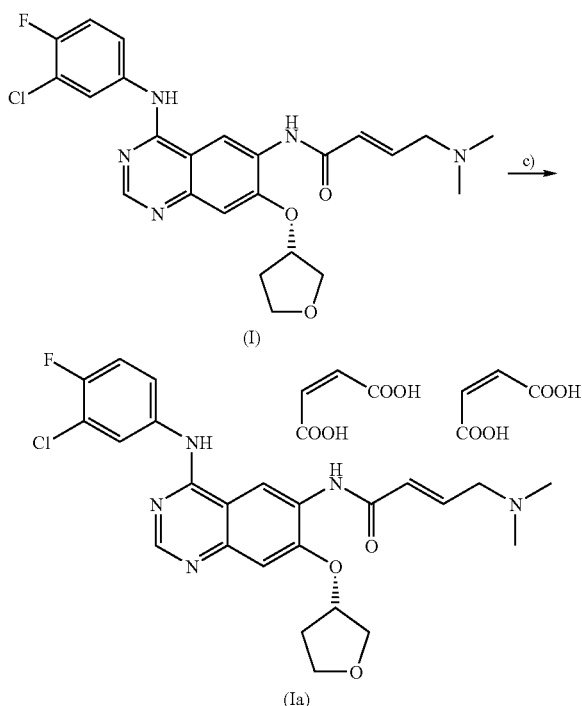
The aminocrotonylamide of formula (VII) thus obtained, for example 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline of formula (I), may then be converted into the salts thereof, particularly the physiologically acceptable 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:



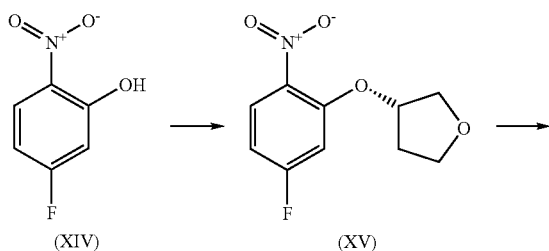
c) Maleic Acid, Ethanol

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).

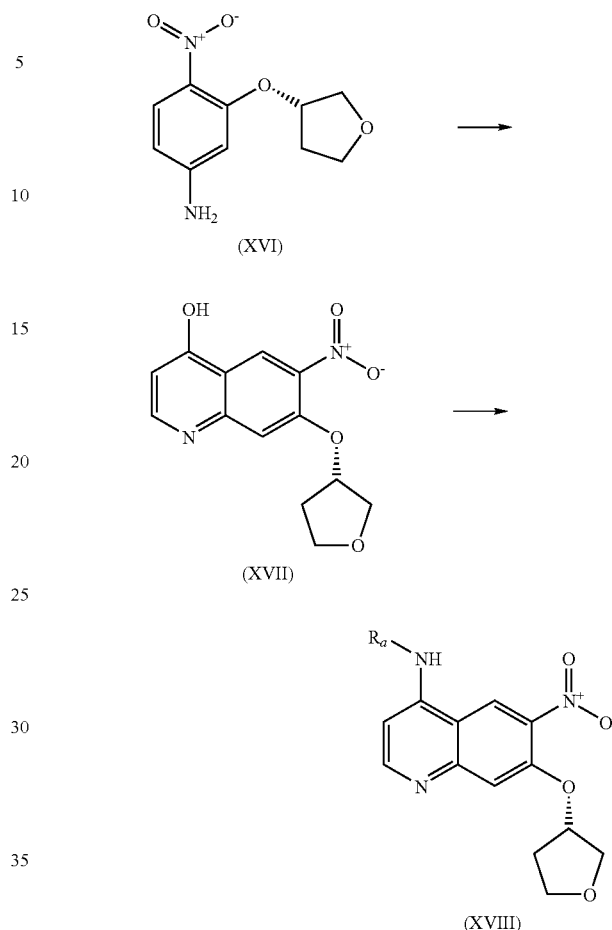
The compound thus obtained (XVII) is then converted into the compound (XVIII) as described in Diagram 6 for the quinazoline analogue

Diagram 5a:



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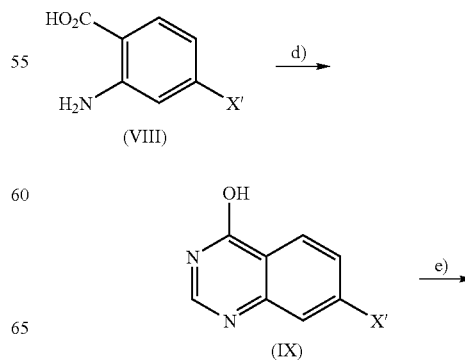
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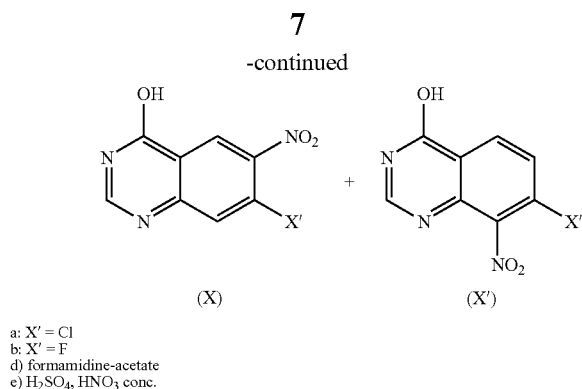
To prepare the compound (V) wherein X=N the following procedure is used:

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:

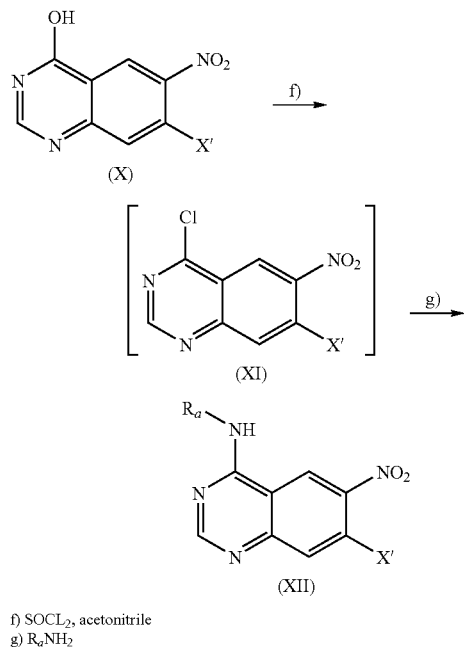


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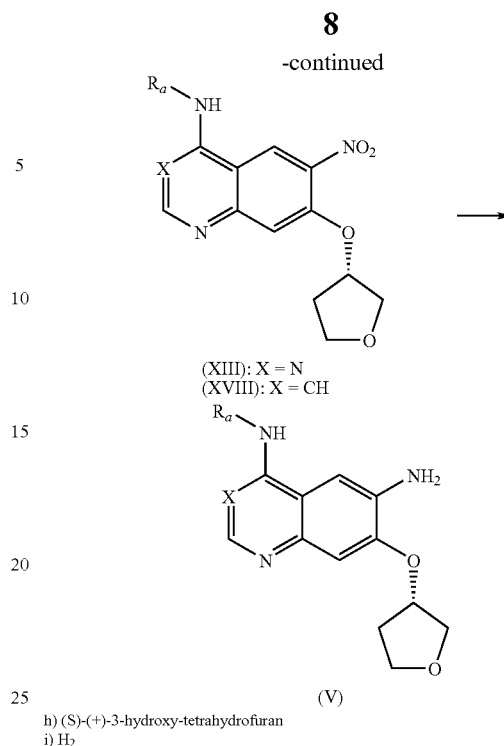
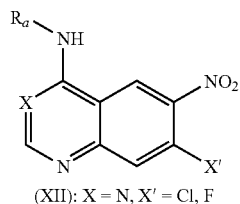
The desired regioisomer (X) of the nitrogenation products thus obtained is then chlorinated, and the chlorination product (XI) is reacted in situ with the corresponding amine (Diagram 6).

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-dimethylamino)-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.

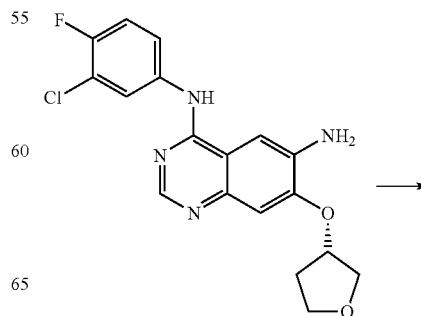
The x-ray powder diagrams were recorded, within the scope of the present invention, using a Bruker D8 Advanced diffractometer fitted with a PSD detector and a Cu anode as the x-ray source (CuK α_1 radiation, $\lambda=1.5418$ Å, 40 kV, 40 mA).

The following Examples are intended to illustrate the invention:

EXAMPLES

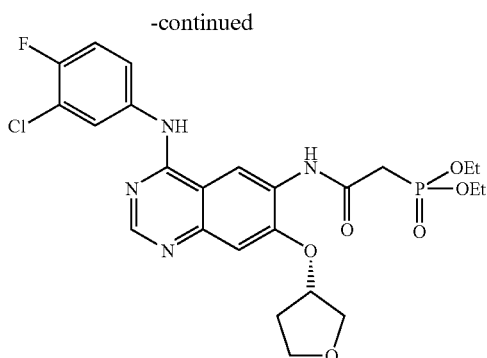
Example 1

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



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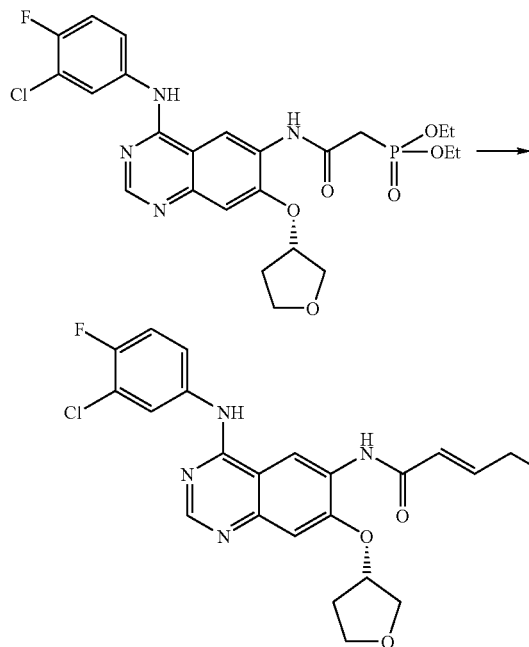
3.58 kg of 1,1-carbonyldiimidazole (22.16 mol) are placed in 12.8 liters of tetrahydrofuran and at 40° C. combined with 4.52 kg (22.16 mol) of diethylphosphonoacetic acid dissolved in 6.5 liters of tetrahydrofuran. The mixture is stirred for 30 minutes at 40° C. The resulting solution is referred to 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 F1 %

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 F1 %, 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 liters 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.

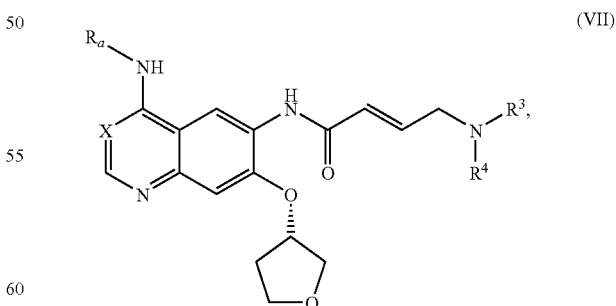
Yield: 8.11 kg (91.5%)

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)

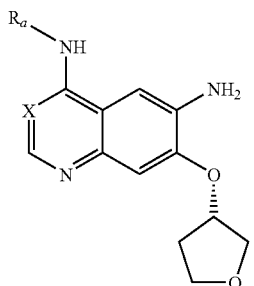


wherein X denotes a methyne group or a nitrogen atom, R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and R³ and R⁴ denote a straight-chain or branched C₁₋₄-alkyl group,

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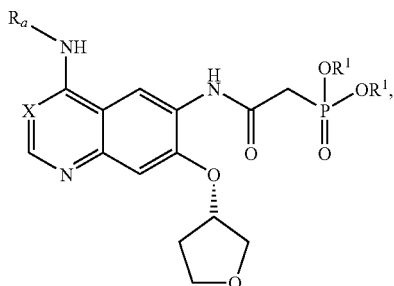
13

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

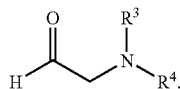


wherein X denotes a methylene group or a nitrogen atom and R_α denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group, in suitable solvents after corresponding activation with di-(C_{1-4} -alkyl)-phosphonoacetic acid and

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



wherein X denotes a methylene group or a nitrogen atom, R_α denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and R^1 denotes a straight-chain or branched C_{1-4} -alkyl group, with the aldehyde of formula



wherein R^3 and R^4 in each case represent a straight-chain or branched C_1 - C_4 -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 N^4 -(3-chloro-4-fluoro-phenyl)-7-(tetrahydrofuran-3-yloxy)quinazoline-4,6-diamine in suitable solvents after corresponding activation with di-(C_{1-4} -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.

(V) 5 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.

10 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):

15 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 2equivalents of maleic acid are used.

25 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 2Θ [°] values obtained by X-ray powder diffraction using $CuK_{\alpha 1}$ radiation, $\lambda=1.5418\text{\AA}$ in the following table:

	2Θ [°]	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.

45 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 2Θ [°] values obtained by X-ray powder diffraction using $CuK_{\alpha 1}$ radiation, $\lambda=1.5418\text{\AA}$ in the following table:

	2Θ [°]	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_{α1} 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.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,426,586 B2
APPLICATION NO. : 11/457622
DATED : April 23, 2013
INVENTOR(S) : Rainer Soyka et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

In column 16, line 25, change “36.38 2.46 71” to

-- 36.38 2.467 1 --.

Signed and Sealed this
Twenty-first Day of July, 2015



Michelle K. Lee
Director of the United States Patent and Trademark Office

EXHIBIT 4



(12) **United States Patent**
Barta

(10) **Patent No.:** **US 10,004,743 B2**
(45) **Date of Patent:** **Jun. 26, 2018**

(54) **PROCESS FOR DRYING OF BIBW2992, OF ITS SALTS AND OF SOLID PHARMACEUTICAL FORMULATIONS COMPRISING THIS ACTIVE INGREDIENT**

(71) Applicant: **Boehringer Ingelheim International GmbH**, Ingelheim am Rhein (DE)

(72) Inventor: **Albert Barta**, Warthausen (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 0 days. days.

(21) Appl. No.: **15/371,252**

(22) Filed: **Dec. 7, 2016**

(65) **Prior Publication Data**

US 2017/0079980 A1 Mar. 23, 2017

Related U.S. Application Data

(62) Division of application No. 13/378,379, filed as application No. PCT/EP2010/059546 on Jul. 5, 2010, now Pat. No. 9,545,381.

(30) **Foreign Application Priority Data**

Jul. 6, 2009 (EP) 09164659
Feb. 24, 2010 (EP) 10154562

(51) **Int. Cl.**

A61K 31/4375 (2006.01)
A61K 9/00 (2006.01)
A61K 9/28 (2006.01)
A61K 31/517 (2006.01)
A61K 9/16 (2006.01)
A61K 9/20 (2006.01)

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

CPC **A61K 31/517** (2013.01); **A61K 9/1641** (2013.01); **A61K 9/1652** (2013.01); **A61K 9/2009** (2013.01); **A61K 9/2013** (2013.01); **A61K 9/2018** (2013.01); **A61K 9/2027** (2013.01); **A61K 9/2054** (2013.01); **A61K 9/2095** (2013.01); **A61K 9/2813** (2013.01); **A61K 9/2826** (2013.01); **A61K 9/2853** (2013.01); **A61K 9/2866** (2013.01)

(58) **Field of Classification Search**

None
See application file for complete search history.

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Primary Examiner — Robert T. Crow
Assistant Examiner — John P Nguyen
(74) *Attorney, Agent, or Firm* — Marc A. Began; Atabak R. Royae

(57) **ABSTRACT**

The present invention relates to a drying process of BIBW 2992 or the salts thereof, preferably the dimaleate salt, as well as of solid pharmaceutical formulations comprising BIBW2992 or a salt thereof, and to pharmaceutical compositions comprising BIBW 2992 or a salt thereof as the active product ingredient, characterized by a water activity of the formulation of not more than 0.20 or a water content (Karl-Fischer) of not more than 4.2%.

5 Claims, 2 Drawing Sheets

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Figure 1: Drying device using compressed air

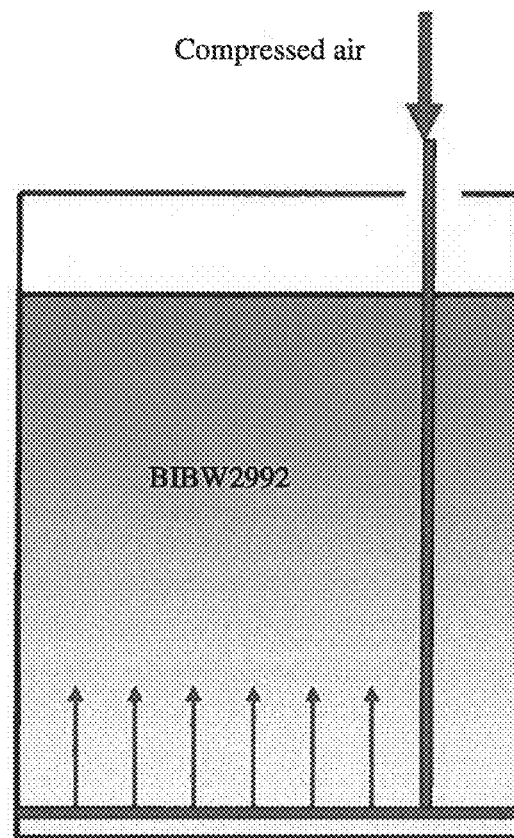
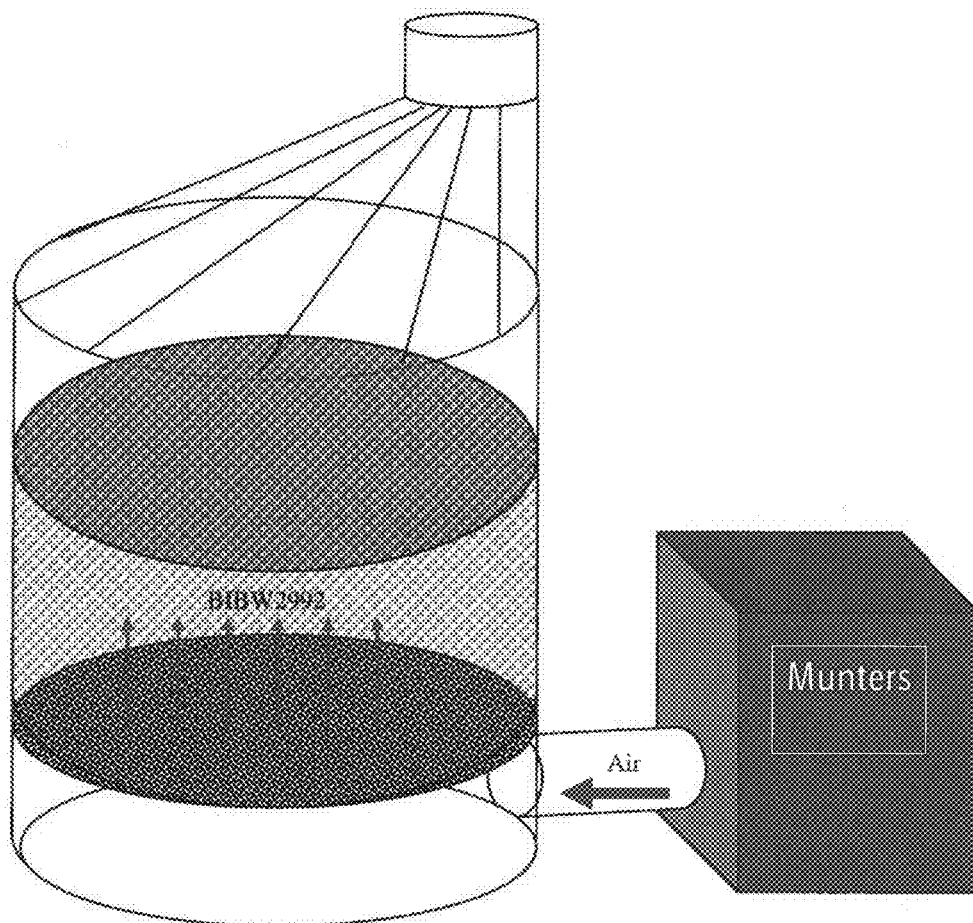


Figure 2: Munters drying device



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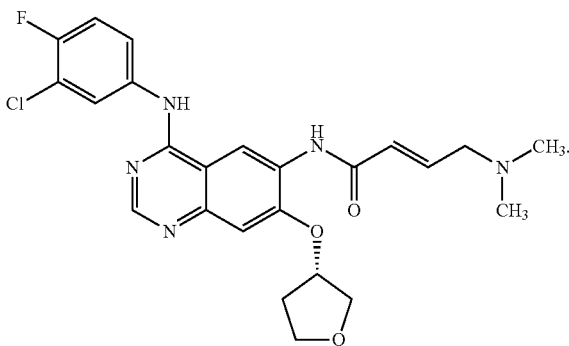
**PROCESS FOR DRYING OF BIBW2992, OF
ITS SALTS AND OF SOLID
PHARMACEUTICAL FORMULATIONS
COMPRISING THIS ACTIVE INGREDIENT**

FIELD OF THE INVENTION

The present invention relates to a drying process of BIBW 2992 or the salts thereof, preferably the dimaleate salt (abbreviated hereinafter BIBW 2992 MA₂), as well as of solid pharmaceutical formulations comprising BIBW 2992 or a salt thereof, and to pharmaceutical compositions comprising BIBW 2992 or a salt thereof as the active product ingredient (API), characterized by a water activity of the formulation of not more than 0.20 or a water content (Karl-Fischer) of the formulation of not more than 4.2%.

BACKGROUND OF THE INVENTION

BIBW 2992 (also named TOMTOVOK®) is known as the compound 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline,



BIBW 2992 is a potent and selective dual inhibitor of erbb1 receptor (EGFR) and erbb2 (Her2/neu) receptor tyrosine kinases. Furthermore, BIBW 2992 was designed to covalently bind to EGFR and HER2 thereby irreversibly inactivating the receptor molecule it has bound to. This compound, salts thereof such as the dimaleate BIBW 2992 MA₂ and its crystalline modification, their preparation as well as pharmaceutical formulations comprising BIBW 2992 or a salt thereof are disclosed in WO 02/50043 and WO 2005/037824. These documents are incorporated by reference regarding these aspects.

BIBW 2992 is suitable for the treatment of tumoral diseases, hypersecretory diseases of the lungs and respiratory tract, diseases of the gastrointestinal tract, the bile duct and gall bladder. Indications to be treated with BIBW 2992 and combination treatments are disclosed in WO 2007/054550 and WO 2007/054551.

Besides the pharmacological activity of an active pharmaceutical ingredient (API) there are a variety of chemical, physical or physicochemical characteristics of the active substance relevant for the preparation of solid oral dosage forms, as oral powders, granules, pellets, tablets, capsules, chewable tablets, dispersible tablets, or lozenges. To achieve adequate formulation characteristics, as correct assay, content and mass uniformity, chemical and physical stability of the drug product and a proper dissolution rate, also the

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characteristics of the product intermediates have to be adequate for robust, fast and cost efficient processing.

Without being restrictive, examples of these parameters relevant for processing of the active agent (the drug substance) are

the stability of the drug substance under various environmental conditions which strongly may influence the stability of the final pharmaceutical formulation (the drug product), and physical characteristics of the drug substance such as bulk densities (i.e. poured and tapped density), particle morphology, shape, the ratio of length to width for needles, size distribution, electrostatic charging and surface adhesive properties, which may vary due to precipitation and drying conditions of the drug substance. These characteristics may significantly influence key features for processing of the drug substance into a final formulation, such as flowability and compressibility.

For actives sensitive to hydrolytic degradation it is substantial to minimize access of moisture within the manufacture of the drug product up to packaging as well as to take effective measures to prevent entrance of water into the final packaging in order to achieve an adequate shelf life of the product.

BIBW 2992 is a moisture sensitive compound and can quickly hydrolytically degrade at humid conditions, e.g. in the presence of water, moisture or moisture released by further excipients in the drug product, resulting a main API degradation product by release of dimethylamine from the side chain attached to position 6 of the quinazoline.

BRIEF SUMMARY OF THE INVENTION

A first object of the present invention is directed to a process for drying of BIBW 2992 or a salt thereof, preferably BIBW 2992 MA₂, comprising drying with a gas which is inert towards BIBW 2992 at the drying conditions and which has a relative humidity (rh) of not more than 15%, preferably not more than 12% rh, at a temperature below 40° C., preferably below 30° C.

A second object of the present invention is directed to a process for drying of a pharmaceutical formulation containing BIBW 2992 or a salt thereof, preferably BIBW 2992 MA₂, as the active ingredient and at least one further excipient, with a gas, e.g. air which is inert towards the ingredients of the mentioned pharmaceutical formulation at the drying conditions, and which has a relative humidity of not more than 15%, preferably not more than 12% rh, at temperatures below 40° C., preferably below 30° C.

A third object of the present invention is a pharmaceutical composition comprising BIBW 2992 or a salt thereof, preferably BIBW 2992 MA₂, as an active ingredient and at least one further excipient, e.g. an oral, pharmaceutical dosage form, such as a tablet, which is characterized by a water activity of not more than 0.20, preferably of not more than 0.17, or, most preferred, of not more than 0.15.

A fourth object of the present invention is a pharmaceutical composition comprising BIBW 2992 or a salt thereof, preferably BIBW 2992 MA₂, as an active ingredient and at least one further excipient, e.g. an oral, pharmaceutical dosage form, such as a tablet, which is characterized by a water content (Karl-Fischer) of not more than 4.2%, preferably of not more than 4.0%, particularly of not more than 3.8%, or, most preferred, of not more than 3.7%.

**DETAILED DESCRIPTION OF THE
INVENTION**

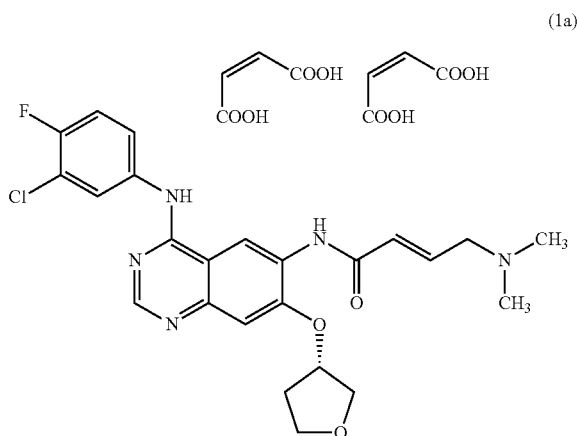
BIBW 2992 to be dried according to the process of the invention or referred to herein within the context of the

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invention includes the API in any form, e.g. in the form of the free base itself, in the form of a solvate and in the form of a salt, preferably a pharmaceutically acceptable salt.

Pharmaceutically acceptable salts are for instance selected from the group consisting of the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydro lactate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably the hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydromaleate, hydrofumarate and hydromethanesulphonate. In a particularly preferred embodiment with regard to any aspects of the invention BIBW 2992 is applied as its hydromaleate, preferably in the ratio BIBW 2992:maleic acid=1:2 as depicted in the formula (1a) below (also denoted herein as the "dimaleate" or BIBW 2992 MA₂).



BIBW 2992 also includes combinations with at least one pharmaceutical excipient, e.g. a pharmaceutical composition comprising BIBW 2992 in the form of the free base, in the form of a solvate or in the form of a salt as the active ingredient, as an intermediate for further processing or as a final dosage form ready for ingestion.

Preferred pharmaceutical compositions as an intermediate for further processing includes a compacted intermediate or a dry granulated intermediate comprising BIBW 2992 MA₂ in form of a powder obtainable by a combined compaction (either roller compaction, briquetting or slugging) or dry granulation and subsequent sieving of the compacted active, optionally in mixture with a lubricant, to adjust and equilibrate its bulk properties and therefore ensure its suitability for further processing into a finished dosage form,

the intermediate and final blends prepared from said compacted (or dry granulated) intermediate, suitable for further processing in the preparation of solid oral dosage forms.

Particularly preferred pharmaceutical compositions are those comprising BIBW 2992 MA₂ in final dosage forms ready for ingestion, including solid oral formulations made from said compacted intermediate, from said intermediate blends or from said final blends, in powdery, compacted, granulated or compressed, form e.g.

dry powder formulations,
uncoated or coated granules,
uncoated or coated pellets, and

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uncoated or film-coated tablets, e.g. prepared by direct-compression,

any of those optionally filled in capsules, e.g. hard gelatin capsules or HPMC (hydroxypropylmethylcellulose) capsules.

The process according to the present invention may be carried out by drying the sample comprising BIBW 2992 (or a pharmaceutically acceptable salt thereof) or any of the pharmaceutical compositions comprising BIBW 2992 (or a pharmaceutically acceptable salt thereof) mentioned hereinbefore, which contains humidity, e.g. water moisture from a formulation procedure, such as aqueous film-coating or adsorbed from a further excipient containing genuine non-crystalline water or moisture adsorbed from environmental air, using continuous contact of the sample with a gas flowing through which is inert towards BIBW2992 at the drying conditions and has a relative humidity of not more than 15%, preferably of not more than 12% rh, at temperatures below 40° C., preferably below 30° C., until the targeted water activity (equilibrium moisture content) in the sample is achieved. The water activity is a measure of the water that is freely available in the sample and is available for exchange with the atmosphere. A desired water activity reduces the water which may be present free or as solvate bound in excipients in the drug product and includes moisture of the form in which BIBW 2992 is present after completion of drying, e.g. 0.20 water activity and less, or Karl-Fischer water content of 4.2% and less.

The water activity mentioned in the context of the invention is meant to be determined as mentioned in the United States Pharmacopeia (USP) <1112>. Furthermore, the Karl-Fischer water content mentioned in the context of the invention is meant to be a titrimetric method (i.e. biamperometric Karl Fischer titration) specified in the United States Pharmacopeia (USP) <921>. Examples for the methods used are provided hereinafter.

It is essential that the gas used, e.g. inert gas, dried compressed or constantly supply dried air, nitrogen or carbon dioxide, has a relative humidity of not more than 15% rh, preferably not more than 12%, in order to guarantee a sufficiently high humidity gradient between the product and the drying gas. Consequently a permanent gas flow has to be assured in order to maintain the humidity gradient and achieve the targeted humidity of BIBW2992. Such could be achieved either by a continuous flow-through of dried compressed air or by continuous flow generated by ventilators (e.g using a Munters® device).

The process according to the present invention is carried out by placing the sample in a container having an inlet and an outlet opening for the supply and removal of the gas.

In one embodiment of the invention the gas stream is purged through the container and the sample as a continuous flow-through of dried compressed air with a pressure at the outlet of approximately 0.5 to 3 bar, preferably 0.8 to 1.5 bar, most preferred about 1 bar. Especially for this purpose containers with a bi-layer bottom are used, in which the upper one is perforated in order to allow the gas to pass through. The gas is introduced into the space between the two bottoms, flows through the perforated upper bottom and then through the product. Finally the gas containing moisture from the product is discharged through the outlet.

In a second embodiment of the invention the gas stream is purged through the container and the sample as a continuous flow generated by ventilators (e.g using a Munters® device) providing an air flow rate of 20-1000 ncm/h, preferably of 30-500 ncm/h, most preferred, of 40-150 ncm/h. The expression "ncm" denotes "norm cubic meter", alter-

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natively abbreviated in the literature as “m³ (i.N.)”, defining a volume of a gas under norm or standard conditions, here of 1013 mbar, a relative humidity (rh) of 0% and a temperature of 0° C.

According to any embodiment of the invention drying temperature is set in the range of 20-40° C., preferably in the range of 20-30° C., e.g. room temperature. During drying, water which may be present as solvate bound in BIBW2992 as dihydrate or Lactose as monohydrate is substantially not removed.

It has been found that at the given conditions drying has to be performed for at least 8 hours, preferably for at least 12 h, most preferred for at least 24 h, in order to achieve the targeted water activity of the formulation of 0.20 and less or Karl-Fischer water content of the formulation of 4.2% and less.

In contrast, an alternative approach to reduce moisture content as conventional drying of film-coated tablets comprising BIBW 2992 in a film-coater at temperatures clearly higher than room temperature e.g. 50° C. led only intermediately to a low level of moisture during the drying process itself. Finally the product (film-coated tablets) have to be cooled down to room temperature associated with moisture re-uptake, since the relative humidity of the cooling air is above 15% rh.

A further alternative conventional approach to reduce moisture content could be storage of BIBW 2992 bulk in close contact with desiccants. The desiccants remove unbound water from the product via physical adsorption of water. For drying of bulk products as e.g. film-coated tablet such a method requires a much longer drying time as the presented method in order to achieve the targeted moisture content and thus is unsuitable to be used in production scale.

SHORT DESCRIPTION OF THE FIGURES

FIG. 1 schematically shows a container suitable for the process according to the present invention comprising an inlet line and an outlet opening for the supply and removal of the gas, a bi-layer bottom (upper and lower bottom) connected with the inlet line, wherein the upper bottom is perforated in order to allow the drying gas to pass through the inner space of the container comprising the sample.

FIG. 2 schematically shows a container suitable for the process according to the present invention with Munters® device gas supply.

The following non-limiting examples serve to illustrate the invention:

EXAMPLE 1

50 kg of film-coated tablets containing 20 mg BIBW 2992 base each are filled into a drying container that is equipped with a double bottom, an air inlet and an air outlet. The tablets are flushed in the container with dried compressed air with relative humidity of not more than 12% and a temperature of approximately 20° C. until the water activity of the formulation is less than 0.15 or the water content (Karl Fischer) of the formulation is not more than 4.0%. Finally a water content of 3.7% (Karl Fischer) after drying was achieved.

After 6 months storage in Alu/Alu-blister at 40° C./75 rh an increase of 1.6% main API degradation product was observed.

EXAMPLE 2 (COMPARATIVE EXAMPLE)

Without initial drying film-coated tablets containing 20 mg BIBW 2992 base showed a water content of the formu-

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lation of 4.3%. After 6 months storage in Alu/Alu-blister at 40° C./75 rh an increase of 2.6% main API degradation product was detected.

EXAMPLE 3: DOSAGE FORMS COMPRISING BIBW 2992 MA₂ (1A) TO BE DRIED USING THE PROCESS OF THE INVENTION

In the following section the manufacturing method for dosage forms of 1a is described.

Process for Preparing Compacted Intermediates Comprising 1a

A compacted intermediate comprising 1a in form of a powder is prepared by a roller compaction step for densification of the material, combined with at least one sieving step additional to the break-up of the ribbon or briquettes, optionally in mixture with a lubricant.

The roller compaction may be carried out with the API 1a alone or, optionally, with

a pre-blend of the API with 0 to 1.0% of a lubricant in a freefall or tumble blender to prevent major sticking on the compaction rolls.

Addition of a lubricant can be avoided if agitated API is used and kept under agitation when loading onto the roller compactor.

The API or pre-blend of the API is compacted on a conventional roller compactor

optionally with horizontally, vertically or 45° angle alignment of the compaction rolls,

which may be smooth or shaped on their surface.

The compaction force may vary between 1 kN/cm and 20 kN/cm,

preferably between 2 kN/cm and 10 kN/cm,

at a compaction speed of the compaction rolls

between 1 rpm and 30 rpm,

preferably between 1 rpm and 10 rpm,

and a gap width between the compaction rolls

between 1 mm and 10 mm

preferably between 1 and 5 mm.

The compacted intermediate is received from the compaction rolls in form of ribbons which are directly broken up into granules by a granulation-unit with a mesh size between 0.5 mm and 1.6 mm, resulting the compacted intermediate in form of granules. In the second step subsequently the granules are sieved by a sieving machine, as e.g. an oscillating or conical sieving machine or hammer mill, with a mesh size of 0.5 to 2.0 mm, preferably about 1.0 mm, resulting the compacted intermediate in the form of a powder. Optionally a second sieving step is performed, whereas this one should be conducted with a mesh size of 0.3 to 0.5 mm, preferably about 0.5 mm.

Process for Preparing Intermediate Blends and Final Blends

Intermediate Blends:

Any intermediate blends comprising 1a in form of a powder are prepared by mixing the API with carrier, binder or combination thereof, glidants, colorants and solid flavours in a freefall or tumble blender.

Final Blends:

Oral Powders:

The intermediate blend comprising 1a in form of a powder is mixed with carriers, binders, glidants, colorants and solid flavours in a freefall or tumble blender.

Oral Granules:

The intermediate blend comprising 1a in form of a powder is mixed with fillers carriers, binders, solid binders, colorants and solid flavours in a freefall or

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tumble blender. The blend is compacted on a roller compactor and broken up by a granulation-unit with a mesh size of about 2 mm.

Pellets in Capsules:

The intermediate blend comprising 1a in form of a powder is mixed with solid polyethylene glycol and microcrystalline cellulose and extruded through a heated extruder. The pellets are spheronized. After spheronization the resulting pellets are filled in capsules, e.g. hard gelatin or HPMC capsules.

Tablets and Filmcoated Tablets:

The intermediate blend comprising 1a in form of a powder is mixed with fillers carriers, binders, glidants and disintegrants in a freefall or tumble blender. Finally the lubricant is added to the main-blend and further mixing is performed.

Process for Preparing the Solid Oral Formulations

Oral Powders:

The final powder blend is filled in sachets.

Oral Granules:

The granules are filled in sachets.

Pellets in Capsules:

After spheronization the resulting pellets are filled in capsules, e.g. hard gelatin or HPMC capsules.

Tablets and Filmcoated Tablets:

The final blend is compressed on a suitable tablet press to produce tablets by an adequate compression force to obtain the quality parameters with regard to resistance to crushing, tablet height and disintegration.

Optionally the tablet cores are coated in a drum-coater by a coating suspension e.g. using a Glatt GC 550/750 or GC 1250 coater.

TABLE 1

Exemplary composition of solid Tablets comprising 1a						
Ingredient	% per tablet	Formulation				
		A mg per tablet	B mg per tablet	C mg per tablet	D mg per tablet	E mg per tablet
1a, un-milled (corresponding to free base 1)	16.42	29.5600 (20.0000)	44.3400 (30.0000)	59.1200 (40.0000)	73.9000 (50.0000)	103.4600 (70.0000)
Lactose monohydrate	68.81	123.8600	185.7900	247.7200	309.6500	433.5100
Microcrystalline cellulose	10.27	18.4800	27.7200	36.9600	46.2000	64.6800
Crospovidone	2.00	3.6000	5.4000	7.2000	9.0000	12.6000
Colloidal anhydrous silica*	0.50	0.9000	1.3500	1.8000	2.2500	3.1500
Magnesium stearate	2.00	3.6000	5.4000	7.2000	9.0000	12.6000
Total	100.00	180.0000	270.0000	360.0000	450.0000	630.0000

Formulations A, B and C, D and E are tablets which can be coated with a film-coat according to Table 2.

TABLE 2

Exemplary composition of filmcoatings for Formulation A-E					
Ingredient	Coating for Formulation				
	A	B	C	D	E
	mg per tablet				
Hypromellose	2.5000	3.5000	4.0000	5.0000	6.0000
Polyethylene glycol 400	0.5000	0.7000	0.8000	1.0000	1.2000

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TABLE 2-continued

Exemplary composition of filmcoatings for Formulation A-E					
Ingredient	Coating for Formulation				
	A	B	C	D	E
	mg per tablet				
Titanium dioxide	1.1300	0.6825	1.8080	0.9750	1.1700
Indigo Carmine aluminum lake	0.0700	0.2450	0.1120	0.3500	0.4200
Talcum	0.6500	1.6625	1.0400	2.3750	2.8500
Polysorbate 80	0.1500	0.2100	0.2400	0.3000	0.3600
Purified water (volatile component)	—	—	—	—	—
Total	5.0000	7.0000	8.0000	10.0000	12.0000

EXAMPLE 4: WATER CONTENT/BIAMPEROMETRIC KARL FISCHER TITRATION

Solvents and Reagents

Solvent: Methanol, anhydrous

Titrant: Hydranal® Composite 1^(*)

^(*) Hydranal® is a registered trademark of Sigma-Aldrich Biotechnology LP and Sigma-Aldrich Co. Hydranal® Composite 1 is a single component pyridine-free Karl Fischer reagent, Sigma-Aldrich® product ID 34827.

Procedure

Apparatus: Karl Fischer apparatus

Syringe 5.0 mL (Hamilton)

Parameter:		
Titrant	Minimum volume increment	Stop drift
Composite 1	6 µL	70 µL/min

Determination: Four film-coated tablets are accurately weighed into a 50 mL injection vial, immediately 25 mL

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anhydrous methanol is added and the vial will be directly tightly closed with a septum and a crimp cap. After 3 hours of shaking (automated equipment) and about 20 hours of sedimentation time a 4.0 mL aliquot is removed with a syringe and transferred into the titration vessel, which contains about 30 mL pre-titrated methanol. Blank titration of extraction vial:

25 mL of anhydrous methanol is added into a 50 mL injection vial (n=2) and the vial will be directly tightly closed with a septum and a crimp cap. After 3 hours of shaking (automated equipment) and about 20 hours of sedimentation time a 4.0 mL aliquot is removed with a syringe and transferred into the titration vessel, which contains about 30 mL pre-titrated methanol.

Sample preparation/determination scheme	
number of separately prepared samples	1

Film-coated tablets should be handled open as short as possible.

Water content [%] is calculated as follows:

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a=volume of Karl Fischer solution required to titrate the test sample [mL]

b=average volume of Karl Fischer solution required for blank titration [mL]

F=factor of titrant [mg water/mL]

WtTS=weight of test sample [mg]

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cup Immediately place the sample into the measurement chamber. Close the instrument and start the measurement with the Start/Stop button. When the a_w -value becomes "stable", the green LED lights up and the a_w -value is displayed.

Sample preparation/determination scheme	
number of determinations	1

Film-coated tablets should be handled open as short as possible.

The invention claimed is:

1. A pharmaceutical composition comprising BIBW 2992 or a salt thereof as the active product ingredient (API) and at least one further excipient, characterized by a water activity of the formulation of not more than 0.17.

2. A pharmaceutical composition comprising BIBW 2992 or a salt thereof as the active product ingredient (API) and at least one further excipient, characterized by a water content of not more than 4.0% as measured by Karl Fischer titration method.

3. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is an uncoated or film-coated tablet.

4. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is selected from uncoated and film-coated tablets comprising BIBW 2992 dimaleate salt as the active product ingredient (API) and each of the tablets is a composition selected from the group consisting of compositions A, B, C, D and E:

Ingredient	% per tablet	Formulation				
		A mg per tablet	B mg per tablet	C mg per tablet	D mg per tablet	E mg per tablet
BIBW 2992 MA ₂ , un-milled (corresponding to free base BIBW 2992)	16.42	29.5600 (20.0000)	44.3400 (30.0000)	59.1200 (40.0000)	73.9000 (50.0000)	103.4600 (70.0000)
Lactose monohydrate	68.81	123.8600	185.7900	247.7200	309.6500	433.5100
Microcrystalline cellulose	10.27	18.4800	27.7200	36.9600	46.2000	64.6800
Crospovidone	2.00	3.6000	5.4000	7.2000	9.0000	12.6000
Colloidal anhydrous silica	0.50	0.9000	1.3500	1.8000	2.2500	3.1500
Magnesium stearate	2.00	3.6000	5.4000	7.2000	9.0000	12.6000
Total	100.00	180.0000	270.0000	360.0000	450.0000	630.0000

EXAMPLE 5: WATER CONTENT/DETERMINATION OF WATER ACTIVITY

Procedure

Apparatus: e.g. Novasina Labmaster a_w

Parameter:	Temperature	25° C.
	Obs. Time aw	1 min
	Obs. Time temp.	1 min

Determination: Fill 20 film-coated tablets (20 mg, 30 mg, or 40 mg) or 15 film-coated tablets (50 mg) into a sample

and wherein said film coat, if present, is selected from the group consisting of formulations A, B, C, D and E:

Ingredient	Coating for Formulation				
	A	B	C	D	E
Hypromellose	2.5000	3.5000	4.0000	5.0000	6.0000
Polyethylene glycol 400	0.5000	0.7000	0.8000	1.0000	1.2000
Titanium dioxide	1.1300	0.6825	1.8080	0.9750	1.1700
Indigo Carmine aluminum lake	0.0700	0.2450	0.1120	0.3500	0.4200
Talcum	0.6500	1.6625	1.0400	2.3750	2.8500
Polysorbate 80	0.1500	0.2100	0.2400	0.3000	0.3600

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-continued

Ingredient	Coating for Formulation					5
	A	B	C	D	E	
Purified water (volatile component)	—	—	—	—	—	
Total	5.0000	7.0000	8.0000	10.0000	12.0000.	10

5. The pharmaceutical composition according to claim 4, wherein each of the tablets is a composition selected from the group consisting of compositions A, B, C and D.

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