Liza M. Walsh
Christine I. Gannon
WALSH PIZZI O'REILLY FALANGA LLP
One Riverfront Plaza
1037 Raymond Boulevard, 6th Floor
Newark, New Jersey 07102
Phone: (973) 757-1100
Fax: (973) 757-1090
lwalsh@walsh.law
cgannon@walsh.law

Attorneys for Plaintiffs
Genzyme Corporation and
sanofi-aventis U.S. LLC

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

GENZYME CORPORATION and SANOFI-AVENTIS U.S. LLC,	)	Civil Action No.
Plaintiffs,	)	
v.	)	**COMPLAINT**
ZYDUS PHARMACEUTICALS (USA) INC.,	)	
Defendant.	)	*Electronically Filed*

Plaintiffs, Genzyme Corporation ("Genzyme") and sanofi-aventis U.S. LLC ("Sanofi"), by their attorneys, for their complaint against Zydus Pharmaceuticals (USA) Inc. ("Zydus"), hereby allege as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement of U.S. Patent Nos. 7,897,590 ("the '590 patent") and 6,987,102 ("the '102 patent") arising under the Patent Laws of the United States, Title 35, United States Code, Sections 100 *et seq*.

2. This action relates to the following Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA"): ANDA No. 208980 filed by Zydus for approval to market Plerixafor Injection 20 mg/mL, 1.2mL, a proposed generic version of Genzyme's Mozobil® drug product.

THE PARTIES

3. Plaintiff Genzyme is a corporation organized and existing under the laws of the State of Massachusetts, having its principal place of business at 500 Kendall Street, Cambridge, Massachusetts 02142.

4. Plaintiff Sanofi is a limited liability company organized and existing under the laws of the State of Delaware with its principal place of business at 55 Corporate Drive, Bridgewater, New Jersey 08807.

5. On information and belief, Defendant Zydus is a corporation organized and existing under the laws of the State of New Jersey having a place of business at 73 Route 31 N., Pennington, New Jersey 08534. Upon information and belief, Defendant Zydus manufactures and/or distributes numerous generic drugs for sale and use throughout the United States, including in this District.

JURISDICTION AND VENUE

6. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 1400(b), 2201, and 2202.

7. On information and belief, Zydus is in the business of, among other things, developing, preparing, manufacturing, selling, marketing, importing, and distributing generic pharmaceutical products throughout the United States, including the State of New Jersey.

8. This Court has personal jurisdiction over Zydus because, *inter alia*, on information and belief, Zydus: (1) is incorporated in and maintains a principal place of business at 73 Route 31 N., Pennington, New Jersey 08534; (2) has substantial, continuous, and systematic contacts with this State; (3) is registered to do business in New Jersey under entity ID #0100915422; (4) regularly does or solicits business in New Jersey through its marketing and distribution of generic pharmaceutical products; (5) is registered as a Wholesale Drug & Medical Device wholesaler by the New Jersey Department of Health and Senior Services; (6) enjoys substantial revenue from sales of its generic pharmaceutical products in this state.

9. This Court also has personal jurisdiction over Zydus because, *inter alia*, Zydus's filing of ANDA No. 208980 has caused tortious injury in New Jersey, namely from the tort of patent infringement under 35 U.S.C. § 271(e)(2) and because Zydus intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in this District. For example, on information and belief, following approval of ANDA No. 208980, Zydus will make, use, sell, offer for sale, and/or import its Plerixafor ANDA Injection Product in/into the United States, including the state of New Jersey, prior to the expiration of the '590 patent and the '102 patent.

10. Venue is proper in this judicial District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENTS AND ACTS GIVING RISE TO THIS ACTION

11. Genzyme is the holder of New Drug Application ("NDA") No. 022311, which relates to Plerixafor solution 20 mg/mL for subcutaneous injection (the "Mozobil® NDA"). On December 15, 2008, the FDA approved the marketing of the drug product described in NDA No. 022311 for use in combination with granulocyte-colony stimulating factor ("G-CSF") to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma (the "Approved Indication"). This drug product is prescribed and sold in the United States using the trademark Mozobil®. Usage of this drug product and the Approved Indication are described in the Mozobil® Prescribing Information (a true and accurate copy of which is attached hereto as Exhibit A). Genzyme and Sanofi both share in the profits from the sale of Mozobil®.

12. United States Patent No. 7,897,590 (a true and accurate copy of which is attached hereto as Exhibit B) was duly and legally issued on March 1, 2011 to inventors Gary J. Bridger, Michael J. Abrams, Geoffrey W. Henson, Ronald Trevor MacFarland, Gary B. Calandra, Hal E. Broxmeyer, and David C. Dale. With patent term adjustment, the '590 patent will expire on July 22, 2023. At all times from the issuance of the '590 patent to the present, Genzyme has been the owner of the '590 patent. Sanofi is Genzyme's exclusive licensee under the '590 patent.

13. United States Patent No. 6,987,102 (a true and accurate copy of which is attached hereto as Exhibit C) was duly and legally issued on January 17, 2006 to inventors Gary J. Bridger, Michael J. Abrams, Geoffrey W. Henson, Ronald Trevor MacFarland, Gary B. Calandra, Hal E. Broxmeyer, and David C. Dale. The '102 patent was assigned to Anormed, Inc., which then assigned the '102 patent to Genzyme in 2008. With patent term adjustment, the

‘102 patent will expire on July 22, 2023. Since 2008, Genzyme has been the owner of the ‘102 patent. Sanofi is Genzyme’s exclusive licensee under the ‘102 patent.

14. The ‘590 patent and ‘102 patent cover the use of Mozobil® according to its Approved Indication.

15. By letter dated May 17, 2016, purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B) (“Notice Letter”), Zydus notified Genzyme that Zydus had submitted ANDA No. 208980 to the FDA under section 505(j) of the Federal Food Drug and Cosmetic Act (21 U.S.C. § 355(j)) seeking approval to engage in the commercial manufacture, importation, use, and sale of 20 mg/mL Plerixafor injection (“Plerixafor ANDA Injection Product”) as a generic version of Genzyme’s Mozobil® drug product prior to the expiration of the ‘590 and ‘102 patents.

16. In addition to the information provided to Plaintiffs in the Notice Letter, counsel for Plaintiffs reviewed the portions of ANDA No. 208980 voluntarily provided by Zydus under the terms of a confidentiality agreement.

17. On information and belief, the active ingredient of the Plerixafor ANDA Injection Product is plerixafor, which is the same active ingredient in Mozobil® and the same active ingredient used in the methods of one or more claims of the ‘590 and ‘102 patents, including, but not limited to, claim 19 of the ‘590 patent and claim 1 of the ‘102 patent.

18. On information and belief, Zydus stated in its ANDA No. 208980 that its Plerixafor ANDA Injection Product is bioequivalent to Genzyme’s Mozobil® drug product. On information and belief, Zydus’s ANDA No. 208980 refers to and relies upon the Mozobil® NDA and contains data that, according to Zydus, demonstrate the bioequivalence of Zydus’s Plerixafor ANDA Injection Product and Mozobil®.

19. On information and belief, Zydus is seeking approval to market its Plerixafor ANDA Injection Product for the same Approved Indication as Genzyme's Mozobil® drug product.

20. On information and belief, Zydus will knowingly accompany its Plerixafor ANDA Injection Product with prescribing information that is substantially similar to the Mozobil® Prescribing Information.

21. Upon information and belief, Zydus's prescribing information for its Plerixafor ANDA Injection Product will instruct users to administer Zydus's Plerixafor Injection Product to human patients to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation.

22. Upon information and belief, Zydus's prescribing information for its Plerixafor ANDA Injection Product will instruct users to administer its Plerixafor Injection Product to human patients after the patients have received granulocyte-colony stimulating factor (G-CSF).

23. Upon information and belief, Zydus has knowledge and/or an expectation that its Plerixafor ANDA Injection Product will be used in accordance with its prescribing information.

24. On information and belief, Zydus knows that the prescribing information for its Plerixafor ANDA Injection Product will induce and/or contribute to others using the Plerixafor ANDA Injection Product in the manner set forth in the prescribing information.

25. On information and belief, physicians, health care providers, and/or patients will directly infringe one or more claims of the '590 patent and the '102 patent, including, but not limited to, claim 19 of the '590 patent and claim 1 of the '102 patent, by using Zydus Plerixafor ANDA Injection Product in accordance with the prescribing information provided by Zydus after the FDA approves ANDA No. 208980.

26. On information and belief, Zydus specifically intends that physicians, health care providers, and/or patients will use the Plerixafor ANDA Injection Product in accordance with the prescribing information provided by Zydus to directly infringe one or more claims of the '590 patent and the '102 patent, including, but not limited to, claim 19 of the '590 patent and claim 1 of the '102 patent.

27. On information and belief, Zydus designed the Plerixafor ANDA Injection Product for use in a way that would infringe the '590 patent and the '102 patent and will instruct users of the Plerixafor ANDA Injection Product to use the Plerixafor ANDA Injection Product in a way that would infringe one or more claims of the '590 patent and the '102 patent, including, but not limited to, claim 19 of the '590 patent and claim 1 of the '102 patent.

28. On information and belief, the Plerixafor ANDA Injection Product is not a staple article or commodity of commerce suitable for substantial non-infringing use.

29. On information and belief, Zydus knowingly has taken and intends to take active steps to induce and/or contribute to physicians, health care providers, and/or patients using the Plerixafor ANDA Injection Product in a manner that directly infringes one or more claims of the '590 patent and the '102 patent, including but not limited to by providing instructions for administering the Plerixafor ANDA Injection Product as claimed in one or more claims of the '590 patent and the '102 patent, including, but not limited to, claim 19 of the '590 patent and claim 1 of the '102 patent.

30. Zydus has knowledge of the '590 patent and the '102 patent.

31. Zydus's ANDA was submitted to obtain FDA approval to engage in the commercial manufacture, importation, use, and sale of Zydus's Plerixafor ANDA Injection Product prior to the expiration of the '590 and '102 patents, both of which are listed in the FDA

publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluation" (the "Orange Book") as being applicable to Genzyme's Mozobil® drug product.

32. On information and belief, Zydus intends to engage in the commercial manufacture, importation, use, sale, and/or offering for sale of its Plerixafor ANDA Injection Product in/into the United States and/or induce or contribute to such acts promptly upon receiving FDA approval to do so and during the terms of the '590 and '102 patents.

33. In the Notice Letter, Zydus notified Genzyme that its ANDA contained a "paragraph IV" certification that, in Zydus's opinion, the '590 patent and '102 patent are invalid or will not be infringed by the manufacture, use, sale, offer to sell, or importation of Zydus's Plerixafor ANDA Injection Product in/into the United States.

34. Zydus is aware of the decision issued by the U.S. District Court for the District of Delaware on May 11, 2016 (Docket No. 215) in *Genzyme Corporation and Sanofi-Aventis U.S. LLC v. Dr. Reddy's Laboratories, Ltd and Dr. Reddy's Laboratories, Inc. and Teva Pharmaceuticals USA, Inc.*, 1:13-cv-1506-GMS, finding claim 19 of the '590 patent not invalid. Upon information and belief, the bases for Zydus's opinion that the '590 and '102 patents are invalid, as set forth in Zydus's Notice Letter, are substantially similar to those addressed in the decision issued by the U.S. District Court for the District of Delaware in 1:13-cv-1506-GMS, Docket No. 215.

35. Plaintiffs commenced this action within 45 days of receiving the Notice Letter.

COUNT I
INFRINGEMENT BY ZYDUS OF U.S. PATENT NO. 7,897,590

36. Plaintiffs repeat and reallege the allegations of paragraphs 1-35 as if fully set forth herein.

37. Zydus's submission of its ANDA to obtain approval from the FDA to engage in the commercial manufacture, importation, use, or sale of its Plerixafor ANDA Injection Product in/into the United States prior to the expiration of the '590 patent constitutes infringement of one or more of the claims of the '590 patent, including but not limited to claims 1-8, 16-19, and 21-22, under 35 U.S.C. § 271(e)(2).

38. Upon FDA approval, Zydus's commercial manufacture, importation, use, offer to sell, or sale of its Plerixafor ANDA Injection Product in/into the United States prior to the expiration of the '590 patent will infringe one or more claims of the '590 patent, including but not limited to claims 1-8, 16-19, and 21-22, under 35 U.S.C. §§ 271(a), (b), and/or (c), unless enjoined by the Court.

39. Zydus's ANDA and Zydus's intent to engage in the commercial manufacture, importation, use, sale, or offer for sale of its Plerixafor ANDA Injection Product in/into the United States upon receiving FDA approval and prior to the expiration of the '590 patent create an actual case or controversy with respect to infringement of one or more claims of the '590 patent, including but not limited to claims 1-8, 16-19, and 21-22.

40. Upon FDA approval of Zydus's ANDA, use of the Zydus ANDA Plerixafor Injection in accordance with the prescribing information to be provided by Zydus will directly infringe one or more claims of the '590 patent, including but not limited to claims 1-8, 16-19, and 21-22, under 35 U.S.C. § 271(a), unless enjoined by this Court.

41. Upon FDA approval of Zydus's ANDA, Zydus will infringe one or more claims of the '590 patent, including but not limited to claims 1-8, 16-19, and 21-22, under 35 U.S.C. § 271(b) and (c) by actively inducing and contributing to infringement by others, unless enjoined by this Court.

42. Zydus has knowledge of the '590 patent and, by the prescribing information it will include with its Plerixafor ANDA Injection Product, knows or should know that it will aid and abet another's direct infringement of at least one of the claims of the '590 patent, including but not limited to claims 1-8, 16-19, and 21-22.

43. Zydus's offering for sale, sale, and/or importation of the Plerixafor ANDA Injection Product in/into the United States with the prescribing information for the Plerixafor ANDA Injection Product will actively induce infringement of at least one of the claims of the '590 patent, including but not limited to claims 1-8, 16-19, and 21-22, under 35 U.S.C. § 271(b).

44. Use of the Plerixafor ANDA Injection Product constitutes a material part of at least one of the claims of the '590 patent; Zydus knows that the Plerixafor ANDA Injection Product is especially made or adapted for use in infringing at least one of the claims of the '590 patent, including but not limited to claims 1-8, 16-19, and 21-22; and Zydus knows that the Plerixafor ANDA Injection Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

45. Zydus's manufacture, use, offering for sale, sale, and/or importation of the Plerixafor ANDA Injection Product in/into the United States will contributorily infringe at least one of the claims of the '590 patent, including but not limited to claims 1-8, 16-19, and 21-22, under 35 U.S.C. § 271(c).

46. Zydus had and will have notice of the '590 patent at the time of its infringement. Zydus also had notice of the decision issued by U.S. District Court for the District of Delaware in 1:13-cv-1506-GMS, Docket No. 215 holding that claim 19 of the '590 patent is not invalid. Zydus's infringement has been, continues to be and will be deliberate and willful.

47. Plaintiffs will be substantially and irreparably harmed if Zydus's infringement is not enjoined. Plaintiffs do not have an adequate remedy at law.

48. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorney fees.

COUNT II
INFRINGEMENT BY ZYDUS OF U.S. PATENT NO. 6,987,102

49. Plaintiffs repeat and reallege the allegations of paragraphs 1-48 as if fully set forth herein.

50. Zydus's submission of its ANDA to obtain approval from the FDA to engage in the commercial manufacture, importation, use, or sale of its Plerixafor ANDA Injection Product in/into the United States prior to the expiration of the '102 patent constitutes infringement of one or more of the claims of the '102 patent, including but not limited to claims 1-8, 12-13, 15-16, and 21-22, under 35 U.S.C. § 271(e)(2).

51. Upon FDA approval, Zydus's commercial manufacture, importation, use, offer to sell, or sale of its Plerixafor ANDA Injection Product in/into the United States prior to the expiration of the '102 patent will infringe one or more claims of the '102 patent, including but not limited to claims 1-8, 12-13, 15-16, and 21-22, under 35 U.S.C. § 271(a), (b), and/or (c), unless enjoined by the Court.

52. Zydus's ANDA and Zydus's intent to engage in the commercial manufacture, importation, use, sale, or offer for sale of its Plerixafor ANDA Injection Product in/into the United States upon receiving FDA approval and prior to the expiration of the '102 patent create an actual case or controversy with respect to infringement of one or more claims of the '102 patent, including but not limited to claims 1-8, 12-13, 15-16, and 21-22.

53. Upon FDA approval of Zydus's ANDA, use of the Zydus ANDA Plerixafor Injection in accordance with the prescribing information to be provided by Zydus will directly infringe one or more claims of the '102 patent, including but not limited to claims 1-8, 12-13, 15-16, and 21-22, under 35 U.S.C. § 271(a), unless enjoined by this Court.

54. Upon FDA approval of Zydus's ANDA, Zydus will infringe one or more claims of the '102 patent, including but not limited to claims 1-8, 12-13, 15-16, and 21-22, under 35 U.S.C. § 271(b) and (c) by actively inducing and contributing to infringement by others, unless enjoined by this Court.

55. Zydus has knowledge of the '102 patent and, by the prescribing information it will include with its Plerixafor ANDA Injection Product, knows or should know that it will aid and abet another's direct infringement of at least one of the claims of the '102 patent, including but not limited to claims 1-8, 12-13, 15-16, and 21-22.

56. Zydus's offering for sale, sale, and/or importation of the Plerixafor ANDA Injection Product in/into the United States with the prescribing information for the Plerixafor ANDA Injection Product will actively induce infringement of at least one of the claims of the '102 patent, including but not limited to claims 1-8, 12-13, 15-16, and 21-22, under 35 U.S.C. § 271(b).

57. Use of the Plerixafor ANDA Injection Product constitutes a material part of at least one of the claims of the '102 patent; Zydus knows that the Plerixafor ANDA Injection Product is especially made or adapted for use in infringing at least one of the claims of the '102 patent, including but not limited to claims 1-8, 12-13, 15-16, and 21-22; and Zydus knows that the Plerixafor ANDA Injection Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

58. Zydus's manufacture, use, offering for sale, sale, and/or importation of the Plerixafor ANDA Injection Product in/into the United States will contributorily infringe at least one of the claims of the '102 patent, including but not limited to claims 1-8, 12-13, 15-16, and 21-22, under 35 U.S.C. § 271(c).

59. Zydus had and will have notice of the '102 patent at the time of its infringement. Zydus also had notice of the decision issued by the U.S. District Court for the District of Delaware in 1:13-cv-1506-GMS, Docket No. 215 holding that claim 19 of the '590 patent is not invalid. Zydus's infringement has been, continues to be, and will be deliberate and willful.

60. Plaintiffs will be substantially and irreparably harmed if Zydus's infringement is not enjoined. Plaintiffs do not have an adequate remedy at law.

61. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorney fees.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

(a) A judgment declaring that Zydus has infringed, and that Zydus's making, using, selling, offering to sell, or importing its Plerixafor ANDA Injection Product in/into the United States will infringe one or more claims of the '590 patent;

(b) A judgment declaring that Zydus has infringed, and that Zydus's making, using, selling, offering to sell, or importing its Plerixafor ANDA Injection Product in/into the United States will infringe one or more claims of the '102 patent;

(c) A judgment under 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any FDA approval of Zydus's ANDA No. 208980 under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) be a date no earlier than July 22, 2023, the

date on which the '590 patent and the '102 patent expire, or the expiration of any other exclusivity to which Plaintiffs become entitled;

(d) Injunctive relief under 35 U.S.C. § 271(e)(4)(B) permanently enjoining Zydus from making, using, selling, offering to sell, or importing its Plerixafor ANDA Injection Product in/into the United States until after July 22, 2023, the date on which the '590 patent and the '102 patent expire, or the expiration of any other exclusivity to which Plaintiffs become entitled;

(e) Damages under 35 U.S.C. § 271(e)(4)(C), which this Court should treble pursuant to 35 U.S.C. § 284, if Zydus infringes the '590 patent or the '102 patent by engaging in the commercial manufacture, importation, use, offer to sell, or sale of its Plerixafor ANDA Injection Product in/into the United States prior to the expiration of the '590 patent and the '102 patent, or the expiration of any other exclusivity to which Plaintiffs become entitled;

(f) A determination that Zydus's infringement is deliberate and willful;

(g) An award of reasonable attorney fees in this action pursuant to 35 U.S.C. § 285;

(h) Costs and expenses in this action; and

(i) Such further and other relief as this Court may deem just and proper.

DATED: June 30, 2016

WALSH PIZZI O'REILLY FALANGA LLP

Of Counsel:
Paul H. Berghoff
Paula S. Fritsch
Jeremy E. Noe
Alison J. Baldwin
Kurt W. Rohde
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

s/ Liza M. Walsh
Liza M. Walsh
Christine I. Gannon
One Riverfront Plaza
1037 Raymond Boulevard, 6th Floor
Newark, New Jersey 07102
Phone: (973) 757-1100
Fax: (973) 757-1090
lwalsh@walsh.law
cgannon@walsh.law

Attorneys for Plaintiffs
Genzyme Corporation and
sanofi-aventis U.S. LLC

RULE 11.2 CERTIFICATION

I hereby certify that the matter in controversy is related to the following action in the United States District Court, District of Delaware: *Genzyme Corp. et al. v. Zydus Pharmaceuticals (USA) Inc.*, Civil Action No. 16-0540, filed June 29, 2016.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other pending or anticipated litigation in any court or arbitration proceeding other than the above referenced matter, nor are there any non-parties known to Plaintiffs that should be joined to this action. In addition, I recognize a continuing obligation during the course of this litigation to file and to serve on all other parties and with the Court an amended certification if there is a change in the facts stated in this original certification.

DATED: June 30, 2016

WALSH PIZZI O'REILLY FALANGA LLP

s/ Liza M. Walsh

Liza M. Walsh
Christine I. Gannon
One Riverfront Plaza
1037 Raymond Boulevard, 6th Floor
Newark, New Jersey 07102
Phone: (973) 757-1100
Fax: (973) 757-1090
lwalsh@walsh.law
cgannon@walsh.law

Attorneys for Plaintiffs
Genzyme Corporation and
sanofi-aventis U.S. LLC

Of Counsel:
Paul H. Berghoff
Paula S. Fritsch
Jeremy E. Noe
Alison J. Baldwin
Kurt W. Rohde
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

RULE 201.1 CERTIFICATION

We hereby certify that the above-captioned matter is not subject to compulsory arbitration in that the Plaintiffs seek, *inter alia*, injunctive relief.

DATED: June 30, 2016

WALSH PIZZI O'REILLY FALANGA LLP

s/ Liza M. Walsh

Liza M. Walsh
Christine I. Gannon
One Riverfront Plaza
1037 Raymond Boulevard, 6th Floor
Newark, New Jersey 07102
Phone: (973) 757-1100
Fax: (973) 757-1090
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Kurt W. Rohde
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

EXHIBIT A

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MOZOBIL safely and effectively. See full prescribing information for MOZOBIL.

MOZOBIL (plerixafor) Injection, for subcutaneous use
Initial U.S. Approval: 2008

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.1, 2.3) 08/2015

----------INDICATIONS AND USAGE----------
Mozobil, a hematopoietic stem cell mobilizer, is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma. (1)

----------DOSAGE AND ADMINISTRATION----------
- Initiate Mozobil treatment after the patient has received G-CSF once daily for 4 days. (2.1)
- Repeat Mozobil dose up to 4 consecutive days. (2.1)
- Dose based on patient weight
  - ≤ 83 kg: 20 mg dose or select dose based on 0.24 mg/kg actual body weight. (2.1)
  - > 83 kg: select dose based on 0.24 mg/kg actual body weight.(2.1)
- Administer by subcutaneous injection approximately 11 hours prior to initiation of apheresis. (2.1)
- Renal impairment: If creatinine clearance is ≤ 50 mL/min, decrease dose by one-third to 0.16 mg/kg. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Single-use vial containing 1.2 mL of a 20 mg/mL solution. (3)

----------CONTRAINDICATIONS----------
- History of hypersensitivity to Mozobil. (4)

----------WARNINGS AND PRECAUTIONS----------
- Anaphylactic shock and Serious Hypersensitivity Reactions have occurred. Monitor patients during and after completion of Mozobil administration. (5.1)
- Tumor Cell Mobilization in Leukemia Patients: Mozobil may mobilize leukemic cells and should not be used in leukemia patients. (5.2)
- Hematologic Effects: Increased circulating leukocytes and decreased platelet counts have been observed. Monitor blood cell counts and platelet counts during Mozobil use. (5.3)
- Potential for Tumor Cell Mobilization: Tumor cells may be released from marrow during HSC mobilization with Mozobil and G-CSF. Effect of reinfusion of tumor cells is unknown. (5.4)
- Potential for Splenic Rupture: Evaluate patients who report left upper abdominal and/or scapular or shoulder pain. (5.5)
- Embryo-fetal Toxicity: May cause fetal harm. Advise women not to become pregnant when taking Mozobil. (5.6, 8.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥ 10%): diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness, and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-877-4MOZOBIL or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Mozobil® (plerixafor injection) is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration

Vials should be inspected visually for particulate matter and discoloration prior to administration and should not be used if there is particulate matter or if the solution is discolored.

Begin treatment with Mozobil after the patient has received G-CSF once daily for four days. *[see Dosage and Administration (2.2)]* Administer Mozobil approximately 11 hours prior to initiation of each apheresis for up to 4 consecutive days.

The recommended dose of Mozobil by subcutaneous injection is based on body weight:

- 20 mg fixed dose or 0.24 mg/kg of body weight for patients weighing ≤83 kg. *[see Clinical Pharmacology (12.3)]*
- 0.24 mg/kg of body weight for patients weighing >83 kg.

Use the patient's actual body weight to calculate the volume of Mozobil to be administered. Each vial delivers 1.2 mL of 20 mg/mL solution, and the volume to be administered to patients should be calculated from the following equation:

0.012 X patient's actual body weight (in kg) = volume to be administered (in mL)

In clinical studies, Mozobil dose has been calculated based on actual body weight in patients up to 175% of ideal body weight. Mozobil dose and treatment of patients weighing more than 175% of ideal body weight have not been investigated.

Based on increasing exposure with increasing body weight, the Mozobil dose should not exceed 40 mg/day. *[see Clinical Pharmacology (12.3)]*

2.2 Recommended Concomitant Medications

Administer daily morning doses of G-CSF 10 micrograms/kg for 4 days prior to the first evening dose of Mozobil and on each day prior to apheresis. *[see Clinical Studies (14)]*

2.3 Dosing in Renal Impairment

In patients with moderate and severe renal impairment (estimated creatinine clearance (CL_{CR}) ≤ 50 mL/min), reduce the dose of Mozobil by one-third based on body weight category as shown in Table 1. If CL_{CR} is ≤ 50 mL/min the dose should not exceed 27 mg/day, as the mg/kg-based dosage results in increased plerixafor exposure with increasing body weight. *[see Clinical Pharmacology (12.3)]* Similar systemic exposure is predicted if the dose is reduced by one-third

in patients with moderate and severe renal impairment compared with subjects with normal renal function. *[see Clinical Pharmacology (12.3)]*

Table 1: Recommended Dosage of Mozobil in Patients with Renal Impairment

Estimated Creatinine Clearance (mL/min)	Dose	
	Body Weight ≤ 83 kg	**Body Weight > 83 kg and < 160 kg**
> 50	20 mg or 0.24 mg/kg once daily	0.24 mg/kg once daily (not to exceed 40 mg/day)
≤ 50	13 mg or 0.16 mg/kg once daily	0.16 mg/kg once daily (not to exceed 27 mg/day)

The following (Cockroft-Gault) formula may be used to estimate CL_{CR}:

Males:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{weight (kg) X (140 – age in years)}}{\text{72 X serum creatinine (mg/dL)}}$$

Females:

Creatinine clearance (mL/min) = 0.85 X value calculated for males

There is insufficient information to make dosage recommendations in patients on hemodialysis.

3 DOSAGE FORMS AND STRENGTHS

Single-use vial containing 1.2 mL of a 20 mg/mL solution.

4 CONTRAINDICATIONS

History of hypersensitivity to Mozobil *[see Warnings and Precautions (5.1)]*. Anaphylactic shock has occurred with use of Mozobil.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylactic shock and Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening with clinically significant hypotension and shock have occurred in patients receiving Mozobil *[see Adverse Reactions (6.2)]*. Observe patients for signs and symptoms of hypersensitivity during and after Mozobil administration for at least 30 minutes and until clinically stable following completion of each administration. Only administer Mozobil when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.

In clinical studies, mild or moderate allergic reactions occurred within approximately 30 minutes after Mozobil administration in less than 1% of patients *[see Adverse Reactions (6.1)]*.

5.2 Tumor Cell Mobilization in Leukemia Patients

For the purpose of HSC mobilization, Mozobil may cause mobilization of leukemic cells and subsequent contamination of the apheresis product. Therefore, Mozobil is not intended for HSC mobilization and harvest in patients with leukemia.

5.3 Hematologic Effects

Leukocytosis

Administration of Mozobil in conjunction with G-CSF increases circulating leukocytes as well as HSC populations. Monitor white blood cell counts during Mozobil use. *[see Adverse Reactions (6.1)]*

Thrombocytopenia

Thrombocytopenia has been observed in patients receiving Mozobil. Monitor platelet counts in all patients who receive Mozobil and then undergo apheresis.

5.4 Potential for Tumor Cell Mobilization

When Mozobil is used in combination with G-CSF for HSC mobilization, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of potential reinfusion of tumor cells has not been well-studied.

5.5 Splenic Enlargement and Potential for Rupture

Higher absolute and relative spleen weights associated with extramedullary hematopoiesis were observed following prolonged (2 to 4 weeks) daily plerixafor SC administration in rats at doses approximately 4-fold higher than the recommended human dose based on body surface area. The effect of Mozobil on spleen size in patients was not specifically evaluated in clinical studies. Evaluate individuals receiving Mozobil in combination with G-CSF who report left upper abdominal pain and/or scapular or shoulder pain for splenic integrity.

5.6 Embryo-fetal Toxicity

Mozobil may cause fetal harm when administered to a pregnant woman. Plerixafor is teratogenic in animals. There are no adequate and well-controlled studies in pregnant women using Mozobil. Advise women of childbearing potential to avoid becoming pregnant while receiving treatment with Mozobil. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. *[see Use In Specific Populations (8.1)]*

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Anaphylactic shock and hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Potential for tumor cell mobilization in leukemia patients *[see Warnings and Precautions (5.2)]*
- Increased circulating leukocytes and decreased platelet counts *[see Warnings and Precautions (5.3)]*
- Potential for tumor cell mobilization *[see Warnings and Precautions (5.4)]*
- Potential for splenic enlargement *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trial 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 most common adverse reactions (≥ 10%) reported in patients who received Mozobil in conjunction with G-CSF regardless of causality and more frequent with Mozobil than placebo during HSC mobilization and apheresis were diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness, and vomiting.

Safety data for Mozobil in combination with G-CSF were obtained from two randomized placebo-controlled studies (301 patients) and 10 uncontrolled studies (242 patients). Patients were primarily treated with Mozobil at daily doses of 0.24 mg/kg SC. Median exposure to Mozobil in these studies was 2 days (range 1 to 7 days).

In the two randomized studies in patients with NHL and MM, a total of 301 patients were treated in the Mozobil and G-CSF group and 292 patients were treated in the placebo and G-CSF group. Patients received daily morning doses of G-CSF 10 micrograms/kg for 4 days prior to the first dose of Mozobil 0.24 mg/kg SC or placebo and on each morning prior to apheresis. The adverse reactions that occurred in ≥ 5% of the patients who received Mozobil regardless of causality and were more frequent with Mozobil than placebo during HSC mobilization and apheresis are shown in Table 2.

Table 2: Adverse Reactions in ≥ 5% of Non-Hodgkin's Lymphoma and Multiple Myeloma Patients Receiving Mozobil® and More Frequent than Placebo During HSC Mobilization and Apheresis

	Percent of Patients (%)					
	Mozobil® and G-CSF (n = 301)			Placebo and G-CSF (n = 292)		
	All Grades[a]	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Gastrointestinal disorders						
Diarrhea	37	< 1	0	17	0	0
Nausea	34	1	0	22	0	0
Vomiting	10	< 1	0	6	0	0
Flatulence	7	0	0	3	0	0
General disorders and administration site conditions						
Injection site reactions	34	0	0	10	0	0
Fatigue	27	0	0	25	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	13	0	0	12	0	0
Nervous system disorders						
Headache	22	< 1	0	21	1	0
Dizziness	11	0	0	6	0	0
Psychiatric disorders						

Insomnia	7	0	0	5	0	0

[a]Grades based on criteria from the World Health Organization (WHO)

In the randomized studies, 34% of patients with NHL or MM had mild to moderate injection site reactions at the site of subcutaneous administration of Mozobil. These included erythema, hematoma, hemorrhage, induration, inflammation, irritation, pain, paresthesia, pruritus, rash, swelling, and urticaria.

Mild to moderate allergic reactions were observed in less than 1% of patients within approximately 30 min after Mozobil administration, including one or more of the following: urticaria (n = 2), periorbital swelling (n = 2), dyspnea (n = 1) or hypoxia (n = 1). Symptoms generally responded to treatments (e.g., antihistamines, corticosteroids, hydration or supplemental oxygen) or resolved spontaneously.

Vasovagal reactions, orthostatic hypotension, and/or syncope can occur following subcutaneous injections. In Mozobil oncology and healthy volunteer clinical studies, less than 1% of subjects experienced vasovagal reactions following subcutaneous administration of Mozobil doses ≤ 0.24 mg/kg. The majority of these events occurred within 1 hour of Mozobil administration. Because of the potential for these reactions, appropriate precautions should be taken.

Other adverse reactions in the randomized studies that occurred in < 5% of patients but were reported as related to Mozobil during HSC mobilization and apheresis included abdominal pain, hyperhidrosis, abdominal distention, dry mouth, erythema, stomach discomfort, malaise, hypoesthesia oral, constipation, dyspepsia, and musculoskeletal pain.

Hyperleukocytosis: In clinical trials, white blood cell counts of 100,000/mcL or greater were observed, on the day prior to or any day of apheresis, in 7% of patients receiving Mozobil and in 1% of patients receiving placebo. No complications or clinical symptoms of leukostasis were observed.

6.2 Post-marketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been reported from post-marketing experience with Mozobil. 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.

Immune System Disorders: Anaphylactic reactions, including anaphylactic shock

Psychiatric disorders: Abnormal dreams and nightmares

7 DRUG INTERACTIONS

Based on *in vitro* data, plerixafor is not a substrate, inhibitor or inducer of human cytochrome P450 isozymes. Plerixafor is not likely to be implicated in *in vivo* drug-drug interactions involving cytochrome P450s. At concentrations similar to what are seen clinically, plerixafor did not act as a substrate or inhibitor of P-glycoprotein in an *in vitro* study. *[see Clinical Pharmacology (12.3)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

Mozobil may cause fetal harm when administered to a pregnant woman. Plerixafor is teratogenic in animals.

Animal Data

Plerixafor administered to pregnant rats induced embryo-fetal toxicities including fetal death, increased resorptions and post-implantation loss, decreased fetal weights, anophthalmia, shortened digits, cardiac interventricular septal defect, ringed aorta, globular heart, hydrocephaly, dilatation of olfactory ventricles, and retarded skeletal development. Embryo-fetal toxicities occurred mainly at a dose of 90 mg/m^2 (approximately 10 times the recommended human dose of 0.24 mg/kg when compared on a mg/m^2 basis or 10 times the AUC in subjects with normal renal function who received a single dose of 0.24 mg/kg).

8.3 Nursing Mothers

It is not known whether plerixafor is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Mozobil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of Mozobil in pediatric patients have not been established in controlled clinical studies.

8.5 Geriatric Use

Of the total number of subjects in controlled clinical studies of Mozobil, 24% were 65 and over, while 0.8% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Since plerixafor is mainly excreted by the kidney, no dose modifications are necessary in elderly individuals with normal renal function. In general, care should be taken in dose selection for elderly patients due to the greater frequency of decreased renal function with advanced age. Dosage adjustment in elderly patients with $CL_{CR} \leq 50$ mL/min is recommended. *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*

8.6 Renal Impairment

In patients with moderate and severe renal impairment ($CL_{CR} \leq 50$ mL/min), reduce the dose of Mozobil by one-third to 0.16 mg/kg. *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*

10 OVERDOSAGE

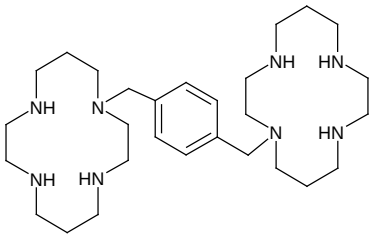
Based on limited data at doses above the recommended dose of 0.24 mg/kg SC, the frequency of gastrointestinal disorders, vasovagal reactions, orthostatic hypotension, and/or syncope may be higher.

11 DESCRIPTION

Mozobil (plerixafor injection) is a sterile, preservative-free, clear, colorless to pale yellow, isotonic solution for subcutaneous injection. Each mL of the sterile solution contains 20 mg of plerixafor. Each single-use vial is filled to deliver 1.2 mL of the sterile solution that contains 24 mg of plerixafor and 5.9 mg of sodium chloride in Water for Injection adjusted to a pH of 6.0 to 7.5 with hydrochloric acid and with sodium hydroxide, if required.

Plerixafor is a hematopoietic stem cell mobilizer with a chemical name l, 1'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11- tetraazacyclotetradecane. It has the molecular formula $C_{28}H_{54}N_{8.}$ The molecular weight of plerixafor is 502.79 g/mol. The structural formula is provided in Figure 1.

Figure 1: Structural Formula



Plerixafor is a white to off-white crystalline solid. It is hygroscopic. Plerixafor has a typical melting point of 131.5 °C. The partition coefficient of plerixafor between 1-octanol and pH 7 aqueous buffer is < 0.1.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Plerixafor is an inhibitor of the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1α (SDF-1α). SDF-1α and CXCR4 are recognized to play a role in the trafficking and homing of human hematopoietic stem cells (HSCs) to the marrow compartment. Once in the marrow, stem cell CXCR4 can act to help anchor these cells to the marrow matrix, either directly via SDF-1α or through the induction of other adhesion molecules. Treatment with plerixafor resulted in leukocytosis and elevations in circulating hematopoietic progenitor cells in mice, dogs and humans. CD34+ cells mobilized by plerixafor were capable of engraftment with long-term repopulating capacity up to one year in canine transplantation models.

12.2 Pharmacodynamics

Data on the fold increase in peripheral blood CD34+ cell count (cells/mcL) by apheresis day were evaluated in two placebo-controlled clinical studies in patients with NHL and MM (Study 1 and Study 2, respectively). The fold increase in CD34+ cell count (cells/mcL) over the 24-hour

period starting from the day prior to the first apheresis and ending the next morning just before the first apheresis is summarized in Table 3. During this 24-hour period, a single dose of Mozobil or placebo was administered 10 to 11 hours prior to apheresis.

Table 3: Fold Increase in Peripheral Blood CD34+ Cell Count Following Pretreatment with G-CSF and Administration of Plerixafor

Study	Mozobil® and G-CSF		Placebo and G-CSF	
	Median	Mean (SD)	Median	Mean (SD)
Study 1	5.0	6.1 (5.4)	1.4	1.9 (1.5)
Study 2	4.8	6.4 (6.8)	1.7	2.4 (7.3)

In pharmacodynamic studies of Mozobil in healthy volunteers, peak mobilization of CD34+ cells was observed between 6 and 9 hours after administration. In pharmacodynamic studies of Mozobil in conjunction with G-CSF in healthy volunteers, a sustained elevation in the peripheral blood CD34+ count was observed from 4 to 18 hours after plerixafor administration with a peak CD34+ count between 10 and 14 hours.

QT/QTc Prolongation
There is no indication of a QT/QTc prolonging effect of Mozobil in single doses up to 0.40 mg/kg. In a randomized, double-blind, crossover study, 48 healthy subjects were administered a single subcutaneous dose of plerixafor (0.24 mg/kg and 0.40 mg/kg) and placebo. Peak concentrations for 0.40 mg/kg Mozobil were approximately 1.8-fold higher than the peak concentrations following the 0.24 mg/kg single subcutaneous dose.

12.3 Pharmacokinetics

The single-dose pharmacokinetics of plerixafor 0.24 mg/kg were evaluated in patients with NHL and MM following pre-treatment with G-CSF (10 micrograms/kg once daily for 4 consecutive days). Plerixafor exhibits linear kinetics between the 0.04 mg/kg to 0.24 mg/kg dose range. The pharmacokinetics of plerixafor were similar across clinical studies in healthy subjects who received plerixafor alone and NHL and MM patients who received plerixafor in combination with G-CSF.

A population pharmacokinetic analysis incorporated plerixafor data from 63 subjects (NHL patients, MM patients, subjects with varying degrees of renal impairment, and healthy subjects) who received a single SC dose (0.04 mg/kg to 0.24 mg/kg) of plerixafor. A two-compartment disposition model with first order absorption and elimination was found to adequately describe the plerixafor concentration-time profile. Significant relationships between clearance and creatinine clearance (CL_{CR}), as well as between central volume of distribution and body weight were observed. The distribution half-life ($t_{1/2\alpha}$) was estimated to be 0.3 hours and the terminal population half-life ($t_{1/2\beta}$) was 5.3 hours in patients with normal renal function.

The population pharmacokinetic analysis showed that the mg/kg-based dosage results in an increased plerixafor exposure ($AUC_{0\text{-}24h}$) with increasing body weight. In order to compare the pharmacokinetics and pharmacodynamics of plerixafor following 0.24 mg/kg-based and fixed (20 mg) doses, a follow-up trial was conducted in patients with NHL (N=61) who were treated with 0.24 mg/kg or 20 mg of plerixafor. The trial was conducted in patients weighing 70 kg or

less. The fixed 20 mg dose showed 1.43-fold higher exposure ($AUC_{0\text{-}10h}$) than the 0.24 mg/kg dose (Table 4). The fixed 20 mg dose also showed numerically higher response rate (5.2% [60.0% vs 54.8%] based on the local lab data and 11.7% [63.3% vs 51.6%] based on the central lab data) in attaining the target of $\geq 5 \times 10^6$ CD34+ cells/kg than the mg/kg-based dose. However, the median time to reach $\geq 5 \times 10^6$ CD34+ cells/kg was 3 days for both treatment groups, and the safety profile between the groups was similar. Based on these results, further analysis was conducted by FDA reviewers and a body weight of 83 kg was selected as an appropriate cut-off point to transition patients from fixed to weight based dosing.

Table 4. Systemic Exposure ($AUC_{0\text{-}10h}$) comparisons of fixed and weight based regimens

Regimen	Geometric Mean AUC
Fixed 20 mg (n=30)	3991.2
0.24 mg/kg (n=31)	2792.7
Ratio (90% CI)	1.43 (1.32,1.54)

There is limited experience with the 0.24 mg/kg dose of plerixafor in patients weighing above 160 kg. Therefore the dose should not exceed that of a 160 kg patient (i.e., 40 mg/day if CL_{CR} is > 50 mL/min and 27 mg/day if CL_{CR} is ≤ 50 mL/min). *[see Dosage and Administration (2.1, 2.3)]*

Absorption
Peak plasma concentrations occurred at approximately 30 - 60 minutes after a SC dose.

Distribution
Plerixafor is bound to human plasma proteins up to 58%. The apparent volume of distribution of plerixafor in humans is 0.3 L/kg demonstrating that plerixafor is largely confined to, but not limited to, the extravascular fluid space.

Metabolism
The metabolism of plerixafor was evaluated with *in vitro* assays. Plerixafor is not metabolized as shown in assays using human liver microsomes or human primary hepatocytes and does not exhibit inhibitory activity *in vitro* towards the major drug metabolizing cytochrome P450 enzymes (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4/5). In *in vitro* studies with human hepatocytes, plerixafor does not induce CYP1A2, CYP2B6, or CYP3A4 enzymes. These findings suggest that plerixafor has a low potential for involvement in cytochrome P450-dependent drug-drug interactions.

Elimination
The major route of elimination of plerixafor is urinary. Following a 0.24 mg/kg dose in healthy volunteers with normal renal function, approximately 70% of the dose was excreted in the urine as the parent drug during the first 24 hours following administration. In studies with healthy subjects and patients, the terminal half-life in plasma ranges between 3 and 5 hours. At concentrations similar to what are seen clinically, plerixafor did not act as a substrate or inhibitor of P-glycoprotein in an *in vitro* study with MDCKII and MDCKII-MDR1 cell models.

Renal Impairment

Following a single 0.24 mg/kg SC dose, plerixafor clearance was reduced in subjects with varying degrees of renal impairment and was positively correlated with CL_{CR}. The mean AUC_{0-24h} of plerixafor in subjects with mild (CL_{CR} 51-80 mL/min), moderate (CL_{CR} 31-50 mL/min), and severe (CL_{CR} < 31 mL/min) renal impairment was 7%, 32%, and 39% higher than healthy subjects with normal renal function, respectively. Renal impairment had no effect on C_{max}. A population pharmacokinetic analysis indicated an increased exposure (AUC_{0-24h}) in patients with moderate and severe renal impairment compared to patients with CL_{CR} > 50 mL/min. These results support a dose reduction of one-third in patients with moderate to severe renal impairment (CL_{CR} ≤ 50 mL/min) in order to match the exposure in patients with normal renal function. The population pharmacokinetic analysis showed that the mg/kg-based dosage results in an increased plerixafor exposure (AUC_{0-24h}) with increasing body weight; therefore if CL_{CR} is ≤ 50 mL/min the dose should not exceed 27 mg/day. *[see Dosage and Administration (2.3)]*

Since plerixafor is primarily eliminated by the kidneys, coadministration of plerixafor with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of plerixafor or the coadministered drug. The effects of coadministration of plerixafor with other drugs that are renally eliminated or are known to affect renal function have not been evaluated.

Race
Clinical data show similar plerixafor pharmacokinetics for Caucasians and African-Americans, and the effect of other racial/ethnic groups has not been studied.

Gender
Clinical data show no effect of gender on plerixafor pharmacokinetics.

Age
Clinical data show no effect of age on plerixafor pharmacokinetics.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with plerixafor have not been conducted.

Plerixafor was not genotoxic in an *in vitro* bacterial mutation assay (Ames test in *Salmonella*), an *in vitro* chromosomal aberration test using V79 Chinese hamster cells, or an *in vivo* bone marrow micronucleus test in rats after subcutaneous doses up to 25 mg/kg (150 mg/m^2).

The effect of plerixafor on human fertility is unknown. The effect of plerixafor on male or female fertility was not studied in designated reproductive toxicology studies. The staging of spermatogenesis measured in a 28-day repeated dose toxicity study in rats revealed no abnormalities considered to be related to plerixafor. No histopathological evidence of toxicity to male or female reproductive organs was observed in 28-day repeated dose toxicity studies.

14 CLINICAL STUDIES

The efficacy and safety of Mozobil in conjunction with G-CSF in non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) were evaluated in two placebo-controlled studies (Studies 1

and 2). Patients were randomized to receive either Mozobil 0.24 mg/kg or placebo on each evening prior to apheresis. Patients received daily morning doses of G-CSF 10 micrograms/kg for 4 days prior to the first dose of Mozobil or placebo and on each morning prior to apheresis. Two hundred and ninety-eight (298) NHL patients were included in the primary efficacy analyses for Study 1. The mean age was 55 years (range 29-75) and 58 years (range 22-75) in the Mozobil and placebo groups, respectively, and 93% of subjects were Caucasian. In study 2, 302 patients with MM were included in the primary efficacy analyses. The mean age (58years) and age range (28-75) were similar in the Mozobil and placebo groups, and 81% of subjects were Caucasian.

In Study 1, 59% of NHL patients who were mobilized with Mozobil and G-CSF collected $\geq 5 \times 10^6$ CD34+ cells/kg from the peripheral blood in four or fewer apheresis sessions, compared with 20% of patients who were mobilized with placebo and G-CSF ($p < 0.001$). Other CD34+ cell mobilization outcomes showed similar findings (Table 5).

Table 5: Study 1 Efficacy Results - CD34+ Cell Mobilization in NHL Patients

Efficacy Endpoint	Mozobil® and G-CSF (n = 150)	Placebo and G-CSF (n = 148)	p-value[a]
Patients achieving $\geq 5 \times 10^6$ cells/kg in ≤ 4 apheresis days	89 (59%)	29 (20%)	< 0.001
Patients achieving $\geq 2 \times 10^6$ cells/kg in ≤ 4 apheresis days	130 (87%)	70 (47%)	< 0.001

[a]p-value calculated using Pearson's Chi-Squared test

The median number of days to reach $\geq 5 \times 10^6$ CD34+ cells/kg was 3 days for the Mozobil group and not evaluable for the placebo group. Table 6 presents the proportion of patients who achieved $\geq 5 \times 10^6$ CD34+ cells/kg by apheresis day.

Table 6: Study 1 Efficacy Results – Proportion of Patients Who Achieved ≥ 5×10^6 CD34+ cells/kg by Apheresis Day in NHL Patients

Days	Proportion[a] in Mozobil® and G-CSF (n=147[b])	Proportion[a] in Placebo and G-CSF (n=142[b])
1	27.9%	4.2%
2	49.1%	14.2%
3	57.7%	21.6%
4	65.6%	24.2%

[a]Percents determined by Kaplan Meier method
[b] n includes all patients who received at least one day of apheresis

In Study 2, 72% of MM patients who were mobilized with Mozobil and G-CSF collected $\geq 6 \times 10^6$ CD34+ cells/kg from the peripheral blood in two or fewer apheresis sessions, compared with 34% of patients who were mobilized with placebo and G-CSF ($p < 0.001$). Other CD34+ cell mobilization outcomes showed similar findings (Table 7).

Table 7: Study 2 Efficacy Results – CD34+ Cell Mobilization in Multiple Myeloma Patients

Efficacy Endpoint	Mozobil® and G-CSF (n = 148)	Placebo and G-CSF (n = 154)	p-value[a]
Patients achieving ≥ 6 X 10^6 cells/kg in ≤ 2 apheresis days	106 (72%)	53 (34%)	< 0.001
Patients achieving ≥ 6 X 10^6 cells/kg in ≤ 4 apheresis days	112 (76%)	79 (51%)	< 0.001
Patients achieving ≥ 2 X 10^6 cells/kg in ≤ 4 apheresis days	141 (95%)	136 (88%)	0.028

[a]p-value calculated using Pearson's Chi-Squared test

The median number of days to reach ≥ 6 x 10^6 CD34+ cells/kg was 1 day for the Mozobil group and 4 days for the placebo group. Table 8 presents the proportion of patients who achieved ≥ 6 x 10^6 CD34+ cells/kg by apheresis day.

Table 8: Study 2 – Proportion of Patients Who Achieved ≥ 6 x 10^6 CD34+ cells/kg by Apheresis Day in MM Patients

Days	Proportion[a] in Mozobil® and G-CSF (n=144[b])	Proportion[a] in Placebo and G-CSF (n=150[b])
1	54.2%	17.3%
2	77.9%	35.3%
3	86.8%	48.9%
4	86.8%	55.9%

[a]Percents determined by Kaplan Meier method
[b]n includes all patients who received at least one day of apheresis

Multiple factors can influence time to engraftment and graft durability following stem cell transplantation. For transplanted patients in the Phase 3 studies, time to neutrophil and platelet engraftment and graft durability were similar across the treatment groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each single-use vial is filled to deliver 1.2 mL of 20 mg/mL solution containing 24 mg of plerixafor.

NDC Number: 0024-5862-01

- Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [see USP Controlled Room temperature]
- Each vial of Mozobil is intended for single use only. Any unused drug remaining after injection must be discarded.

17 PATIENT COUNSELING INFORMATION

Advise patients of the potential for anaphylactic reactions, including signs and symptoms such as urticaria, periorbital swelling, dyspnea, or hypoxia during and following Mozobil injection and to report these symptoms immediately to a health care professional *[see Adverse Reactions (6.1), (6.2)]*.

Advise patients to inform a health care professional immediately if symptoms of vasovagal reactions such as orthostatic hypotension or syncope occur during or shortly after their Mozobil injection. *[see Adverse Reactions (6.1)]*

Advise patients who experience itching, rash, or reaction at the site of injection to notify a health care professional, as these symptoms have been treated with over-the-counter medications during clinical trials. *[see Adverse Reactions (6.1)]*

Advise patients that Mozobil may cause gastrointestinal disorders, including diarrhea, nausea, vomiting, flatulence, and abdominal pain. Patients should be told how to manage specific gastrointestinal disorders and to inform their health care professional if severe events occur following Mozobil injection. *[see Adverse Reactions (6.1)]*

Advise female patients with reproductive potential to use effective contraceptive methods during Mozobil use. *[see Warnings and Precautions (5. 6) and Use In Specific Populations (8.1)]*

Manufactured by: Patheon UK Ltd., Swindon, UK

Manufactured for: Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142 USA

EXHIBIT B

US007897590B2

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

(10) **Patent No.: US 7,897,590 B2**
(45) **Date of Patent: *Mar. 1, 2011**

(54) **METHODS TO MOBILIZE PROGENITOR/STEM CELLS**

(75) Inventors: **Gary J. Bridger**, Bellingham, WA (US); **Michael J. Abrams**, Custer, WA (US); **Geoffrey W. Henson**, Ferndale, WA (US); **Ronald Trevor MacFarland**, Vancouver (CA); **Gary B. Calandra**, Cresco, PA (US); **Hal E. Broxmeyer**, Indianapolis, IN (US); **David C. Dale**, Seattle, WA (US)

(73) Assignee: **Genzyme Corporation**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 840 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/841,837**

(22) Filed: **Aug. 20, 2007**

(65) **Prior Publication Data**

US 2008/0063624 A1 Mar. 13, 2008

Related U.S. Application Data

(60) Continuation of application No. 11/446,390, filed on Jun. 2, 2006, now abandoned, which is a division of application No. 11/269,773, filed on Nov. 8, 2005, which is a division of application No. 10/209,001, filed on Jul. 30, 2002, now Pat. No. 6,987,102.

(60) Provisional application No. 60/309,196, filed on Jul. 31, 2001, provisional application No. 60/382,155, filed on May 20, 2002.

(51) **Int. Cl.**

A61K 31/33	(2006.01)
C07D 245/00	(2006.01)
C07D 487/00	(2006.01)

(52) **U.S. Cl.** **514/183**; 540/473; 540/474

(58) **Field of Classification Search** ..... None

See application file for complete search history.

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Primary Examiner — Andrew D Kosar

(74) *Attorney, Agent, or Firm* — Morrison & Foerster LLP

(57) **ABSTRACT**

Methods to elevate progenitor and stem cell counts in animal subjects using compounds which bind to the chemokine receptor CXCR4 are disclosed. Preferred embodiments of such compounds are of the formula

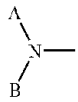
Z-linker-Z'

(1)

or pharmaceutically acceptable salt thereof

wherein Z is a cyclic polyamine containing 9-32 ring members of which 3-8 are nitrogen atoms, said nitrogen atoms separated from each other by at least 2 carbon atoms, and wherein said heterocycle may optionally contain additional heteroatoms besides nitrogen and/or may be fused to an additional ring system;

or Z is of the formula



wherein A comprises a monocyclic or bicyclic fused ring system containing at least one N and B is H or an organic moiety of 1-20 atoms,

Z' may be embodied in a form as defined by Z above, or alternatively may be of the formula

—N(R)—$(CR_2)_n$—X

wherein each R is independently H or straight, branched or cyclic alkyl (1-6C), n is 1 or 2, and X is an aromatic ring, including heteroaromatic rings, or is a mercaptan;

"linker" represents a bond, alkylene (1-6C) or may comprise aryl, fused aryl, oxygen atoms contained in an alkylene chain, or may contain keto groups or nitrogen or sulfur atoms.

29 Claims, 1 Drawing Sheet

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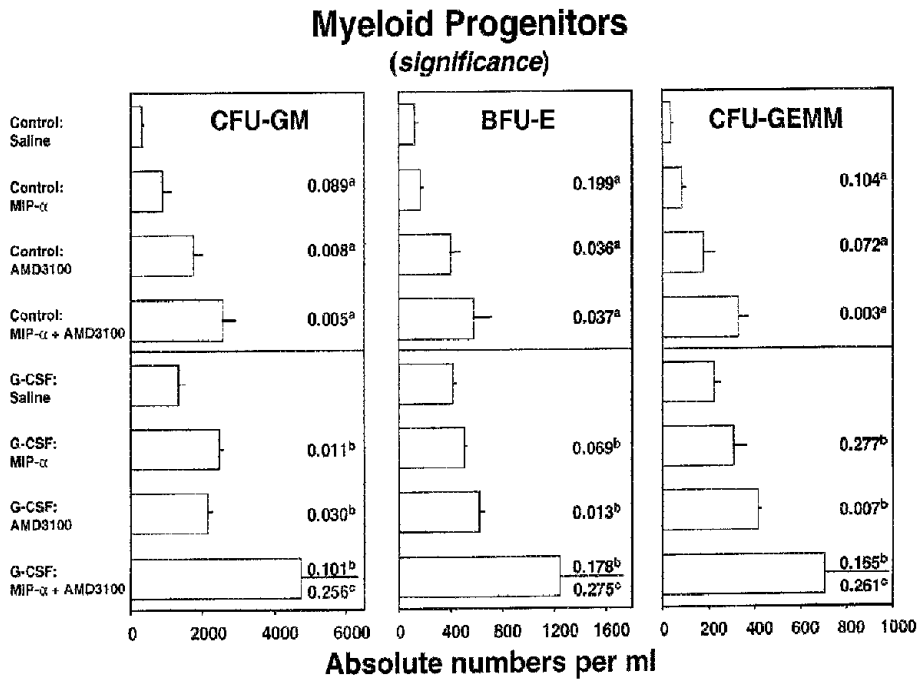
Figure 1.



a = P-value compared to Control/Saline
b = P-value compared to G-CSF/Saline
c = P-value compared to Control/MIP-1α+AMD3100

METHODS TO MOBILIZE PROGENITOR/STEM CELLS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 11/446,390 filed 2 Jun. 2006 which is a divisional of U.S. Ser. No. 11/269,773 filed 8 Nov. 2005 which is a divisional of U.S. Ser. No. 10/209,001 filed 30 Jul. 2002 which claims priority under 35 U.S.C. §119(e) to U.S. provisional application Ser. No. 60/309,196 filed 31 Jul. 2001 and to U.S. provisional application Ser. No. 60/382,155 filed 20 May 2002. The contents of these applications are incorporated herein by reference.

TECHNICAL FIELD

The invention is in the field of therapeutics and medicinal chemistry. More particularly, the invention concerns methods to mobilize progenitor/stem cells in subjects by administering certain polyamines.

BACKGROUND ART

Blood cells play a crucial part in maintaining the health and viability of animals, including humans. White blood cells include neutrophils, macrophage, eosinophils and basophils/mast cells as well the B and T cells of the immune system. White blood cells are continuously replaced via the hematopoietic system, by the action of colony stimulating factors (CSF) and various cytokines on stem cells and progenitor cells in hematopoietic tissues. The nucleotide sequences encoding a number of these growth factors have been cloned and sequenced. Perhaps the most widely known of these is granulocyte colony stimulating factor (G-CSF) which has been approved for use in counteracting the negative effects of chemotherapy by stimulating the production of white blood cells and progenitor cells (peripheral blood stem cell mobilization). A discussion of the hematopoietic effects of this factor can be found, for example, in U.S. Pat. No. 5,582,823, incorporated herein by reference.

Several other factors have been reported to increase white blood cells and progenitor cells in both human and animal subjects. These agents include granulocyte-macrophage colony stimulating factor (GM-CSF), Interleukin-1 (IL-1), Interleukin-3 (IL-3), Interleukin-8 (IL-8), PIXY-321 (GM-CSF/IL-3 fusion protein), macrophage inflammatory protein, stem cell factor, thrombopoietin and growth related oncogene, as single agents or in combination (Dale, D., et al., *Am. J. of Hematol.* (1998) 57:7-15; Rosenfeld, C., et al., *Bone Marrow Transplantation* (1997) 17:179-183; Pruijt, J., et al., *Cur. Op. in Hematol.* (1999) 6:152-158; Broxmeyer, H., et al., *Exp. Hematol.* (1995) 23:335-340; Broxmeyer, et al., *Blood Cells, Molecules and Diseases* (1998) 24:14-30; Glaspy, J., et al., *Cancer Chemother. Pharmacol.* (1996) 38 (suppl): S53-S57; Vadhan-Raj, S., et al., *Ann. Intern. Med.* (1997) 126:673-81; King, A., et al., *Blood* (2001) 97:1534-1542; Glaspy, J., et al., *Blood* (1997) 90:2939-2951).

While endogenous growth factors are pharmacologically effective, the well known disadvantages of employing proteins and peptides as pharmaceuticals underlies the need to add to the repertoire of such growth factors with agents that are small molecules. In another aspect, such small molecules are advantageous over proteins and peptides where production in large quantities are desired.

A number of cyclic polyamine antiviral agents have been described in a series of U.S. patents and applications over the last several years. These patents, U.S. Pat. Nos. 5,021,409; 6,001,826; 5,583,131; 5,698,546; and 5,817,807 are incorporated herein by reference. Also incorporated by reference are PCT publications WO 00/02870 based on an application filed 8 Jul. 1998 and WO 01/44229, based on an application filed 17 Dec. 1999, which describe additional compounds. These publications describe the structural characteristics of the cyclic polyamine antiviral agents.

The structural characteristics of a number of non-cyclic amine antiviral agents have also been described in a series of U.S. applications, now published as PCT publications. These publications, WO 00/56729, based on an application filed 24 Mar. 2000; WO 02/22600, based on applications filed 15 and 20 Sep. 2000; WO 02/22599, based on applications filed 15 and 22 Sep. 2000 as well as WO 02/34745 published 2 May 2002, are incorporated herein by reference in their entirety.

In addition, improved methods for preparation of some of the cyclic polyamine compounds are described in U.S. Pat. Nos. 5,612,478; 5,756,728; 5,801,281; and 5,606,053 and PCT publication WO 02/26721, based on an application filed 29 Sep. 2000. The disclosures of these U.S. documents are also incorporated herein by reference in their entirety.

We have previously found, and have disclosed in PCT publication WO 02/58653, based on an application filed 1 Feb. 2000, that some of the polyamine antiviral agents described in the above mentioned publications have the effect of increasing the white blood cell count. It has now been found that the polyamine antiviral agents described in the above-mentioned publications also have the effect of increasing progenitor cells and/or stem cells.

The development and maturation of blood cells is a complex process. Mature blood cells are derived from hematopoietic precursor cells (progenitor) cells and stem cells present in specific hematopoietic tissues including bone marrow. Within these environments hematopoietic cells proliferate and differentiate prior to entering the circulation. The chemokine receptor CXCR4 and its natural ligand stromal cell derived factor-1 (SDF-1) appear to be important in this process (for reviews see Maekawa, T., et al., *Internal Med.* (2000) 39:90-100; Nagasawa, T., et al., *Int. J. Hematol.* (2000) 72:408-411). This is demonstrated by reports that CXCR4 or SDF-1 knockout mice exhibit hematopoietic defects (Ma, Q., et al., *Proc. Natl. Acad. Sci USA* (1998) 95:9448-9453; Tachibana, K., et al., *Nature* (1998) 393:591-594; Zou, Y-R., et al., *Nature* (1998) 393:595-599). It is also known that CD34+ progenitor cells express CXCR4 and require SDF-1 produced by bone marrow stromal cells for chemoattraction and engraftment (Peled, A., et al., *Science* (1999) 283:845-848) and that in vitro, SDF-1 is chemotactic for both CD34+ cells (Aiuti, A., et al., *J. Exp. Med.* (1997) 185:111-120; Viardot, A., et al., *Ann. Hematol.* (1998) 77:194-197) and for progenitor/stem cells (Jo, D-Y., et al., *J. Clin. Invest.* (2000) 105:101-111). SDF-1 is also an important chemoattractant, signaling via the CXCR4 receptor, for several other more committed progenitors and mature blood cells including T-lymphocytes and monocytes (Bleul, C., et al., *J. Exp. Med.* (1996) 184:1101-1109), pro-and pre-B lymphocytes (Fedyk, E. R., et al., *J. Leukoc. Biol.* (1999) 66:667-673; Ma, Q., et al., *Immunity* (1999) 10:463-471) and megakaryocytes (Hodohara, K., et al., *Blood* (2000) 95:769-775; Riviere, C., et al., *Blood* (1999) 95:1511-1523; Majka, M., et al., *Blood* (2000) 96:4142-4151; Gear, A., et al., *Blood* (2001) 97:937-945; Abi-Younes, S., et al., *Circ. Res.* (2000) 86:131-138).

Thus, in summary, it appears that SDF-1 is able to control the positioning and differentiation of cells bearing CXCR4 receptors whether these cells are stem cells (i.e., cells which are CD34+) and/or progenitor cells (which result in formation

of specified types of colonies in response to particular stimuli; that can be $CD34^+$ or $CD34^-$) or cells that are somewhat more differentiated.

Recently, considerable attention has been focused on the number of CD34+ cells mobilized in the pool of peripheral blood progenitor cells used for autologous stem cell transplantation. The CD34+ population is the component thought to be primarily responsible for the improved recovery time after chemotherapy and the cells most likely responsible for long-term engraftment and restoration of hematopoiesis (Croop, J. M., et al., *Bone Marrow Transplantation* (2000) 26:1271-1279). The mechanism by which CD34+ cells re-engraft may be due to the chemotactic effects of SDF-1 on CXCR4 expressing cells (Voermans, C., *Blood*, 2001, 97, 799-804; Ponomaryov, T., et al., *J. Clin. Invest.* (2000) 106: 1331-1339). More recently, adult hematopoietic stem cells were shown to be capable of restoring damaged cardiac tissue in mice (Jackson, K., et al., *J. Clin. Invest.* (2001) 107:1395-1402; Kocher, A., et al., *Nature Med.* (2001) 7:430-436).

Thus, the role of the CXCR4 receptor in managing cell positioning and differentiation has assumed considerable significance.

Citation of the above documents is not intended as an admission that any of the foregoing is pertinent prior art. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents. Further, all documents referred to throughout this application are incorporated in their entirety by reference herein.

DISCLOSURE OF THE INVENTION

The invention is directed to methods of treating animal subjects, in particular, veterinary and human subjects, to enhance the number of progenitor cells and/or stem cells. The progenitor and/or stem cells may be harvested and used in cell transplantation. The methods of the invention employ polyamines including those described in the patents and publications incorporated hereinabove by reference.

In one aspect, therefore, the invention is directed to a method to elevate the progenitor cells and/or stem cells, in a subject, which method comprises administering to said subject an amount of a compound of formula (1) or of a pharmaceutical composition thereof effective to elevate progenitor cell and/or stem cell levels. In one embodiment, bone marrow progenitor and/or stem cells are mobilized for myocardial repair.

The methods of the invention also include treatment of cell populations ex vivo with the compounds of formula (1) and introducing the treated populations into a compatible subject. The compounds of formula (1) may be used alone or in combination with other compounds and compositions to enhance the population of stem cells and/or progenitor cells in the peripheral blood. An enhanced production of white blood cells in the bone marrow may result as well.

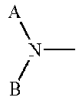
In additional aspects, the invention is directed to pharmaceutical compositions containing the compound of formula (1) for use in effecting an elevation of progenitor cells and/or stem cells in animal subjects.

The compounds of formula (1) are of the formula:

$$\text{Z-linker-Z'} \qquad (1)$$

wherein Z is a cyclic polyamine containing 9-32 ring members of which 2-8 are nitrogen atoms, said nitrogen atoms separated from each other by at least 2 carbon atoms, and wherein said heterocycle may optionally contain additional heteroatoms besides nitrogen and/or may be fused to an additional ring system;

or Z is of the formula



wherein A comprises a monocyclic or bicyclic fused ring system containing at least one N and B is H or an organic moiety of 1-20 atoms;

Z' may be embodied in a form as defined by Z above, or alternatively may be of the formula

$$\text{—N(R)—(CR}_2\text{)}_n\text{—X}$$

wherein each R is independently H or straight, branched or cyclic alkyl (1-6C),

n is 1 or 2, and

X is an aromatic ring, including heteroaromatic rings, or is a mercaptan;

"linker" represents a bond, alkylene (1-6C) or may comprise aryl, fused aryl, oxygen atoms contained in an alkylene chain, or may contain keto groups or nitrogen or sulfur atoms.

The preferred forms of the compounds of the invention are discussed below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a graph of obtaining myeloid progenitors in response to treatment with 1,1'-[1,4-phenylene-bis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane (AMD3100) in combination with macrophage inflammatory protein after administration of G-CSF.

MODES OF CARRYING OUT THE INVENTION

The compounds useful in the invention are of the general formula set forth as formula (1) above. Certain embodiments are preferred; included among these are the compounds set forth in the above-incorporated U.S. patents and other patent documents.

The cyclic polyamine and non-cyclic amine antiviral agents described in the above-mentioned documents inhibit HIV replication via inhibition of CXCR4, the co-receptor required for fusion and entry of T-tropic HIV strains, and also inhibit the binding and signaling induced by the natural ligand, the chemokine SDF-1. While not wishing to be bound by any theory, the compounds of formula (1) which inhibit the binding of SDF-1 to CXCR4 effect an increase in stem and/or progenitor cells by virtue of such inhibition. Enhancing the stem and/or progenitor cells in blood is helpful in treatments to alleviate the effects of protocols that adversely affect the bone marrow, such as those that result in leukopenia. These are known side-effects of chemotherapy and radiotherapy. The compounds of formula (1) also enhance the success of bone marrow transplantation, enhance wound healing and burn treatment, and aid in restoration of damaged organ tissue. They also combat bacterial infections that are prevalent in leukemia. The compounds of formula (1) are used to mobilize and harvest CD34+ cells via apheresis with and without combinations with other mobilizing factors. The harvested cells are used in treatments requiring stem cell transplantations.

As used herein, the term "progenitor cells" refers to cells that, in response to certain stimuli, can form differentiated hematopoietic or myeloid cells. The presence of progenitor cells can be assessed by the ability of the cells in a sample to form colony-forming units of various types, including, for example, CFU-GM (colony-forming units, granulocyte-macrophage); CFU-GEMM (colony-forming units, multipotential); BFU-E (burst-forming units, erythroid); HPP-CFC (high proliferative potential colony-forming cells); or other types of differentiated colonies which can be obtained in culture using known protocols.

As used herein, "stem" cells are less differentiated forms of progenitor cells. Typically, such cells are often positive for CD34. Some stem cells do not contain this marker, however. These CD34+ cells can be assayed using fluorescence activated cell sorting (FACS) and thus their presence can be assessed in a sample using this technique.

In general, CD34+ cells are present only in low levels in the blood, but are present in large numbers in bone marrow. While other types of cells such as endothelial cells and mast cells also may exhibit this marker, CD34 is considered an index of stem cell presence.

In general, in compounds of formula (1), preferred embodiments of Z and Z' are cyclic polyamine moieties having from 9-24C that include 3-5 nitrogen atoms. Particularly preferred are 1,5,9,13-tetraazacyclohexadecane; 1,5,8,11,14-pentaazacyclohexadecane: 1,4,8,11-tetraazacylotetradecane; 1,5,9-triazacyclododecane; 1,4,7,10-tetraazacyclododecane; and the like, including such cyclic polyamines which are fused to an additional aromatic or heteroaromatic rings and/or containing a heteroatom other than nitrogen incorporated in the ring. Embodiments wherein the cyclic polyamine contains a fused additional cyclic system or one or more additional heteroatoms are described in U.S. Pat. No. 5,698,546 and WO 01/44229 incorporated hereinabove by reference. Also preferred are

3,7,11,17-tetraazabicyclo(13.3.1)heptadeca-1(17),13,15-triene;

4,7,10,17-tetraazabicyclo(13.3.1)heptadeca-1(17),13,15-triene;

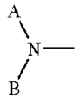
1,4,7,10-tetraazacyclotetradecane; 1,4,7-triazacyclotetradecane; and

4,7,10-triazabicyclo(13.3.1)heptadeca-1(17),13,15-triene.

When Z' is other than a cyclic polyamine as defined in Z, its preferred embodiments are set forth in U.S. Pat. No. 5,817,807, also incorporated herein by reference.

Preferred forms where

Z is of the formula



wherein A comprises a monocyclic or bicyclic fused ring system containing at least one N and B is H or an organic moiety of 1-20 atoms are disclosed in WO 00/56729; WO 02/22600; WO 02/34745; and WO 02/22599 cited above and all incorporated herein by reference.

Preferred forms of the linker moiety include those wherein the linker is a bond, or wherein the linker includes an aromatic moiety flanked by alkylene, preferably methylene moieties. Preferred linking groups include the methylene bracketed forms of 1,3-phenylene, 2,6-pyridine, 3,5-pyridine, 2,5-thiophene, 4,4'-(2,2'-bipyrimidine); 2,9-(1,10-phenanthroline) and the like. A particularly preferred linker is 1,4-phenylene-bis-(methylene).

Particularly preferred embodiments of the compound of the formula (1) include 2,2'-bicyclam; 6,6'-bicyclam; the embodiments set forth in U.S. Pat. Nos. 5,021,409, and 6,001,826, and in particular 1,1'-[1,4-phenylene-bis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane, set forth in U.S. Pat. No. 5,583,131, and designated herein AMD3100.

Other preferred embodiments include

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-aminomethyl)pyridine;

7,7'-[1,4-phenylenebis(methylene)]bis-4,7,10,17-tetraazabicyclo-[13.3.1]heptadeca-1(17),13,15-triene;

7,7'-[1,4-phenylenebis(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene;

1,1'-[1.3-phenylenebis(methylene)]-bis-1,4,8,11-tetra-aza-cyclotetradecane;

1,1'-[1.4-phenylenebis(methylene)]-bis-1,4,8,11-tetra-aza-cyclotetradecane;

1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraaza-cyclotetradecane;

1,1'-[1,3-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraaza-cyclotetradecane;

11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

N-[4-(1,4,7-triazacyclotetra-decane)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,7,10-triazabicyclo[13.3.1]heptadeca-1(17),13,15-triene)-1,4-phenylenebis(methylene)]-2-(aminomethyl) pyridine;

N-[7-(4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-[4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

3,3'-(bis-1,5,9,13-tetraazacyclohexadecane);

3,3'-(bis-1,5,8,11,14-pentaazacyclohexadecane), methylene (or polymethylene) di-1-N-1,4,8,11-tetraazacyclotetradecane;

3,3'-bis-1,5,9,13,-tetraazacyclohexadecane;

3,3'-bis-1,5,8,11,14-pentaazacyclohexadecane;

5,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,6'-bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-butanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-pentanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-hexanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

3,3'-bis-1,5,9,13-tetraazacyclohexadecane;

3,3'-bis-1,5,8,11,14-pentaazacyclohexadecane;

5,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,6'-bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-butanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-pentanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-hexanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[1,3-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane;

1,1'-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane;

1,1'-|3,3'-biphenylene-bis-(methylene)|-bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-|1,4-phenylene-bis-(methylene)|-bis-1,4,7,11-tetraazacyclotetradecane;

1,11'-[1,4-phenylene-bis(methylene)]-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,6-pyridine-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1-[3,5-pyridine-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,5-thiophene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[4,4'-(2,2'-bipyridine)-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,9-(1,10-phenanthroline)-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane:

1,1'-[1,3-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;

1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;

1,1'-[5-nitro-1,3-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,4,5,6-tetrachloro-1,3-phenyleneis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,3,5,6-tetrafluoro-1,4-phenylenebis(methylene)]bis-1,4,8,1 1-tetraazacyclotetradecane;

1,1'-[1,4-naphthylene-bis-(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[1,3-phenylenebis-(methylene)]bis-1,5,9-triazacyclododecane;

1,1'-[1,4-phenylene-bis-(methylene)]-1,5,9-triazacyclododecane;

1,1'-[2,5-dimethyl-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,5-dichloro-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2-bromo-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[6-phenyl-2,4-pyridinebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

7,7'-|1,4-phenylene-bis(methylene)|bis-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene;

7,7'-[1,4-phenylene-bis(methylene)]bis[15-chloro-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene];

7,7'-[1,4-phenylene-bis(methylene)]bis[15-methoxy-3,7,11,17-tetraazabicyclo|13.3.1|heptadeca-1(17),13,15-triene|;

7,7'-[1,4-phenylene-bis(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1]-heptadeca-13,16-triene-15-one;

7,7'-[1,4-phenylene-bis(methylene)]bis-4,7,10,17-tetraazabicyclo[13.3.1]-heptadeca-1(17),13,15-triene;

8,8'-|1,4-phenylene-bis(methylene)|bis-4,8,12,19-tetraazabicyclo[15.3.1]nonadeca-1(19),15,17-triene;

6,6'-[1,4-phenylene-bis(methylene)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene;

6,6'-[1,3-phenylene-bis(methylene)]bis-3,6,9,15-tetraazabicyclo|11.3.1|pentadeca-1(15),11,13-triene;

17,17'-[1,4-phenylene-bis(methylene)]bis-3,6,14,17,23,24-hexaazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8,10,12(24),19,21-hexaene;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-methyl)pyridine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-N-methyl-2-(aminomethyl)pyridine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-)amino-methyl)pyridine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-3-(amino-methyl)pyridine;

N-|1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-(2-amino-methyl-5-methyl)pyrazine;

N-|1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-ethyl)pyridine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-methyl)thiophene;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-ethyl)mercaptan;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-amino-benzylamine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-amino-benzylamine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-(amino-ethyl)imidazole;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-benzylamine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-purine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-phenylpiperazine;

N-[4-(1,4,7-triazacyclotetra-decanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,7,10-triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-[4,7,10-triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[1-(1,4,7-triazacyclotetra-decanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-[4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[3-(3,6,17-triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[3-(3,6,17-triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,3-phenylenebis(methylene)|-2-(aminomethyl)pyridine;

N-[4-(4,7,17-triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-|7-(4,7,17-triazabicyclo|13.3.1|heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[6-(3,6,9-triazabicyclo[11.3.1]pentadeca-1(15),11,13-trienyl)-1,3-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,10,17-triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(1,7-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)|-2-(aminomethyl)pyridine;

N-[7-(4,10-diazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-fluoro-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[4-(11,11-difluoro-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[4-(1,4,7-triazacyclotetradecan-2-one)-yl))-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[12-(5-oxa-1,9-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-|4-(11-oxa-1,7-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-|4-(11-thia-1,7-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[4-(11-sulfoxo-1,7-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[4-(11-sulfono-1,7-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[4-(1,4,7-triazacyclotetradecan-3-one)-yl))-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-(2-pyridinylmethyl)-N'-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(1-naphthalenyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-[2-[(2-pyridinylmethyl)amino]ethyl]-N'-(1-methyl-1,2,3,4-tetrahydro-8-quinolinyl)-1,4-benzene dimethanamine;
N-(2-pyridinylmethyl)-N'-[2-[(1H-imidazol-2-ylmethyl)amino]ethyl]-N'-(1-methyl-1,2,3,4-tetrahydro-8-quinolinyl)-1,4-benzene dimethanamine;
N-(2-pyridinylmethyl)-N'-(1,2,3,4-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-[2-[(1H-imidazol-2-ylmethyl)amino]ethyl]-N'-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,4-benzene dimethanamine;
N-(2-pyridinylmethyl)-N'-(2-phenyl-5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N,N'-bis(2-pyridinylmethyl)-N'-(2-phenyl-5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-5-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-5-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-|(2-amino-3-phenyl)propyl|-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(1H-imidazol-4-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(2-quinolinylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(2-(2-naphthoyl)aminoethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-[(S)-(2-acetylamino-3-phenyl)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-[(S)-(2-acetylamino-3-phenyl)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-|3-((2-naphthalenylmethyl)amino)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-|2-(S)-pyrollidinylmethyl|-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-|2-(R)-pyrollidinylmethyl|-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-|3-pyrazolylmethyl|-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-[2-pyrrolylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-[2-thiopheneylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine
N-(2-pyridinylmethyl)-N'-|2-thiazolylmethyl|-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-[2-furanylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-[2-[(phenylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene-dimethanamine;
N-(2-pyridinylmethyl)-N'-(2-aminoethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-3-pyrrolidinyl-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine
N-(2-pyridinylmethyl)-N'-4-piperidinyl-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-[2-[(phenyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(7-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(6-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(1-methyl-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(7-methoxy-3,4-dihydronaphthalenyl)-1-(aminomethyl)-4-benzamide;
N-(2-pyridinylmethyl)-N'-(6-methoxy-3,4-dihydronaphthalenyl)-1-(aminomethyl)-4-benzamide;
N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(7-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(8-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(8-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(8-Fluoro-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(8-Fluoro-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzene-dimethanamine;
N-(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-7-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-7-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-[2-[(2-naphthalenylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;
N-(2-pyridinylmethyl)-N'-[2-(isobutylamino)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-pyridinylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-furanylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-guanidinoethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[bis-[(2-methoxy)phenylmethyl]amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene dimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1H-imidazol-4-ylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene dimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1H-imidazol-2-ylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(phenylureido)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[[N"-(n-butyl)carboxamido]methyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(carboxamidomethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(N"-phenyl)carboxamidomethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(carboxymethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(phenylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1H-benzimidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6-dimethyl-1H-benzimidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine (hydrobromide salt);

N-(2-pyridinylmethyl)-N'-(5-nitro-1H-benzimidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(1H)-5-azabenzimidazol-2-ylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N-(4-phenyl-1H-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(2-pyridinyl)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-benzoxazolyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(trans-2-aminocyclohexyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-phenylethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(3-phenylpropyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(trans-2-aminocyclopentyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-glycinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-alaninamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-aspartamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-pyrazinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-prolinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-lysinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-benzamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-picolinamide;

N'-benzyl-N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-urea;

N'-phenyl-N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-urea;

N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-4-[[(2-pyridinylmethyl)amino]methyl]benzamide;

N-(5,6,7,8-tetrahydro-8-quinolinyl)-4-[[(2-pyridinylmethyl)amino]methyl]benzamide;

N,N'-bis(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(6,7-dihydro-5H-cyclopenta[bacteriapyridin-7-yl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-[(5,6,7,8-tetrahydro-8-quinolinyl)methyl]-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'[(6,7-dihydro-5H-cyclopenta[bacteriapyridin-7-yl)methyl]-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N-(2-methoxyethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N-[2-(4-methoxyphenyl)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-1,4-(5,6,7,8-tetrahydro-8-quinolinyl)benzenedimethanamine;

N-[(2,3-dimethoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[1-(N"-phenyl-N"-methylureido)-4-piperidinyl]-1,3-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[N"-p-toluenesulfonylphenylalanyl)-4-piperidinyl]-1,3-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[1-[3-(2-chlorophenyl)-5-methyl-isoxazol-4-oyl]-4-piperidinyl]-1,3-benzenedimethanamine;

N-[(2-hydroxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(4-acetamidophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(4-phenoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(1-methyl-2-carboxamido)ethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(4-benzyloxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(thiophene-2-yl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[1-(benzyl)-3-pyrrolidinyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-||1-methyl-3-(pyrazol-3-yl)|propyl|-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-|1-(phenyl)ethyl|-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(3,4-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[1-benzyl-3-carboxymethyl-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(3,4-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(3-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[[1-methyl-2-(2-tolyl)carboxamido]ethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(1,5-dimethyl-2-phenyl-3-pyrazolinone-4-yl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(4-propoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(1-phenyl-3,5-dimethylpyrazolin-4-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1H-imidazol-4-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(3-methoxy-4,5-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(3-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(3-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(5-ethylthiophene-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(5-ethylthiophene-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2,6-difluorophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-|(2,6-difluorophenyl)methyl|-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2-difluoromethoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-difluoromethoxyphenylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1,4-benzodioxan-6-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta|b|pyridin-9-yl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[1-(N"-phenyl-N"-methylureido)-4-piperidinyl]-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[N"-p-toluenesulfonylphenylalanyl)-4-piperidinyl]-1,4-benzenedimethanamine;

N-[1-(3-pyridinecarboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(cyclopropylcarboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-|1-(1-phenylcyclopropylcarboxamido)-4-piperidinyl|-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(1,4-benzodioxan-6-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-[3-(2-chlorophenyl)-5-methyl-isoxazol-4-carboxamido|-4-piperidinyl|-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(2-thiomethylpyridine-3-carboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(2,4-difluorophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1-methylpyrrol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2-hydroxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(3-methoxy-4,5-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(3-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[2-(N"-morpholinomethyl)-1-cyclopentyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(1-methyl-3-piperidinyl)propyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(1-methylbenzimidazol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-(benzyl)-3-pyrrolidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[[(1-phenyl-3-(N"-morpholino)]propyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(iso-propyl)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(ethoxycarbonyl)-4-piperidinyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(1-methyl-3-pyrazolyl)propyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-methyl-2-(N",N"-diethylcarboxamido)ethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(1-methyl-2-phenylsulfonyl)ethyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2-chloro-4,5-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-|1-methyl-2-|N"-(4-chlorophenyl)carboxamido|ethyl|-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1-acetoxyindol-3-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(3-benzyloxy-4-methoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(3-quinolylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(8-hydroxy)-2-quinolylmethyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-quinolylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-acetamidophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[1H-imidazol-2-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(3-quinolylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-thiazolylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(4-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(5-benzyloxy)benzo[b]pyrrol-3-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(1-methylpyrazol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-methyl)-1H-imidazol-5-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[[(4-dimethylamino)-1-napthalenyl]methyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1,5-dimethyl-2-phenyl-3-pyrazolinone-4-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-[(1-acetyl-2-(R)-prolinyl]-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-[2-acetamidobenzoyl-4-piperidinyl]-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(2-cyano-2-phenyl)ethyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(N"-acetyltryptophanyl)-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(N"-benzoylvalinyl)-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(4-dimethylaminophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(4-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1-methylbenzimadazol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[1-butyl-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-benzoyl-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-(benzyl)-3-pyrrolidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(1-methyl)benzo[b]pyrrol-3-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1H-imidazol-4-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-(benzyl)-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-methylbenzimidazol-2-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(2-phenyl)benzo[b]pyrrol-3-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(6-methylpyridin-2-yl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(3-methyl-1H-pyrazol-5-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(2-methoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(2-ethoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,3-benzenedimethanamine;

N-(benzyloxyethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(2-ethoxy-1-naphthalenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(6-methylpyridin-2-yl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]guanidine;

N-(2-pyridinylmethyl)-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1,4-benzenedimethanamine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]homopiperazine;

1-[[3-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]homopiperazine;

trans and cis-1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-3,5-piperidinediamine;

N,N'-[1,4-phenylenebis(methylene)]bis-4-(2-pyrimidyl)piperazine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-1-(2-pyridinyl)methylamine;

2-(2-pyridinyl)-5-[[(2-pyridinylmethyl)amino]methyl]-1,2,3,4-tetrahydroisoquinoline;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-3,4-diaminopyrrolidine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-3,4-diacetylaminopyrrolidine;

8-[[4-[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-2,5,8-triaza-3-oxabicyclo[4.3.0]nonane; and

8-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-2,5,8-triazabicyclo[4.3.0]nonane.

Methods to synthesize the compounds useful in the method of the invention are set forth in the U.S. patents and application incorporated hereinabove by reference.

As provided above, AMD3100 is an antagonist with the CXCR4 chemokine receptor (Gerlach, et al., *J. Biol. Chem.* (2001) 276:14153-14160). This compound interferes with the binding of bone marrow stromal cell derived SDF-1 with CXCR4 on stem cells which leads to the release of hematopoietic stem cells from bone marrow into the circulation (Broxmeyer, et al., *Blood* (2001) 98:811a (Abstract)). In a Phase 1 study at the University of Washington, Seattle, a single dose of 80 μg/kg of AMD3100 resulted in a WBC count of 17,000/μl and a peak 6-fold increase in circulating CD34+ progenitor/stem cells at the 6 hour time point (Liles, et al., *Blood* (2001) 98:737a (Abstract)). In another recent study

mice were injected with rhG-CSF and recombinant rat Stem Cell Factor (rrSCF) in order to mobilize large numbers of bone marrow stem cells into the circulation and then we induced a heart attack. The combination of rrSCF and rhG-CSF provides a peak number of circulating stem cells after 5 daily injections. At 27 days post surgery there was a 68% improvement in survival in the treated group versus the controls. At this time the dead tissue was replaced with regenerating myocardium and all functional parameters tested were improved compared with controls (Orlic, et al., *PNAS* (2001) 98:10344-10349).

The compounds of the invention may be prepared in the form of prodrugs, i.e., protected forms which release the compounds of the invention after administration to the subject. Typically, the protecting groups are hydrolyzed in body fluids such as in the bloodstream thus releasing the active compound or are oxidized or reduced in vivo to release the active compound. A discussion of prodrugs is found in *Smith and Williams Introduction to the Principles of Drug Design*, Smith, H. J.; Wright, 2nd ed., London (1988).

The compounds of the invention, as they are polyamines, may be administered prepared in the forms of their acid addition salts or metal complexes thereof. Suitable acid addition salts include salts of inorganic acids that are biocompatible, including HCl, HBr, sulfuric, phosphoric and the like, as well as organic acids such as acetic, propionic, butyric and the like, as well as acids containing more than one carboxyl group, such as oxalic, glutaric, adipic and the like. Typically, at physiological pH, the compounds of the invention will be in the forms of the acid addition salts. Particularly preferred are the hydrochlorides. In addition, when prepared as purified forms, the compounds may also be crystallized as the hydrates.

The compounds of the invention may be administered as sole active ingredients, as mixtures of various compounds of formula (1), and/or in admixture with additional active ingredients that are therapeutically or nutritionally useful, such as antibiotics, vitamins, herbal extracts, anti-inflammatories, glucose, antipyretics, analgesics, granulocyte-macrophage colony stimulating factor (GM-CSF), Interleukin-1 (IL-1), Interleukin-3 (IL-3), Interleukin-8 (IL-8), PIXY-321 (GM-CSF/IL-3 fusion protein), macrophage inflammatory protein, stem cell factor, thrombopoietin, growth related oncogene or chemotherapy and the like.

The compounds of the invention may be formulated for administration to animal subject using commonly understood formulation techniques well known in the art. Formulations which are suitable for particular modes of administration and for compounds of the type represented by those of formula (1) may be found in *Remington's Pharmaceutical Sciences*, latest edition, Mack Publishing Company, Easton, Pa.

Preferably, the compounds are administered by injection, most preferably by intravenous injection, but also by subcutaneous or intraperitoneal injection, and the like. Additional parenteral routes of administration include intramuscular and intraarticular injection. For intravenous or parenteral administration, the compounds are formulated in suitable liquid form with excipients as required. The compositions may contain liposomes or other suitable carriers. For injection intravenously, the solution is made isotonic using standard preparations such as Hank's solution.

Besides injection, other routes of administration may also be used. The compounds may be formulated into tablets, capsules, syrups, powders, or other suitable forms for administration orally. By using suitable excipients, these compounds may also be administered through the mucosa using suppositories or intranasal sprays. Transdermal administration can also be effected by using suitable penetrants and controlling the rate of release.

The formulation and route of administration chosen will be tailored to the individual subject, the nature of the condition to be treated in the subject, and generally, the judgment of the attending practitioner.

Suitable dosage ranges for the compounds of formula (1) vary according to these considerations, but in general, the compounds are administered in the range of about 0.1 μg/kg-5 mg/kg of body weight; preferably the range is about 1 μg/kg-300 μg/kg of body weight; more preferably about 10 μg/kg-100 μg/kg of body weight. For a typical 70-kg human subject, thus, the dosage range is from about 0.7 μg-350 mg; preferably about 700 μg-21 mg; most preferably about 700 μg-7 mg. Dosages may be higher when the compounds are administered orally or transdermally as compared to, for example, i.v. administration.

The compounds may be administered as a single bolus dose, a dose over time, as in i.v. or transdermal administration, or in multiple dosages.

In addition to direct administration to the subject, the compounds of formula (1) can be used in ex vivo treatment protocols to prepare cell cultures which are then used to replenish the blood cells of the subject. Ex vivo treatment can be conducted on autologous cells harvested from the peripheral blood or bone marrow or from allografts from matched donors. The concentration of the compound or compounds of formula (1) alone or in combination with other agents, such as macrophage inflammatory protein is a matter of routine optimization.

Subjects that will respond favorably to the method of the invention include medical and veterinary subjects generally, including human patients. Among other subjects for whom the methods of the invention is useful are cats, dogs, large animals, avians such as chickens, and the like. In general, any subject who would benefit from an elevation of progenitor cells and/or stem cells, or whose progenitor cells and/or stem cells are desirable for stem cell transplantation are appropriate for administration of the invention method.

Typical conditions which may be ameliorated or otherwise benefited by the method of the invention include hematopoietic disorders, such as aplastic anemia, leukemias, drug-induced anemias, and hematopoietic deficits from chemotherapy or radiation therapy. The method of the invention is also useful in enhancing the success of transplantation during and following immunosuppressive treatments as well as in effecting more efficient wound healing and treatment of bacterial inflammation. The method of the present invention is further useful for treating subjects who are immunocompromised or whose immune system is otherwise impaired. Typical conditions which are ameliorated or otherwise benefited by the method of the present invention, include those subjects who are infected with a retrovirus and more specifically who are infected with human immunodeficiency virus (HIV). The method of the invention thus targets a broad spectrum of conditions for which elevation of progenitor cells and/or stem cells in a subject would be beneficial or, where harvesting of progenitor cells and/or stem cell for subsequent stem cell transplantation would be beneficial.

The invention compounds are also administered to regenerate myocardium by mobilizing bone marrow stem cells.

Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention, unless specified.

EXAMPLE 1

Elevation of Mouse Progenitor Cell Levels

The effects of subcutaneous (s.c.) administration of 1,1'-[1,4-phenylene-bis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane (AMD3100) to C3H/H3 J mice on numbers of granulocyte macrophage (CFU-GM), erythroid (BFU-E), and multipotential (CFU-GEMM) progenitor cells per mL of blood were measured. Progenitors were stimulated to form colonies in vitro with the combination of 1 U/ml rhu Epo, 50 ng/ml rhu SLF, 5% Vol/Vol pokeweed mitogen mouse spleen cell conditioned medium (PWMSCM), and 0.1 mM hemin. Plates were scored 7 days after incubation.

The time dependent effects on the number of progenitors mobilized with AMD3100 are for a single s.c. injection of 5 mg/Kg and are shown in Table 1.

TABLE 1

	Absolute Progenitors Per ML Blood Methylcellulose Culture		
	CFU-GM	BFU-E	CFU-GEMM
Control	289.8	49.4	25.8
AMD3100: 15"	791.6	134.5	90.4
AMD3100: 30"	1805.5	209.3	113.5
AMD3100: 120"	828.7	102.3	47.6

To measure the dose-dependent effects, AMD3100 was administered at 1, 2.5, 5 and 10 mg/Kg via a single s.c. injection and the number of progenitors per mL of blood was measured at 1 hour post administration, and the results are shown in Table 2.

TABLE 2

	Absolute Number Progenitors Per ML Blood Methylcellulose Culture		
	CFU-GM	BFU-E	CFU-GEMM
Saline	188.1	16	19
AMD3100: 10 mg/kg	825.6	120.5	79.8
AMD3100: 5 mg/kg	608.4	92.8	69.5
AMD3100: 2.5 mg/kg	687.6	98.9	70.6
AMD3100: 1 mg/kg	424	62	27.1

Fold Change Compared to Time 0

	Progenitors Methylcellulose Culture		
Time	GM	BFU-E	CFU-GEMM
15"	2.73	2.72	3.51
30"	6.23	4.24	4.41
2'	2.86	2.07	1.85

Maximum mobilization of mouse progenitors is achieved at a dose of 2.5 to 10 mg/kg AMD3100, and was observed at 0.25 to 2 hours after injection, as shown in Table 2 above.

EXAMPLE 2

Mobilization of Mouse Progenitor Cells in Combination with MIP-1α and G-CSF

The progenitor cell mobilization capacity of AMD3100 in combination with mouse (mu) macrophage inflammatory protein (MIP-1α) was tested with or without prior administration of rhu G-CSF. MIP-1α has been previously shown to mobilize progenitor cells in mice and humans (Broxmeyer, H. E., et al., *Blood Cells, Molecules, and Diseases* (1998) 24(2): 14-30).

Groups of mice were randomized to receive control diluent (saline) or G-CSF at a dose of 2.5 μg per mouse, twice a day, for two days via s.c. injection. Eleven hours after the final injection of saline or G-CSF, the mice were divided into groups to receive MIP-1α administered i.v. at a total dose of 5 μg, AMD3100 administered s.c. at a dose of 5 mg/Kg, or a combination of both MIP-1α and AMD3100 at the same doses. One hour later, the mice were sacrificed and the number of progenitor cells per mL of blood were measured. These data are summarized in FIG. **1**.

AMD3100 acts in an additive to greater than additive manner for mobilization of progenitor cells when used in combination with mouse (mu) macrophage inflammatory protein (MIP)-1α, each given 11 hours after the addition of rhu G-CSF or control diluent (saline) and 1 hour prior to assessing the blood.

EXAMPLE 3

Clinical Elevation of Progenitor Cell Levels

Five healthy human volunteers having initial white blood cell counts of 4,500-7,500 cells/mm^3 were used in the study. Each patient was given a single subcutaneous (s.c.) injection of 80 μg/kg AMD3100 (i.e., 1,1'-[1,4-phenylene-bis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane) in 0.9% saline, from a stock solution of 10 mg/mL AMD3100 in saline, under sterile conditions. Blood samples were obtained via catheter prior to the dose, and at various times up to 24 hours after dosing.

The blood samples were evaluated for total white blood cells, CD34 positive progenitor cells (via FACS analysis) as a percentage of total white blood cells, as well as the absolute numbers per mL and cycling status of granulocyte macrophage (CFU-GM), erythroid (BFU-E), and multipotential (CFU-GEMM) progenitor cells.

As shown in Tables 3 and 4, administration of AMD3100 caused an elevation of the white blood cell count and of CD34 positive progenitor cells in human volunteers which maximized at 6 hours post-administration.

TABLE 3

AMD3100 induced mobilization of white blood cells in individual volunteers (x 10^3 WBC's).

		TREATMENT							
ID	Screen	Base-line	30 Min	1 Hr	2 Hr	4 Hr	6 Hr	9 Hr	Day 2
P1	7.4	6.41	8.02	14.8	21.4	23.2	26.2	22.3	7.07
P2	6.04	5.45	6.53	8.93	13.5	18.00	19.2	19.6	8.03
P3	4.38	5.8	7.14	9.28	ND	18.10	17.9	18.4	4.98
P4	5.08	5.31	4.37	7.38	12.4	14.6	15.8	13.9	4.98
P5	4.53	5.02	6.08	8.43	ND	16.90	19.3	19.00	4.57

TABLE 4

AMD3100 induced mobilization of CD34 positive cells, expressed as the percentage of the total WBC's in individual volunteers.

		TREATMENT				
ID	Baseline	1 Hr	3 Hr	6 Hr	9 Hr	Day 2
P1	.07	.04	.07	.11	.11	.08
P2	.08	.06	.08	.13	.11	.12
P3	.07	.16	.06	ND	.11	.07
P4	.05	.07	.09	.09	.1	.1
P5	.12	.12	.13	.2	.2	.16

The blood was also analyzed for AMD3100 mobilized these progenitors.

Absolute numbers of unseparated and low density (Ficohypaque separated) nucleated cells per ml of blood, as well as the absolute numbers per ml and cycling status of granulocyte macrophage (CFU-GM), erythroid (BFU-E), and multipotential (CFU-GEMM) progenitor cells were measured in normal donors injected s.c. with AMD3100. The above parameters were assessed prior to injection and at 1, 3, 6, 9 and 24 hours after injection of AMD3100. All progenitor cell results are based on the scoring of 3 culture plates per assay per point.

For the progenitor cell numbers and cycling status, the numbers of CFU-GM, BFU-E and CFU-GEMM in methylcellulose cultures by stimulation of the cells with 1 Unit (U)/ml recombinant human (rhu) erythropoietin, 100 U/ml rhu granulocyte-macrophage colony stimulating factor (GM-CSF), 100 U/ml rhu interleukin-3 (IL-3) and 50 ng/ml rhu steel factor (SLF=stem cell factor (SCF)). The CFU-GM were also evaluated in agar cultures stimulated with 100 U/ml rhu GM-CSF and 50 ng/ml rhu SLF. For both types of assays, colonies were scored after 14 day incubation in a humidified atmosphere with 5% CO_2 and lowered (5%) O_2 tension. Cell cycling status of progenitors was measured using a high specific activity tritiated thymidine kill technique as previously described (Broxmeyer, H. E., et al., *Exp. Hematol.* (1989) 17:455-459).

The results are given first, as the mean fold change in absolute numbers of nucleated cells and progenitors at 1, 3, 6, 9 and 24 hours compared to the preinjection (=Time (T) 0) counts for all five donors, as seen in Tables 5-7.

In the tables below,

STD—Standard deviation

STE—Standard error

PBL-US—peripheral blood-unseparated

PBL-LD—peripheral blood-low density (Ficoll Separated)

P—Significance using a 2 tailed t test

TABLE 5

Fold Change Compared to TIME = 0 (Average of 5 donors)

	NUCLEATED CELLULARITY									
	PBL-US					PBL-LD				
	MEAN	STD	STE	% CHG	P	MEAN	STD	STE	% CHG	P
T = 0	1.00	0.00	0.00	0.0%		1.00	0.00	0.00	0.0%	
T = 1	1.69	0.00	0.00	68.6%	0.017	1.86	0.00	0.00	86.2%	0.000
T = 3	2.80	0.51	0.23	180.2%	0.000	2.86	0.28	0.12	185.6%	0.000
T = 6	3.26	0.61	0.27	225.8%	0.000	3.66	0.43	0.19	266.3%	0.001
T = 9	3.09	0.69	0.31	209.4%	0.000	3.64	1.18	0.53	264.3%	0.001
T = 24	1.07	0.65	0.29	7.0%	0.553	1.05	1.19	0.53	4.6%	0.815

TABLE 6

	METHYLCELLULOSE CULTURE														
	CFU-GM					BFU-E					CFU-GEMM				
	MEAN	STD	STE	% CHG	P	MEAN	STD	STE	% CHG	P	MEAN	STD	STE	% CHG	P
T = 0	1.00	0.00	0.00	0.0%		1.00	0.00	0.00	0.0%		1.00	0.00	0.00	0.0%	
T = 1	4.77	0.00	0.00	376.7%	0.001	1.99	0.00	0.00	98.9%	0.002	2.32	0.00	0.00	131.8%	0.000
T = 3	13.66	1.56	0.70	1266.5%	0.001	3.21	0.50	0.22	221.3%	0.004	4.33	0.44	0.20	332.5%	0.000
T = 6	21.71	5.78	2.58	2070.6%	0.000	6.01	1.25	0.56	500.5%	0.006	10.07	0.59	0.27	907.2%	0.002
T = 9	10.47	5.09	2.28	947.3%	0.000	4.34	2.99	1.34	334.4%	0.000	5.25	4.54	2.03	425.4%	0.014
T = 24	1.56	3.01	1.34	55.5%	0.005	1.26	1.02	0.45	26.3%	0.194	1.53	3.04	1.36	53.2%	0.199

TABLE 7

	AGAR CULTURE CFU-GM				
	MEAN	STD	STE	% CHG	P
T = 0	1.00	0.00	0.00	0.0%	
T = 1	2.81	0.00	0.00	180.8%	0.001
T = 3	8.54	0.75	0.34	754.1%	0.000
T = 6	17.93	1.62	0.72	1692.8%	0.000
T = 9	10.25	4.57	2.04	924.9%	0.000
T = 24	2.08	2.06	1.03	108.3%	0.073

The results are then shown as a fold change from T=0 levels for each individual donor, as shown in Tables 8-10.

TABLE 8

FOLD CHANGE COMPARED TO TIME = 0 for each individual patient [P]

	NUCLEATED CELLULARITY									
	PBL-US					PBL-LD				
	P1	P2	P3	P4	P5	P1	P2	P3	P4	P5
T = 0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
T = 1	2.54	1.38	1.38	1.36	1.76	2.07	1.99	1.48	1.66	2.10
T = 3	3.55	2.74	2.02	2.46	3.23	2.83	3.25	2.17	2.82	3.20
T = 6	3.97	2.94	2.74	2.60	4.04	4.07	3.90	2.27	2.78	5.30
T = 9	3.27	3.30	2.69	2.24	3.96	3.65	4.43	2.47	2.48	5.17
T = 24	1.21	1.43	0.96	0.77	0.99	1.01	1.71	0.79	0.60	1.12

TABLE 9

	PROGENITORS														
	METHYL CELLULOSE CULTURE														
	CFU-GM					BFU-E					CFU-GEMM				
	P1	P2	P3	P4	P5	P1	P2	P3	P4	P5	P1	P2	P3	P4	P5
T = 0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
T = 1	5.09	5.33	3.70	6.87	2.84	2.58	1.48	2.30	1.46	2.13	2.07	2.26	2.22	1.96	3.07
T = 3	7.12	17.02	15.07	20.72	8.40	5.13	1.98	2.61	2.60	3.75	4.25	3.47	4.34	5.14	4.43
T = 6	14.66	23.96	20.99	28.54	20.39	9.14	3.67	4.54	3.34	9.35	7.47	9.35	6.52	9.10	17.92
T = 9	6.26	12.51	9.42	14.08	10.09	5.43	4.61	3.71	2.93	5.05	2.64	7.09	2.47	4.52	9.55
T = 24	1.10	1.91	1.43	1.51	1.83	1.06	1.88	1.14	0.79	1.44	1.12	2.62	0.69	0.98	2.25

TABLE 10

	AGAR CULTURE CFU-GM				
	P1	P2	P3	P4	P5
T = 0	1.00	1.00	1.00	1.00	1.00
T = 1	3.05	3.74	1.67	2.71	2.87
T = 3	8.88	9.49	7.47	10.46	6.40
T = 6	17.77	24.01	14.04	13.07	20.75

TABLE 10-continued

	AGAR CULTURE CFU-GM				
	P1	P2	P3	P4	P5
T = 9		10.28	7.72	10.22	12.78
T = 24		3.69	1.13	1.30	2.20

The actual nucleated cell and progenitor cell numbers per ml of blood and the cycling status (−% progenitors in DNA synthesis (S) phase of the cell cycle) of progenitors for each of the five donors (#'s P1, P2, P3, P4, and P5) is shown in Tables 11 and 12.

TABLE 11

	CFU-GM		BFU-E P1		CFU-GEMM		CFU-GM		BFU-E P2		CFU-GEMM	
	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors
T = 0	247	6%	261	0%	127	6%	273	0%	410	2%	120	0%
T = 1	1259	1%	674	0%	264	0%	1455	0%	608	3%	272	6%
T = 3	1760	1%	1340	13%	540	7%	4646	2%	809	0%	418	0%
T = 6	3624	0%	2388	0%	949	0%	6540	0%	1502	0%	1126	0%
T = 9	1547	2%	1418	11%	335	0%	3416	0%	1886	0%	854	4%
T = 24	271	0%	278	0%	142	0%	521	3%	768	2%	316	0%

	CFU-GM		BFU-E P3		CFU-GEMM		CFU-GM		BFU-E P4		CFU-GEMM	
	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors
T = 0	281	0%	351	0%	140	0%	138	0%	460	0%	101	0%
T = 1	1040	0%	806	0%	312	0%	947	0%	672	0%	199	0%
T = 3	4233	1%	915	0%	610	0%	2857	5%	1195	9%	519	0%
T = 6	5895	0%	1593	0%	916	0%	3936	0%	1533	0%	920	8%
T = 9	2647	0%	1302	0%	347	0%	1942	0%	1348	0%	457	0%
T = 24	402	0%	402	0%	97	0%	208	5%	362	3%	99	0%

	CFU-GM		BFU-E P5		CFU-GEMM	
	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors
T = 0	169	0%	343	1%	55	0%
T = 1	481	0%	730	0%	169	0%
T = 3	1423	5%	1288	3%	244	0%
T = 6	3454	0%	3208	1%	987	0%
T = 9	1710	0%	1731	0%	526	0%
T = 24	310	0%	495	0%	124	0%

TABLE 12

	AGAR Culture CFU-GM P1		AGAR Culture CFU-GM P2		AGAR Culture CFU-GM P3		AGAR Culture CFU-GM P4		AGAR Culture CFU-GM P5	
	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Stauts of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors
T = 0	233	6%	100	0%	140	0%	124	0%	104	0%
T = 1	710	0%	376	0%	234	0%	336	0%	298	3%
T = 3	2070	0%	953	1%	1049	0%	1299	0%	664	0%
T = 6	4142	0%	2409	3%	1972	3%	1623	0%	2153	1%
T = 9			1032	0%	1085	0%	1268	0%	1326	0%
T = 24			371	0%	159	0%	162	0%	229	0%

The results for all five donors were very consistent with maximal fold increases in circulating levels of progenitor cells seen 6 hours after injection of AMD3100 into the human donor subjects. Progenitors were in a slow or non-cycling state prior to and 1, 3, 6, 9 and 24 hours after injection of AMD3100.

EXAMPLE 4

Mobilized Bone Marrow Stem Cells for Myocardial Repair

Adult rats are anesthetized and a thoracotomy is performed. The descending branch of the left coronary artery is ligated and not reperfused. Within 4 to 6 hours after ligation the animals are injected with limit dilution AMD3100 or AMD3100 plus rhG-CSF. Control rats are not treated with the reagents. The animals are monitored at one-week intervals by echocardiography and MRI. The experiment is terminated at 2, 6 to 12 weeks post-surgery. On the day of sacrifice, the hemodynamic functions are analyzed for left ventricle-end diastolic pressure, left ventricle-developed pressure and the rate of rise and fall of left ventricle pressure. The heart is then arrested in diastole and perfused via the abdominal aorta to flush residual blood from the vascular network of the myocardium. This is followed by perfusion of the heart with 10% formalin. Several slices are made through the fixed heart and these are embedded in paraffin and sections. The sections are stained and analyzed by light microscopy to determine the size of the infarct in the treated and control animals. Tissue sections from hearts taken at 2 weeks after surgery are stained with antibodies specific for immature, developing myocyte and blood vessel proteins and analyzed by confocal microscopy. The immunohistochemical analysis involves the identification of transcription factors and surface markers expressed in early stages of myocyte development. The results of this experiment will show that when the reagent AMD3100 is administered within hours after induction of cardiac ischemia, together with or without rhG-CSF, this reagent mobilizes bone marrow stem cells rapidly, and will result in a block to cardiac remodeling and scar formation and will lead to regeneration of the dead myocardium.

The invention claimed is:

1. A method to obtain progenitor and/or stem cells from a subject which method comprises:

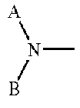
(a) administering to said subject a compound of the formula

Z-linker-Z' (1)

or a pharmaceutically acceptable salt thereof

wherein Z is a cyclic polyamine containing 9-32 ring members of which 2-8 are nitrogen atoms, said nitrogen atoms separated from each other by at least 2 carbon atoms, and wherein said heterocycle may optionally contain additional heteroatoms besides nitrogen and/or may be fused to an additional ring system;

or Z is of the formula



wherein A comprises a monocyclic or bicyclic fused ring system containing at least one N and B is H or an organic moiety of 1-20 atoms,

Z' is either embodied in a form as defined by Z above, or is of the formula

—N(R)—$(CR_2)_n$—X

wherein each R is independently H or straight, branched or cyclic alkyl (1-6C), n is 1 or 2, and X is an aromatic ring, including heteroaromatic rings, or is a mercaptan;

"linker" represents a bond, alkylene (1-6C) or may comprise aryl, fused aryl, and/or oxygen atoms contained in an alkylene chain, and/or may contain keto groups and/or nitrogen or sulfur atoms;

in an amount effective to mobilize said progenitor and/or stem cells into the peripheral blood of said subject; followed by

(b) harvesting said progenitor and/or stem cells.

2. The method of claim **1** wherein Z and Z' are both cyclic polyamines.

3. The method of claim **1** wherein Z and Z' are identical.

4. The method of claim **1** wherein Z is a cyclic polyamine that contains 10-24 members and contains 4 nitrogen atoms.

5. The method of claim **3** wherein Z and Z' are both 1,4,8,11-tetraazacyclotetradecane.

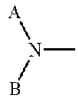
6. The method of claim **1** wherein the linker comprises an aromatic ring bracketed by two methylene moieties.

7. The method of claim **6** wherein the linker is 1,4-phenylene-bis-methylene.

8. The method of claim **1** wherein the compound of formula (1) is 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane or a pharmaceutically acceptable salt thereof.

9. The method of claim **1** wherein

Z is of the formula



wherein A comprises a monocyclic or bicyclic fused ring system containing at least one N and B is H or an organic moiety of 1-20 atoms.

10. The method of claim **1** wherein Z' is

—N(R)—$(CR_2)_n$—X

wherein each R, N and X are as therein defined in.

11. The method of claim **10** wherein the linker is 1,4-phenylene-bis-(methylene).

12. The method of claim **1** wherein Z' is 2-aminomethylpyridine.

13. The method of claim **1** wherein the compound of formula (1) is N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylene-bis-(methylene)]-2-aminomethylpyridine, or a pharmaceutically acceptable salt thereof.

14. The method of claim **1** wherein formula (1) is in the form of an acid addition salt.

15. The method of claim **14** wherein the acid addition salt is hydrochloride.

16. The method of claim **1** wherein the compound of formula (1) or a pharmaceutically acceptable salt thereof is administered to said subject by an intravenous or subcutaneous route.

17. The method of claim **1** wherein the compound of formula (1) or a pharmaceutically acceptable salt thereof is administered to said subject in the dosage range of about 0.1 μg/kg-5 mg/kg of body weight.

18. The method of claim 1 which further comprises administering G-CSF to said subject prior to administering the compound of formula (1) or a pharmaceutically acceptable salt thereof.

19. The method of claim 8 which further comprises administering G-CSF to said subject prior to administering the 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane or a pharmaceutically acceptable salt thereof.

20. The method of claim 13 which further comprises administering G-CSF to said subject prior to administering the N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylene-bis-(methylene)]-2-aminomethylpyridine, or a pharmaceutically acceptable salt thereof.

21. The method of claim 1 wherein the subject is human.

22. The method of claim 18 wherein the subject is human.

23. The method of claim 8 wherein the compound of formula (1) is in the form of an acid addition salt.

24. The method of claim 23 wherein the acid addition salt is hydrochloride.

25. The method of claim 8 wherein the compound of formula (1) or a pharmaceutically acceptable salt thereof is administered to said subject by a subcutaneous route.

26. The method of claim 8 wherein the compound of formula (1) or a pharmaceutically acceptable salt thereof is administered to said subject in the dosage range of about 0.1 μg/kg-5 mg/kg of body weight.

27. The method of claim 8 wherein the subject is human.

28. The method of claim 1 which further comprises administering macrophage inflammatory protein to said subject.

29. The method of claim 8 which further comprises administering macrophage inflammatory protein to said subject.

* * * * *

EXHIBIT C

US006987102B2

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

(10) **Patent No.: US 6,987,102 B2**
(45) **Date of Patent: Jan. 17, 2006**

(54) **METHODS TO MOBILIZE PROGENITOR/STEM CELLS**

(75) Inventors: **Gary J. Bridger**, Bellingham, WA (US); **Michael J. Abrams**, Custer, WA (US); **Geoffrey W. Henson**, Ferndale, WA (US); **Ronald Trevor MacFarland**, Vancouver (CA); **Gary B. Calandra**, Cresco, PA (US); **Hal E. Broxmeyer**, Indianapolis, IN (US); **David C. Dale**, Seattle, WA (US)

(73) Assignee: **Anormed, Inc.**, Langley (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 357 days.

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(65) **Prior Publication Data**

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Related U.S. Application Data

(60) Provisional application No. 60/309,196, filed on Jul. 31, 2001, provisional application No. 60/382,155, filed on May 20, 2002.

(51) **Int. Cl.**
A61K 31/33 (2006.01)
C07D 245/00 (2006.01)
C07D 487/00 (2006.01)

(52) **U.S. Cl.** **514/183**; 540/473; 540/474

(58) **Field of Classification Search** 514/183; 540/473, 474
See application file for complete search history.

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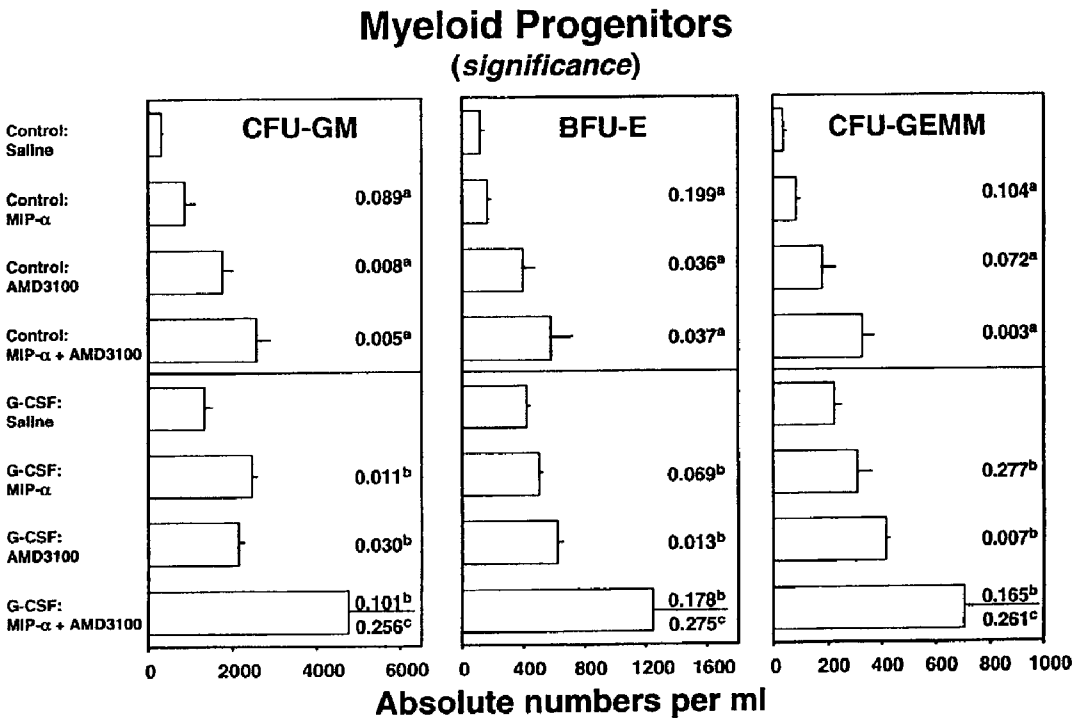
Primary Examiner—Bruce R. Campell
Assistant Examiner—Andrew D. Kosar
(74) *Attorney, Agent, or Firm*—Morrison & Foerster LLP

(57) **ABSTRACT**

Certain nitrogen-containing compounds that bind the chemokine receptor CXCR4 are able to mobilize progenitor and/or stem cells into the peripheral blood to permit harvesting them for stem cell transplantation.

22 Claims, 1 Drawing Sheet

Figure 1.



a = P-value compared to Control/Saline
b = P-value compared to G-CSF/Saline
c = P-value compared to Control/MIP-1α+AMD3100

METHODS TO MOBILIZE PROGENITOR/STEM CELLS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119 (e) to U.S. provisional application Ser. No. 60/309,196 filed 31 Jul. 2001 and to U.S. provisional application Ser. No. 60/382,155 filed 20 May 2002. The contents of these applications are incorporated herein by reference.

TECHNICAL FIELD

The invention is in the field of therapeutics and medicinal chemistry. More particularly, the invention concerns methods to mobilize progenitor/stem cells in subjects by administering certain polyamines.

BACKGROUND ART

Blood cells play a crucial part in maintaining the health and viability of animals, including humans. White blood cells include neutrophils, macrophage, eosinophils and basophils/mast cells as well the B and T cells of the immune system. White blood cells are continuously replaced via the hematopoietic system, by the action of colony stimulating factors (CSF) and various cytokines on stem cells and progenitor cells in hematopoietic tissues. The nucleotide sequences encoding a number of these growth factors have been cloned and sequenced. Perhaps the most widely known of these is granulocyte colony stimulating factor (G-CSF) which has been approved for use in counteracting the negative effects of chemotherapy by stimulating the production of white blood cells and progenitor cells (peripheral blood stem cell mobilization). A discussion of the hematopoietic effects of this factor can be found, for example, in U.S. Pat. No. 5,582,823, incorporated herein by reference.

Several other factors have been reported to increase white blood cells and progenitor cells in both human and animal subjects. These agents include granulocyte-macrophage colony stimulating factor (GM-CSF), Interleukin-1 (IL-1), Interleukin-3 (IL-3), Interleukin-8 (IL-8), PIXY-321 (GM-CSF/IL-3 fusion protein), macrophage inflammatory protein, stem cell factor, thrombopoietin and growth related oncogene, as single agents or in combination (Dale, D., et al., *Am. J. of Hematol.* (1998) 57:7–15; Rosenfeld, C., et al., *Bone Marrow Transplantation* (1997) 17:179–183; Pruijt, J., et al., *Cur. Op. in Hematol.* (1999) 6:152–158; Broxmeyer, H., et al., *Exp. Hematol.* (1995) 23:335–340; Broxmeyer, et al., *Blood Cells, Molecules and Diseases* (1998) 24:14–30; Glaspy, J., et al., *Cancer Chemother. Pharmacol.* (1996) 38 (suppl): S53–S57; Vadhan-Raj, S., et al., *Ann. Intern. Med.* (1997) 126:673–81; King, A., et al., *Blood* (2001) 97:1534–1542; Glaspy, J., et al., *Blood* (1997) 90:2939–2951).

While endogenous growth factors are pharmacologically effective, the well known disadvantages of employing proteins and peptides as pharmaceuticals underlies the need to add to the repertoire of such growth factors with agents that are small molecules. In another aspect, such small molecules are advantageous over proteins and peptides where production in large quantities are desired.

A number of cyclic polyamine antiviral agents have been described in a series of U.S. patents and applications over the last several years. These patents, U.S. Pat. Nos. 5,021,409; 6,001,826; 5,583,131; 5,698,546; and 5,817,807 are

incorporated herein by reference. Also incorporated by reference are PCT publications WO 00/02870 based on an application filed 8 Jul. 1998 and WO 01/44229, based on an application filed 17 Dec. 1999, which describe additional compounds. These publications describe the structural characteristics of the cyclic polyamine antiviral agents.

The structural characteristics of a number of non-cyclic amine antiviral agents have also been described in a series of U.S. applications, now published as PCT publications. These publications, WO 00/56729, based on an application filed 24 Mar. 2000; WO 02/22600, based on applications filed 15 and 20 Sep. 2000; WO 02/22599, based on applications filed 15 and 22 Sep. 2000 as well as WO 02/34745 published 2 May 2002, are incorporated herein by reference in their entirety.

In addition, improved methods for preparation of some of the cyclic polyamine compounds are described in U.S. Pat. Nos. 5,612,478; 5,756,728; 5,801,281; and 5,606,053 and PCT publication WO 02/26721, based on an application filed 29 Sep. 2000. The disclosures of these U.S. documents are also incorporated herein by reference in their entirety.

We have previously found, and have disclosed in PCT publication WO 02/58653, based on an application filed 1 Feb. 2000, that some of the polyamine antiviral agents described in the above mentioned publications have the effect of increasing the white blood cell count. It has now been found that the polyamine antiviral agents described in the above-mentioned publications also have the effect of increasing progenitor cells and/or stem cells.

The development and maturation of blood cells is a complex process. Mature blood cells are derived from hematopoletic precursor cells (progenitor) cells and stem cells present in specific hematopoietic tissues including bone marrow. Within these environments hematopoietic cells proliferate and differentiate prior to entering the circulation. The chemokine receptor CXCR4 and its natural ligand stromal cell derived factor-1 (SDF-1) appear to be important in this process (for reviews see Maekawa, T., et al., *Internal Med.* (2000) 39:90–100; Nagasawa, T., et al., *Int. J. Hematol.* (2000) 72:408–411). This is demonstrated by reports that CXCR4 or SDF-1 knock-out mice exhibit hematopoietic defects (Ma, Q., et al., *Proc. Natl. Acad. Sci USA* (1998) 95:9448–9453; Tachibana, K., et al., *Nature* (1998) 393: 591–594; Zou, Y-R., et al., *Nature* (1998) 393:595–599) is also known that CD34+ progenitor cells express CXCR4 and require SDF-1 produced by bone marrow stromal cells for chemoattraction and engraftment (Peled, A., et al., *Science* (1999) 283:845–848) and that in vitro, SDF-1 is chemotactic for both CD34+ cells (Aiuti, A., et al., *J. Exp. Med.* (1997) 185:111–120; Viardot, A., et al., *Ann. Hematol.* (1998) 77:194–197) and for progenitor/stem cells (Jo, D-Y., et al., *J. Clin. Invest.* (2000) 105: 101–111). SDF-1 is also an important chemoattractant, signaling via the CXCR4 receptor, for several other more committed progenitors and mature blood cells including T-lymphocytes and monocytes (Bleul, C., et al., *J. Exp. Med.* (1996) 184:1101–1109), pro-and pre-B lymphocytes (Fedyk, E. R., et al., *J. Leukoc. Biol.* (1999) 66:667–673; Ma, Q., et al., *Immunity* (1999) 10:463–471) and megakaryocytes (Hodohara, K., et al., *Blood* (2000) 95:769–775; Riviere, C., et al., *Blood* (1999) 95:1511–1523; Majka, M., et al., *Blood* (2000) 96:4142–4151; Gear, A., et al., *Blood* (2001) 97:937–945; Abi-Younes, S., et al, *Circ. Res.* (2000) 86:131–138).

Thus, in summary, it appears that SDF-1 is able to control the positioning and differentiation of cells bearing CXCR4 receptors whether these cells are stem cells (i.e., cells which are CD34+) and/or progenitor cells (which result in forma-

tion of specified types of colonies in response to particular stimuli; that can be $CD34^+$ or $CD34^-$) or cells that are somewhat more differentiated.

Recently, considerable attention has been focused on the number of CD34+ cells mobilized in the pool of peripheral blood progenitor cells used for autologous stem cell transplantation. The CD34+ population is the component thought to be primarily responsible for the improved recovery time after chemotherapy and the cells most likely responsible for long-term engraftment and restoration of hematopoiesis (Croop, J. M., et al., *Bone Marrow Transplantation* (2000) 26:1271–1279). The mechanism by which CD34+ cells re-engraft may be due to the chemotactic effects of SDF-1 on CXCR4 expressing cells (Voermans, C. Blood, 2001, 97, 799–804; Ponomaryov, T., et al., *J. Clin. Invest.* (2000) 106:1331–1339). More recently, adult hematopoietic stem cells were shown to be capable of restoring damaged cardiac tissue in mice (Jackson, K., et al., *J. Clin. Invest.* (2001) 107:1395–1402; Kocher, A., et al., *Nature Med.* (2001) 7:430–436).

Thus, the role of the CXCR4 receptor in managing cell positioning and differentiation has assumed considerable significance.

Citation of the above documents is not intended as an admission that any of the foregoing is pertinent prior art. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents. Further, all documents referred to throughout this application are incorporated in their entirety by reference herein.

DISCLOSURE OF THE INVENTION

The invention is directed to methods of treating animal subjects, in particular, veterinary and human subjects, to enhance the number of progenitor cells and/or stem cells. The progenitor and/or stem cells may be harvested and used in cell transplantation. The methods of the invention employ polyamines including those described in the patents and publications incorporated hereinabove by reference.

In one aspect, therefore, the invention is directed to a method to elevate the progenitor cells and/or stem cells, in a subject, which method comprises administering to said subject an amount of a compound of formula (1) or of a pharmaceutical composition thereof effective to elevate progenitor cell and/or stem cell levels. In one embodiment, bone marrow progenitor and/or stem cells are mobilized for myocardial repair.

The methods of the invention also include treatment of cell populations ex vivo with the compounds of formula (1) and introducing the treated populations into a compatible subject. The compounds of formula (1) may be used alone or in combination with other compounds and compositions to enhance the population of stem cells and/or progenitor cells in the peripheral blood. An enhanced production of white blood cells in the bone marrow may result as well.

In additional aspects, the invention is directed to pharmaceutical compositions containing the compound of formula (1) for use in effecting an elevation of progenitor cells and/or stem cells in animal subjects.

The compounds of formula (1) are of the formula:

Z-linker-Z' (1)

wherein Z is a cyclic polyamine containing 9–32 ring members of which 2–8 are nitrogen atoms, said nitrogen atoms separated from each other by at least 2 carbon atoms, and wherein said heterocycle may optionally contain additional heteroatoms besides nitrogen and/or may be fused to an additional ring system;

or Z is of the formula

wherein A comprises a monocyclic or bicyclic fused ring system containing at least one N and B is H or an organic moiety of 1–20 atoms;

Z' may be embodied in a form as defined by Z above, or alternatively may be of the formula

$$—N(R)—(CR_2)_n—X$$

wherein each R is independently H or straight, branched or cyclic alkyl (1–6C),

n is 1 or 2, and

X is an aromatic ring, including heteroaromatic rings, or is a mercaptan;

"linker" represents a bond, alkylene (1–6C) or may comprise aryl, fused aryl, oxygen atoms contained in an alkylene chain, or may contain keto groups or nitrogen or sulfur atoms.

The preferred forms of the compounds of the invention are discussed below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a graph of obtaining myeloid progenitors in response to treatment with 1,1'-[1,4-phenylene-bis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane (AMD3100) in combination with macrophage inflammatory protein after administration of G-CSF.

MODES OF CARRYING OUT THE INVENTION

The compounds useful in the invention are of the general formula set forth as formula (1) above. Certain embodiments are preferred; included among these are the compounds set forth in the above-incorporated U.S. patents and other patent documents.

The cyclic polyamine and non-cyclic amine antiviral agents described in the above-mentioned documents inhibit HIV replication via inhibition of CXCR4, the co-receptor required for fusion and entry of T-tropic HIV strains, and also inhibit the binding and signaling induced by the natural ligand, the chemokine SDF-1. While not wishing to be bound by any theory, the compounds of formula (1) which inhibit the binding of SDF-1 to CXCR4 effect an increase in stem and/or progenitor cells by virtue of such inhibition. Enhancing the stem and/or progenitor cells in blood is helpful in treatments to alleviate the effects of protocols that adversely affect the bone marrow, such as those that result in leukopenia. These are known side-effects of chemotherapy and radiotherapy. The compounds of formula (1) also enhance the success of bone marrow transplantation, enhance wound healing and bum treatment, and aid in restoration of damaged organ tissue. They also combat bacterial infections that are prevalent in leukemia. The compounds of formula (1) are used to mobilize and harvest CD34+ cells via apheresis with and without combinations

with other mobilizing factors. The harvested cells are used in treatments requiring stem cell transplantations.

As used herein, the term "progenitor cells" refers to cells that, in response to certain stimuli, can form differentiated hematopoietic or myeloid cells. The presence of progenitor cells can be assessed by the ability of the cells in a sample to form colony-forming units of various types, including, for example, CFU-GM (colony-forming units, granulocyte-macrophage); CFU-GEMM (colony-forming units, multipotential); BFU-E (burst-forming units, erythroid); HPP-CFC (high proliferative potential colony-forming cells); or other types of differentiated colonies which can be obtained in culture using known protocols.

As used herein, "stem" cells are less differentiated forms of progenitor cells. Typically, such cells are often positive for CD34. Some stem cells do not contain this marker, however. These CD34+ cells can be assayed using fluorescence activated cell sorting (FACS) and thus their presence can be assessed in a sample using this technique.

In general, CD34+ cells are present only in low levels in the blood, but are present in large numbers in bone marrow. While other types of cells such as endothelial cells and mast cells also may exhibit this marker, CD34 is considered an index of stem cell presence.

In general, in compounds of formula (1), preferred embodiments of Z and Z' are cyclic polyamine moieties having from 9–24C that include 3–5 nitrogen atoms. Particularly preferred are 1,5,9,13-tetraazacyclohexadecane; 1,5,8,11,14-pentaazacyclohexadecane; 1,4,8,11-tetraazacyclotetradecane; 1,5,9-triazacyclododecane; 1,4,7,10-tetraazacyclododecane; and the like, including such cyclic polyamines which are fused to an additional aromatic or heteroaromatic rings and/or containing a heteroatom other than nitrogen incorporated in the ring. Embodiments wherein the cyclic polyamine contains a fused additional cyclic system or one or more additional heteroatoms are described in U.S. Pat. No. 5,698,546 and WO 01/44229 incorporated hereinabove by reference. Also preferred are

3,7,11,17-tetraazabicyclo(13.3.1)heptadeca-1(17),13,15-triene;

4,7,10,17-tetraazabicyclo(13.3.1)heptadeca-1(17),13,15-triene;

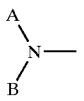
1,4,7,10-tetraazacyclotetradecane; 1,4,7-triazacyclotetradecane; and

4,7,10-triazabicyclo(13.3.1)heptadeca-1(17),13,15-triene.

When Z' is other than a cyclic polyamine as defined in Z, its preferred embodiments are set forth in U.S. Pat. No. 5,817,807, also incorporated herein by reference.

Preferred forms where

Z is of the formula



wherein A comprises a monocyclic or bicyclic fused ring system containing at least one N and B is H or an organic moiety of 1–20 atoms are disclosed in WO 00/56729; WO 02/22600; WO 02/34745; and WO 02/22599 cited above and all incorporated herein by reference.

Preferred forms of the linker moiety include those wherein the linker is a bond, or wherein the linker includes an aromatic moiety flanked by alkylene, preferably methylene moieties. Preferred linking groups include the methylene bracketed forms of 1,3-phenylene, 2,6-pyridine, 3,5-pyridine, 2,5-thiophene, 4,4'-(2,2'-bipyrimidine); 2,9-(1,10-phenanthroline) and the like. A particularly preferred linker is 1,4-phenylene-bis-(methylene).

Particularly preferred embodiments of the compound of the formula (1) include 2,2'-bicyclam; 6,6'-bicyclam; the embodiments set forth in U.S. Pat. Nos. 5,021,409, and 6,001,826, and in particular 1,1'-[1,4-phenylene-bis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane, set forth in U.S. Pat. No. 5,583,131, and designated herein AMD3100.

Other preferred embodiments include

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis (methylene)]-2-aminomethyl)pyridine;

7,7'-[1,4-phenylenebis(methylene)]bis-4,7,10,17-tetraazabicyclo-[13.3.1]heptadeca-1(17),13,15-triene;

7,7'-[1,4-phenylenebis(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene;

1,1'-[1,3-phenylenebis(methylene)]-bis-1,4,8,11-tetra-aza-cyclotetradecane;

1,1'-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetra-aza-cyclotetradecane;

1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraaza-cyclotetradecane;

1,1'-[1,3-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraaza-cyclotetradecane;

11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

N-[4-(1,4,7-triazacyclotetra-decane)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,7,10-triazabicyclo[13.3.1]heptadeca-1(17),13,15-triene)-1,4-phenylenebis(methylene)]-2-(aminomethyl) pyridine;

N-[7-(4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-[4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

3,3'-(bis-1,5,9,13-tetraazacyclohexadecane); 3,3'-(bis-1,5,8,11,14-pentaazacyclohexadecane), methylene (or polymethylene) di-1-N-1,4,8,11-tetraazacyclotetradecane;

3,3'-bis-1,5,9,13,-tetraazacyclohexadecane;

3,3'-bis-1,5,8,11,14-pentaazacyclohexadecane;

5,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,6'-bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-butanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-pentanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-hexanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

3,3'-bis-1,5,9,13-tetraazacyclohexadecane;

3,3'-bis-1,5,8,11,14-pentaazacyclohexadecane;

5,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,6'-bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-butanediyl)bis-1,4,8,11-tetraazacyclotetradecane;
11,11'-(1,2-pentanediyl)bis-1,4,8,11-tetraazacyclotetradecane;
11,11'-(1,2-hexanediyl)bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[1,3-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane;
1,1'-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane;
1,1'-[3,3'-biphenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;
11,11'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,11-tetraazacyclotetradecane;
1,11'-[1,4-phenylene-bis(methylene)]-1,4,8,11-tetraazacyclotetradecane;
1,1'-[2,6-pyridine-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;
1,1-[3,5-pyridine-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[2,5-thiophene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[4,4'-(2,2'-bipyridine)-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[2,9-(1,10-phenanthroline)-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[1,3-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;
1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;
1,1'-[5-nitro-1,3-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[2,4,5,6-tetrachloro-1,3-phenyleneis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[2,3,5,6-tetrafluoro-1,4-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[1,4-naphthylene-bis-(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[1,3-phenylenebis-(methylene)]bis-1,5,9-triazacyclododecane;
1,1'-[1,4-phenylene-bis-(methylene)]-1,5,9-triazacyclododecane;
1,1'-[2,5-dimethyl-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[2,5-dichloro-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[2-bromo-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[6-phenyl-2,4-pyridinebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;
7,7'-[1,4-phenylene-bis(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene;
7,7'-[1,4-phenylene-bis(methylene)]bis[15-chloro-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene];
7,7'-[1,4-phenylene-bis(methylene)]bis[15-methoxy-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene];
7,7'-[1,4-phenylene-bis(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1]-heptadeca-13,16-triene-15-one;
7,7'-[1,4-phenylene-bis(methylene)]bis-4,7,10,17-tetraazabicyclo[13.3.1]-heptadeca-1(17),13,15-triene;
8,8'-[1,4-phenylene-bis(methylene)]bis-4,8,12,19-tetraazabicyclo[15.3.1]nonadeca-1(19),15,17-triene;
6,6'-[1,4-phenylene-bis(methylene)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene;
6,6'-[1,3-phenylene-bis(methylene)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene;
17,17'-[1,4-phenylene-bis(methylene)]bis-3,6,14,17,23,24-hexaazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8,10,12(24),19,21-hexaene;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-methyl)pyridine;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-N-methyl-2-(aminomethyl)pyridine;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-)amino-methyl)pyridine;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-3-(amino-methyl)pyridine;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-(2-amino-methyl-5-methyl)pyrazine;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-ethyl)pyridine;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-methyl)thiophene;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-ethyl)mercaptan;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-amino-benzylamine;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-amino-benzylamine;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-(amino-ethyl)imidazole;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-benzylamine;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-purine;
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-phenylpiperazine;
N-[4-(1,4,7-Triazacyclotetra-decanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[7-(4,7,10,17-Tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[7-(4,7,10-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[4-[4,7,10-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[1-(1,4,7-Triazacyclotetra-decanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[4-[4,7,10,17-Tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[3-(3,6,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[3-(3,6,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,3-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[4-(4,7,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[7-(4,7,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[6-(3,6,9-Triazabicyclo[11.3.1]pentadeca-1(15),11,13-trienyl)-1,3-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[7-(4,10,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[4-(1,7-Diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,10-Diazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl) pyridine;

N-[4-(11-Fluoro-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11,11-difluoro-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(1,4,7-triazacyclotetradecan-2-one)-yl))-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[12-(5-oxa-1,9-diazacyclotetradecanyl)-1,4-phenylenebis (methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-oxa-1,7-diazacyclotetradecanyl)-1,4-phenylenebis (methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-thia-1,7-diazacyclotetradecanyl)-1,4-phenylenebis (methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-sulfoxo-1,7-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-sulfono-1,7-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(1,4,7-triazacyclotetradecan-3-one)-yl))-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-(2-pyridinylmethyl)-N'-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(6,7-dihydro-5H-cyclopenta[b] pyridin-7-yl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-pyridinylmethyl)amino] ethyl]-N'-(1-methyl-1,2,3,4-tetrahydro-8-quinolinyl)-1,4-benzene dimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1H-imidazol-2-ylmethyl) amino]ethyl]-N'-(1-methyl-1,2,3,4-tetrahydro-8-quinolinyl)-1,4-benzene dimethanamine;

N-(2-pyridinylmethyl)-N'-(1,2,3,4-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1H-imidazol-2-ylmethyl) amino]ethyl]-N'-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,4-benzene dimethanamine;

N-(2-pyridinylmethyl)-N'-(2-phenyl-5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(2-phenyl-5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-5-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-5-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(2-amino-3-phenyl)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1H-imidazol-4-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-quinolinylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-(2-naphthoyl)aminoethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(S)-(2-acetylamino-3-phenyl) propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(S)-(2-acetylamino-3-phenyl) propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[3-((2-naphthalenylmethyl) amino)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(S)-pyrollidinylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(R)-pyrollidinylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[3-pyrazolylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-pyrrolylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-thiopheneylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine

N-(2-pyridinylmethyl)-N'-[2-thiazolylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-furanylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(phenylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-aminoethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-3-pyrrolidinyl-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine

N-(2-pyridinylmethyl)-N'-4-piperidinyl-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(phenyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(7-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(6-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1-methyl-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(7-methoxy-3,4-dihydronaphthalenyl)-1-(aminomethyl)-4-benzamide;

N-(2-pyridinylmethyl)-N'-(6-methoxy-3,4-dihydronaphthalenyl)-1-(aminomethyl)-4-benzamide;

N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(7-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(8-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(8-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(8-Fluoro-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(8-Fluoro-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-7-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-7-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-naphthalenylmethyl) amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(isobutylamino)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-pyridinylmethyl)amino] ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene-dimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-furanylmethyl)amino] ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene-dimethanamine;

N-(2-pyridinylmethyl)-N'-(2-guanidinoethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[bis-[(2-methoxy)phenylm-ethyl]amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene dimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1H-imidazol-4-ylmethyl) amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene dimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1H-imidazol-2-ylmethyl) amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(phenylureido)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[[N"-(n-butyl)carboxamido]methyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene-dimethanamine;

N-(2-pyridinylmethyl)-N'-(carboxamidomethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(N"-phenyl)carboxamidom-ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene-dimethanamine;

N-(2-pyridinylmethyl)-N'-(carboxymethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(phenylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1H-benzimidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene-dimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6-dimethyl-1H-benzimidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine (hydrobromide salt);

N-(2-pyridinylmethyl)-N'-(5-nitro-1H-benzimidazol-2-ylm-ethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene-dimethanamine;

N-(2-pyridinylmethyl)-N'-[(1H)-5-azabenzimidazol-2-ylm-ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene-dimethanamine;

N-(2-pyridinylmethyl)-N-(4-phenyl-1H-imidazol-2-ylm-ethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzene-dimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(2-pyridinyl)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-benzoxazolyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(trans-2-aminocyclohexyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimetha-namine;

N-(2-pyridinylmethyl)-N'-(2-phenylethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(3-phenylpropyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(trans-2-aminocyclopentyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimetha-namine;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-glycinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-alaninamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-aspartamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-pyrazinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-prolinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-lysinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-benzamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-picolinamide;

N'-Benzyl-N-[[4-[[(2-pyridinylmethyl) amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-urea;

N'-phenyl-N-[[4-[[(2-pyridinylmethyl) amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-urea;

N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-4-[[(2-pyridinylmethyl)amino]methyl]benzamide;

N-(5,6,7,8-tetrahydro-8-quinolinyl)4-[[(2-pyridinylmethyl) amino]methyl]benzamide;

N,N'-bis(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimetha-namine;

N,N'-bis(2-pyridinylmethyl)-N'-(6,7-dihydro-5H-cyclo-penta[bacteriapyridin-7-yl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-[(5,6,7,8-tetrahydro-8-quinolinyl)methyl]-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'[(6,7-dihydro-5H-cyclo-penta[bacteriapyridin-7-yl)methyl] -1,4-benzenedimetha-namine;

N-(2-pyridinylmethyl)-N-(2-methoxyethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N-[2-(4-methoxyphenyl)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimetha-namine;

N,N'-bis(2-pyridinylmethyl)-1,4-(5,6,7,8-tetrahydro-8-quinolinyl)benzenedimethanamine;

N-[(2,3-dimethoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimetha-namine;

N,N'-bis(2-pyridinylmethyl)-N-[1-(N"-phenyl-N"-methy-lureido)-4-piperidinyl]-1,3-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[N"-p-toluenesulfonylphe-nylalanyl)-4-piperidinyl]-1,3-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[1-[3-(2-chlorophenyl)-5-methyl-isoxazol-4-oyl]-4-piperidinyl]-1,3-benzene-dimethanamine;

N-[(2-hydroxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(4-acetamidophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimetha-namine;

N-[(4-phenoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(1-methyl-2-carboxamido)ethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(4-benzyloxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(thiophene-2-yl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[1-(benzyl)-3-pyrrolidinyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[[1-methyl-3-(pyrazol-3-yl)]propyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-(phenyl)ethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(3,4-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[1-benzyl-3-carboxymethyl-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(3,4-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(3-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[[1-methyl-2-(2-tolyl)carboxamido]ethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(1,5-dimethyl-2-phenyl-3-pyrazolinone-4-yl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(4-propoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(1-phenyl-3,5-dimethylpyrazolin-4-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1H-imidazol-4-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(3-methoxy-4,5-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta [b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(3-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(3-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(5-ethylthiophene-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(5-ethylthiophene-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2,6-difluorophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(2,6-difluorophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2-difluoromethoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-difluoromethoxyphenylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1,4-benzodioxan-6-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[1-(N"-phenyl-N"-methylureido)-4-piperidinyl]-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[N"-p-toluenesulfonylphenylalanyl)-4-piperidinyl]-1,4-benzenedimethanamine;

N-[1-(3-pyridinecarboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(cyclopropylcarboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(1-phenylcyclopropylcarboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(1,4-benzodioxan-6-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-[3-(2-chlorophenyl)-5-methyl-isoxazol-4-carboxamido]-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(2-thiomethylpyridine-3-carboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(2,4-difluorophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1-methylpyrrol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2-hydroxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(3-methoxy-4,5-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(3-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[2-(N"-morpholinomethyl)-1-cyclopentyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(1-methyl-3-piperidinyl)propyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(1-methylbenzimidazol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-(benzyl)-3-pyrrolidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[[(1-phenyl-3-(N"-morpholino)]propyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(iso-propyl)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(ethoxycarbonyl)-4-piperidinyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(1-methyl-3-pyrazolyl)propyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-methyl-2-(N",N"-diethylcarboxamido)ethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(1-methyl-2-phenylsulfonyl)ethyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2-chloro-4,5-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-methyl-2-[N"-(4-chlorophenyl)carboxamido]ethyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1-acetoxyindol-3-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(3-benzyloxy-4-methoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(3-quinolylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(8-hydroxy)-2-quinolylmethyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-quinolylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-acetamidophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[1H-imidazol-2-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(3-quinolylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-thiazolylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(4-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(5-benzyloxy)benzo[b]pyrrol-3-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(1-methylpyrazol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-methyl)-1H-imidazol-5-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[[(4-dimethylamino)-1-napthalenyl]methyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1,5-dimethyl-2-phenyl-3-pyrazolinone-4-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-[(1-acetyl-2-(R)-prolinyl]-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-[2-acetamidobenzoyl-4-piperidinyl]-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(2-cyano-2-phenyl)ethyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(N"-acetyltryptophanyl)-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(N"-benzoylvalinyl)-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(4-dimethylaminophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(4-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1-methylbenzimadazol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[1-butyl-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-benzoyl-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-(benzyl)-3-pyrrolidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(1-methyl)benzo[b]pyrrol-3-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1H-imidazol-4-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-(benzyl)-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-methylbenzimidazol-2-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(2-phenyl)benzo[b]pyrrol-3-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(6-methylpyridin-2-yl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(3-methyl-1H-pyrazol-5-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(2-methoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(2-ethoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,3-benzenedimethanamine;

N-(benzyloxyethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(2-ethoxy-1-naphthalenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(6-methylpyridin-2-yl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl] guanidine;

N-(2-pyridinylmethyl)-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1,4-benzenedimethanamine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl] homopiperazine;

1-[[3-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl] homopiperazine;

trans and cis-1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-3,5-piperidinediamine;

N,N'-[1,4-Phenylenebis(methylene)]bis-4-(2-pyrimidyl) piperazine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-1-(2-pyridinyl)methylamine;

2-(2-pyridinyl)-5-[[(2-pyridinylmethyl)amino]methyl]-1,2,3,4-tetrahydroisoquinoline;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-3,4-diaminopyrrolidine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-3,4-diacetylaminopyrrolidine;

8-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-2,5,8-triaza-3-oxabicyclo[4.3.0]nonane; and

8-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-2,5,8-triazabicyclo[4.3.0]nonane.

Methods to synthesize the compounds useful in the method of the invention are set forth in the U.S. patents and application incorporated hereinabove by reference.

As provided above, AMD3100 is an antagonist with the CXCR4 chemokine receptor (Gerlach et al., *J. Biol. Chem.* (2001) 276:14153–14160). This compound interferes with the binding of bone marrow stromal cell derived SDF-1 with CXCR4 on stem cells which leads to the release of hematopoietic stem cells from bone marrow into the circulation (Broxmeyer et al., *Blood* (2001) 98:811a (Abstract)). In a

Phase 1 study at the University of Washington, Seattle, a single dose of 80 μg/kg of AMD-3100 resulted in a WBC count of 17,000/μl and a peak 6-fold increase in circulating CD34+ progenitor/stem cells at the 6 hour time point (Liles et al., *Blood* 2001 98:737a (Abstract)). In another recent study mice were injected with rhG-CSF and recombinant rat Stem Cell Factor (rrSCF) in order to mobilize large numbers of bone marrow stem cells into the circulation and then we induced a heart attack. The combination of rrSCF and rhG-CSF provides a peak number of circulating stem cells after 5 daily injections. At 27 days post surgery there was a 68% improvement in survival in the treated group versus the controls. At this time the dead tissue was replaced with regenerating myocardium and all functional parameters tested were improved compared with controls (Orlic et al., *PNAS* (2001) 98:10344–10349).

The compounds of the invention may be prepared in the form of prodrugs, i.e., protected forms which release the compounds of the invention after administration to the subject. Typically, the protecting groups are hydrolyzed in body fluids such as in the bloodstream thus releasing the active compound or are oxidized or reduced in vivo to release the active compound. A discussion of prodrugs is found in *Smith and Williams Introduction to the Principles of Drug Design*, Smith, H. J.; Wright, 2nd ed., London (1988).

The compounds of the invention, as they are polyamines, may be administered prepared in the forms of their acid addition salts or metal complexes thereof. Suitable acid addition salts include salts of inorganic acids that are biocompatible, including HCl, HBr, sulfuric, phosphoric and the like, as well as organic acids such as acetic, propionic, butyric and the like, as well as acids containing more than one carboxyl group, such as oxalic, glutaric, adipic and the like. Typically, at physiological pH, the compounds of the invention will be in the forms of the acid addition salts. Particularly preferred are the hydrochlorides. In addition, when prepared as purified forms, the compounds may also be crystallized as the hydrates.

The compounds of the invention may be administered as sole active ingredients, as mixtures of various compounds of formula (1), and/or in admixture with additional active ingredients that are therapeutically or nutritionally useful, such as antibiotics, vitamins, herbal extracts, anti-inflammatories, glucose, antipyretics, analgesics, granulocyte-macrophage colony stimulating factor (GM-CSF), Interleukin-1 (IL-1), Interleukin-3 (IL-3), Interleukin-8 (IL-8), PIXY-321 (GM-CSF/IL-3 fusion protein), macrophage inflammatory protein, stem cell factor, thrombopoietin, growth related oncogene or chemotherapy and the like.

The compounds of the invention may be formulated for administration to animal subject using commonly understood formulation techniques well known in the art. Formulations which are suitable for particular modes of administration and for compounds of the type represented by those of formula (1) may be found in *Remington's Pharmaceutical Sciences*, latest edition, Mack Publishing Company, Easton, Pa.

Preferably, the compounds are administered by injection, most preferably by intravenous injection, but also by subcutaneous or intraperitoneal injection, and the like. Additional parenteral routes of administration include intramuscular and intraarticular injection. For intravenous or parenteral administration, the compounds are formulated in suitable liquid form with excipients as required. The compositions may contain liposomes or other suitable carriers. For injection intravenously, the solution is made isotonic using standard preparations such as Hank's solution.

Besides injection, other routes of administration may also be used. The compounds may be formulated into tablets, capsules, syrups, powders, or other suitable forms for administration orally. By using suitable excipients, these compounds may also be administered through the mucosa using suppositories or intranasal sprays. Transdermal administration can also be effected by using suitable penetrants and controlling the rate of release.

The formulation and route of administration chosen will be tailored to the individual subject, the nature of the condition to be treated in the subject, and generally, the judgment of the attending practitioner.

Suitable dosage ranges for the compounds of formula (1) vary according to these considerations, but in general, the compounds are administered in the range of about 0.1 μg/kg–5 mg/kg of body weight; preferably the range is about 1 μg/kg–300 μg/kg of body weight; more preferably about 10 μg/kg–100 μg/kg of body weight. For a typical 70-kg human subject, thus, the dosage range is from about 0.7 μg–350 mg; preferably about 700 μg–21 mg; most preferably about 700 μg–7 mg. Dosages may be higher when the compounds are administered orally or transdermally as compared to, for example, i.v. administration.

The compounds may be administered as a single bolus dose, a dose over time, as in i.v. or transdermal administration, or in multiple dosages.

In addition to direct administration to the subject, the compounds of formula (1) can be used in ex vivo treatment protocols to prepare cell cultures which are then used to replenish the blood cells of the subject. Ex vivo treatment can be conducted on autologous cells harvested from the peripheral blood or bone marrow or from allografts from matched donors. The concentration of the compound or compounds of formula (1) alone or in combination with other agents, such as macrophage inflammatory protein is a matter of routine optimization.

Subjects that will respond favorably to the method of the invention include medical and veterinary subjects generally, including human patients. Among other subjects for whom the methods of the invention is useful are cats, dogs, large animals, avians such as chickens, and the like. In general, any subject who would benefit from an elevation of progenitor cells and/or stem cells, or whose progenitor cells and/or stem cells are desirable for stem cell transplantation are appropriate for administration of the invention method.

Typical conditions which may be ameliorated or otherwise benefited by the method of the invention include hematopoietic disorders, such as aplastic anemia, leukemias, drug-induced anemias, and hematopoictic deficits from chemotherapy or radiation therapy. The method of the invention is also useful in enhancing the success of transplantation during and following immunosuppressive treatments as well as in effecting more efficient wound healing and treatment of bacterial inflammation. The method of the present invention is further useful for treating subjects who are immunocompromised or whose immune system is otherwise impaired. Typical conditions which are ameliorated or otherwise benefited by the method of the present invention, include those subjects who are infected with a retrovirus and more spe

cifically who are infected with human immunodeficiency virus (HIV). The method of the invention thus targets a broad spectrum of conditions for which elevation of progenitor cells and/or stem cells in a subject would be beneficial or, where harvesting of progenitor cells and/or stem cell for subsequent stem cell transplantation would be beneficial.

The invention compounds are also administered to regenerate myocardium by mobilizing bone marrow stem cells.

Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention, unless specified.

EXAMPLE 1

Elevation of Mouse Progenitor Cell Levels

The effects of subcutaneous (s.c.) administration of 1,1'-[1,4-phenylene-bis(methylene)] -bis-1,4,8,11-tetraazacyclotetradecane (AMD3100) to C3H/H3 J mice on numbers of granulocyte macrophage (CFU-GM), erythroid (BFU-E), and multipotential (CFU-GEMM) progenitor cells per mL of blood were measured. Progenitors were stimulated to form colonies in vitro with the combination of 1 U/ml rhu Epo, 50 ng/ml rhu SLF, 5% $^{Vol}/_{Vol}$ pokeweed mitogen mouse spleen cell conditioned medium (PWMSCM), and 0.1 mM hemin. Plates were scored 7 days after incubation.

The time dependent effects on the number of progenitors mobilized with AMD3100 are for a single s.c. injection of 5 mg/Kg and are shown in Table 1.

TABLE 1

	Absolute Progenitors Per ML Blood Methylcellulose Culture		
	CFU-GM	BFU-E	CFU-GEMM
Control	289.8	49.4	25.8
AMD3100: 15"	791.6	134.5	90.4
AMD3100: 30"	1805.5	209.3	113.5
AMD3100: 120"	828.7	102.3	47.6

To measure the dose-dependent effects, AMD3100 was administered at 1, 2.5, 5 and 10 mg/Kg via a single s.c. injection and the number of progenitors per mL of blood was measured at 1 hour post administration, and the results are shown in Table 2.

TABLE 2

	Absolute Number Progenitors Per ML Blood Methylcellulose Culture		
	CFU-GM	BFU-E	CFU-GEMM
Saline	188.1	16	19
AMD3100: 10 mg/kg	825.6	120.5	79.8
AMD3100: 5 mg/kg	608.4	92.8	69.5
AMD3100: 2.5 mg/kg	687.6	98.9	70.6
AMD3100: 1 mg/kg	424	62	27.1

Fold Change Compared to Time 0

	Progenitors Methylcellulose Culture		
Time	GM	BFU-E	CFU-GEMM
15"	2.73	2.72	3.51
30"	6.23	4.24	4.41
2'	2.86	2.07	1.85

Maximum mobilization of mouse progenitors is achieved at a dose of 2.5 to 10 mg/kg AMD3100, and was observed at 0.25 to 2 hours after injection, as shown in Table 2 above.

EXAMPLE 2

Mobilization of Mouse Progenitor Cells in Combination with MIP-1α and G-CSF

The progenitor cell mobilization capacity of AMD3100 in combination with mouse (mu) macrophage inflammatory protein (MIP-1α) was tested with or without prior administration of rhu G-CSF. MIP-1α has been previously shown to mobilize progenitor cells in mice and humans (Broxmeyer, H. E., et al., *Blood Cells, Molecules, and Diseases* (1998) 24(2):14–30).

Groups of mice were randomized to receive control diluent (saline) or G-CSF at a dose of 2.5 μg per mouse, twice a day, for two days via s.c. injection. Eleven hours after the final injection of saline or G-CSF, the mice were divided into groups to receive MIP-1α administered I.V. at a total dose of 5 μg, AMD3100 administered s.c. at a dose of 5 mg/Kg, or a combination of both MIP-1α and AMD3100 at the same doses. One hour later, the mice were sacrificed and the number of progenitor cells per mL of blood were measured. These data are summarized in FIG. **1**.

AMD3100 acts in an additive to greater than additive manner for mobilization of progenitor cells when used in combination with mouse (mu) macrophage inflammatory protein (MIP)-1α, each given 11 hours after the addition of rhu G-CSF or control diluent (saline) and 1 hour prior to assessing the blood.

EXAMPLE 3

Clinical Elevation of Progenitor Cell Levels

Five healthy human volunteers having initial white blood cell counts of 4,500–7,500 cells/mm^3 were used in the study. Each patient was given a single subcutaneous (s.c.) injection of 80 μg/kg AMD3100 (i.e., 1,1'-[1,4-phenylene-bis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane) in 0.9% saline, from a stock solution of 10 mg/mL AMD3100 in saline, under sterile conditions. Blood samples were obtained via catheter prior to the dose, and at various times up to 24 hours after dosing.

The blood samples were evaluated for total white blood cells, CD34 positive progenitor cells (via FACS analysis) as a percentage of total white blood cells, as well as the absolute numbers per mL and cycling status of granulocyte macrophage (CFU-GM), erythroid (BFU-E), and multipotential (CFU-GEMM) progenitor cells.

As shown in Tables 3 and 4, administration of AMD3100 caused an elevation of the white blood cell count and of CD34 positive progenitor cells in human volunteers which maximized at 6 hours post-administration.

TABLE 3

AMD3100 induced mobilization of white blood cells in individual volunteers (× 10^3 WBC's).

			TREATMENT						
ID	Screen	Base-line	30 Min	1 Hr	2 Hr	4 Hr	6 Hr	9 Hr	Day 2
P1	7.4	6.41	8.02	14.8	21.4	23.2	26.2	22.3	7.07
P2	6.04	5.45	6.53	8.93	13.5	18.00	19.2	19.6	8.03
P3	4.38	5.8	7.14	9.28	ND	18.10	17.9	18.4	4.98
P4	5.08	5.31	4.37	7.38	12.4	14.6	15.8	13.9	4.98
P5	4.53	5.02	6.08	8.43	ND	16.90	19.3	19.00	4.57

TABLE 4

AMD3100 induced mobilization of CD34 positive cells, expressed as the percentage of the total WBC's in individual volunteers.

		TREATMENT				
ID	Baseline	1 Hr	3 Hr	6 Hr	9 Hr	Day 2
P1	.07	.04	.07	.11	.11	.08
P2	.08	.06	.08	.13	.11	.12
P3	.07	.16	.06	ND	.11	.07
P4	.05	.07	.09	.09	.1	.1
P5	.12	.12	.13	.2	.2	.16

The blood was also analyzed for AMD3100 mobilized these progenitors.

Absolute numbers of unseparated and low density (Ficohypaque separated) nucleated cells per ml of blood, as well as the absolute numbers per ml and cycling status of granulocyte macrophage (CFU-GM), erythroid (BFU-E), and multipotential (CFU-GEMM) progenitor cells were measured in normal donors injected s.c. with AMD3100. The above parameters were assessed prior to injection and at 1, 3, 6, 9 and 24 hours after injection of AMD3100. All progenitor cell results are based on the scoring of 3 culture plates per assay per point.

For the progenitor cell numbers and cycling status, the numbers of CFU-GM, BFU-E and CFU-GEMM in methylcellulose cultures by stimulation of the cells with 1 Unit (U)/ml recombinant human (rhu) erythropoietin, 100 U/ml rhu granulocyte-macrophage colony stimulating factor (GM-CSF), 100 U/ml rhu interleukin-3 (IL-3) and 50 ng/ml rhu steel factor (SLF=stem cell factor (SCF)). The CFU-GM were also evaluated in agar cultures stimulated with 100 U/ml rhu GM-CSF and 50 ng/ml rhu SLF. For both types of assays, colonies were scored after 14 day incubation in a humidified atmosphere with 5% CO_2 and lowered (5%) O_2 tension. Cell cycling status of progenitors was measured using a high specific activity tritiated thymidine kill technique as previously described (Broxmeyer, H. E., et al., *Exp. Hematol.* (1989) 17:455–459).

The results are given first, as the mean fold change in absolute numbers of nucleated cells and progenitors at 1, 3, 6, 9 and 24 hours compared to the preinjection (=Time(T)0) counts for all five donors, as seen in Tables 5–7.

In the tables below

TABLE 5

Fold Change Compared to TIME = 0 (Average of 5 donors)

	NUCLEATED CELLULARITY									
	PBL-US					PBL-LD				
	MEAN	STD	STE	% CHG	P	MEAN	STD	STE	% CHG	P
T = 0	1.00	0.00	0.00	0.0%		1.00	0.00	0.00	0.0%	
T = 1	1.69	0.00	0.00	68.6%	0.017	1.86	0.00	0.00	86.2%	0.000
T = 3	2.80	0.51	0.23	180.2%	0.000	2.86	0.28	0.12	185.6%	0.000
T = 6	3.26	0.61	0.27	225.8%	0.000	3.66	0.43	0.19	266.3%	0.001
T = 9	3.09	0.69	0.31	209.4%	0.000	3.64	1.18	0.53	264.3%	0.001
T = 24	1.07	0.65	0.29	7.0%	0.553	1.05	1.19	0.53	4.6%	0.815

STD - Standard deviation
STE - Standard error
PEL-US - peripheral blood-unseparated
PBL-LD - peripheral blood-low density (Ficoll Separated)
P - Significance using a 2 tailed t test

TABLE 6

	METHYLCELLULOSE CULTURE														
	CFU-GM					BFU-E					CFU-GEMM				
	MEAN	STD	STE	% CHG	P	MEAN	STD	STE	% CHG	P	MEAN	STD	STE	% CHG	P
T = 0	1.00	0.00	0.00	0.0%		1.00	0.00	0.00	0.0%		1.00	0.00	0.00	0.0%	
T = 1	4.77	0.00	0.00	376.7%	0.001	1.99	0.00	0.00	98.9%	0.002	2.32	0.00	0.00	131.8%	0.000
T = 3	13.66	1.56	0.70	1266.5%	0.001	3.21	0.50	0.22	221.3%	0.004	4.33	0.44	0.20	332.5%	0.000
T = 6	21.71	5.78	2.58	2070.6%	0.000	6.01	1.25	0.56	500.5%	0.006	10.07	0.59	0.27	907.2%	0.002
T = 9	10.47	5.09	2.28	947.3%	0.000	4.34	2.99	1.34	334.4%	0.000	5.25	4.54	2.03	425.4%	0.014
T = 24	1.56	3.01	1.34	55.5%	0.005	1.26	1.02	0.45	26.3%	0.194	1.53	3.04	1.36	53.2%	0.199

TABLE 7

	AGAR CULTURE CFU-GM				
	MEAN	STD	STE	% CHG	P
T = 0	1.00	0.00	0.00	0.0%	
T = 1	2.81	0.00	0.00	180.8%	0.001
T = 3	8.54	0.75	0.34	754.1%	0.000
T = 6	17.93	1.62	0.72	1692.8%	0.000
T = 9	10.25	4.57	2.04	924.9%	0.000
T = 24	2.08	2.06	1.03	108.3%	0.073

The results are then shown as a fold change from T=0 levels for each individual donor, as shown in Tables 8–10.

TABLE 8

FOLD CHANGE COMPARED TO TIME = 0 for each individual patient [P]

	NUCLEATED CELLULARITY									
	PBL-US					PBL-LD				
	P1	P2	P3	P4	P5	P1	P2	P3	P4	P5
T = 0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
T = 1	2.54	1.38	1.38	1.36	1.76	2.07	1.99	1.48	1.66	2.10
T = 3	3.55	2.74	2.02	2.46	3.23	2.83	3.25	2.17	2.82	3.20
T = 6	3.97	2.94	2.74	2.60	4.04	4.07	3.90	2.27	2.78	5.30
T = 9	3.27	3.30	2.69	2.24	3.96	3.65	4.43	2.47	2.48	5.17
T = 24	1.21	1.43	0.96	0.77	0.99	1.01	1.71	0.79	0.60	1.12

TABLE 9

PROGENITORS

	METHYLCELLULOSE CULTURE														
	CFU-GM					BFU-E					CFU-GEMM				
	P1	P2	P3	P4	P5	P1	P2	P3	P4	P5	P1	P2	P3	P4	P5
T = 0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
T = 1	5.09	5.33	3.70	6.87	2.84	2.58	1.48	2.30	1.46	2.13	2.07	2.26	2.22	1.96	3.07
T = 3	7.12	17.02	15.07	20.72	8.40	5.13	1.98	2.61	2.60	3.75	4.25	3.47	4.34	5.14	4.43
T = 6	14.66	23.96	20.99	28.54	20.39	9.14	3.67	4.54	3.34	9.35	7.47	9.35	6.52	9.10	17.92
T = 9	6.26	12.51	9.42	14.08	10.09	5.43	4.61	3.71	2.93	5.05	2.64	7.09	2.47	4.52	9.55
T = 24	1.10	1.91	1.43	1.51	1.83	1.06	1.88	1.14	0.79	1.44	1.12	2.62	0.69	0.98	2.25

TABLE 10

	AGAR CULTURE CFU-GM				
	P1	P2	P3	P4	P5
T = 0	1.00	1.00	1.00	1.00	1.00
T = 1	3.05	3.74	1.67	2.71	2.87
T = 3	8.88	9.49	7.47	10.46	6.40
T = 6	17.77	24.01	14.04	13.07	20.75
T = 9		10.28	7.72	10.22	12.78
T = 24		3.69	1.13	1.30	2.20

The actual nucleated cell and progenitor cell numbers per ml of blood and the cycling status (=% progenitors in DNA synthesis (S) phase of the cell cycle) of progenitors for each of the five donors (#'s P1, P2, P3, P4, and P5) is shown in Tables 11 and 12.

TABLE 11

	CFU-GM		BFU-E P1		CFU-GEMM		CFU-GM		BFU-E P2		CFU-GEMM	
	Absolute # of Pro-genitors per ML	Cycling Status of Pro-genitors	Absolute # of Pro-genitors per ML	Cycling Status of Pro-genitors	Absolute # of Pro-genitors per ML	Cycling Status of Pro-genitors	Absolute # of Pro-genitors per ML	Cycling Status of Pro-genitors	Absolute # of Pro-genitors per ML	Cycling Status of Pro-genitors	Absolute # of Pro-genitors per ML	Cycling Status of Pro-genitors
T = 0	247	6%	261	0%	127	6%	273	0%	410	2%	120	0%
T = 1	1259	1%	674	0%	264	0%	1455	0%	608	3%	272	6%
T = 3	1760	1%	1340	13%	540	7%	4646	2%	809	0%	418	0%
T = 6	3624	0%	2388	0%	949	0%	6540	0%	1502	0%	1126	0%
T = 9	1547	2%	1418	11%	335	0%	3416	0%	1886	0%	854	4%
T = 24	271	0%	278	0%	142	0%	521	3%	768	2%	316	0%

	CFU-GM		BFU-E P3		CFU-GEMM		CFU-GM		BFU-E P4		CFU-GEMM	
	Absolute # of Pro-genitors per ML	Cycling Status of Pro-genitors	Absolute # of Pro-genitors per ML	Cycling Status of Pro-genitors	Absolute # of Pro-genitors per ML	Cycling Status of Pro-genitors	Absolute # of Pro-genitors per ML	Cycling Status of Pro-genitors	Absolute # of Pro-genitors per ML	Cycling Status of Pro-genitors	Absolute # of Pro-genitors per ML	Cycling Status of Pro-genitors
T = 0	281	0%	351	0%	140	0%	138	0%	460	0%	101	0%
T = 1	1040	0%	806	0%	312	0%	947	0%	672	0%	199	0%
T = 3	4233	1%	915	0%	610	0%	2857	5%	1195	9%	519	0%
T = 6	5895	0%	1593	0%	916	0%	3936	0%	1533	0%	920	8%
T = 9	2647	0%	1302	0%	347	0%	1942	0%	1348	0%	457	0%
T = 24	402	0%	402	0%	97	0%	208	5%	362	3%	99	0%

	CFU-GM		BFU-E P5		CFU-GEMM	
	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors
T = 0	169	0%	343	1%	55	0%
T = 1	481	0%	730	0%	169	0%
T = 3	1423	5%	1288	3%	244	0%
T = 6	3454	0%	3208	1%	987	0%
T = 9	1710	0%	1731	0%	526	0%
T = 24	310	0%	495	0%	124	0%

TABLE 12

	AGAR Culture CFU-GM P1		AGAR Culture CFU-GM P2		AGAR Culture CFU-GM P3		AGAR Culture CFU-GM P4		AGAR Culture CFU-GM P5	
	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors	Absolute # of Progenitors per ML	Cycling Status of Progenitors
T = 0	233	6%	100	0%	140	0%	124	0%	104	0%
T = 1	710	0%	376	0%	234	0%	336	0%	298	3%
T = 3	2070	0%	953	1%	1049	0%	1299	0%	664	0%
T = 6	4142	0%	2409	3%	1972	3%	1623	0%	2153	1%
T = 9			1032	0%	1085	0%	1268	0%	1326	0%
T = 24			371	0%	159	0%	162	0%	229	0%

The results for all five donors were very consistent with maximal fold increases in circulating levels of progenitor cells seen 6 hours after injection of AMD3100 into the human donor subjects. Progenitors were in a slow or non-cycling state prior to and 1, 3, 6, 9 and 24 hours after injection of AMD3100.

EXAMPLE 4

Mobilized Bone Marrow Stem Cells for Myocardial Repair

Adult rats are anesthetized and a thoracotomy is performed. The descending branch of the left coronary artery is ligated and not reperfused. Within 4 to 6 hours after ligation the animals are injected with limit dilution AMD-3100 or AMD-3100 plus rhG-CSF. Control rats are not treated with the reagents. The animals are monitored at one-week intervals by echocardiography and MRI. The experiment is terminated at 2, 6 to 12 weeks post-surgery. On the day of sacrifice, the hemodynamic functions are analyzed for left ventricle-end diastolic pressure, left ventricle-developed pressure and the rate of rise and fall of left ventricle pressure. The heart is then arrested in diastole and perfused via the abdominal aorta to flush residual blood from the vascular network of the myocardium. This is followed by perfusion of the heart with 10% formalin. Several slices are made through the fixed heart and these are embedded in paraffin and sections. The sections are stained and analyzed by light microscopy to determine the size of the infarct in the treated and control animals. Tissue sections from hearts taken at 2 weeks after surgery are stained with antibodies specific for immature, developing myocyte and blood vessel proteins and analyzed by confocal microscopy. The immunohistochemical analysis involves the identification of transcription factors and surface markers expressed in early stages of myocyte development. The results of this experiment will show that when the reagent AMD-3100 is administered within hours after induction of cardiac ischemia, together with or without rhG-CSF, this reagent mobilizes bone marrow stem cells rapidly, and will result in a block to cardiac remodeling and scar formation and will lead to regeneration of the dead myocardium.

What is claimed is:

1. A method to obtain progenitor and/or stem cells from a subject

which method comprises

(a) administering to said subject a compound of the formula

Z-linker-Z' (1)

or pharmaceutically acceptable salt or prodrug form thereof

wherein Z is a cyclic polyamine containing 9–32 ring members of which 2–8 are nitrogen atoms, said nitrogen atoms separated from each other by at least 2 carbon atoms, and wherein said heterocycle may optionally contain additional heteroatoms besides nitrogen and/or may be fused to an additional ring system;

or Z is of the formula

wherein A comprises a monocyclic or bicyclic fused ring system containing at least one N and B is H or an organic moiety of 1–20 atoms,

Z' is either embodied in a form as defined by Z above, or is of the formula

—N(R)—$(CR_2)_n$—X

wherein each R is independently H or straight, branched or cyclic alkyl (1–6C), n is 1 or 2, and X is an aromatic ring, including heteroaromatic rings, or is a mercaptan;

"linker" represents a bond, alkylene (1–6C) or may comprise aryl, fused aryl, and/or oxygen atoms contained in an alkylene chain, and/or may contain keto groups and/or nitrogen or sulfur atoms;

in an amount effective to mobilize said progenitor and/or stem cells into the peripheral blood of said subject; followed by

(b) harvesting said progenitor and/or stem cells by apheresis.

2. The method of claim **1** wherein Z and Z' are both cyclic polyamines.

3. The method of claim **1** wherein Z and Z' are identical.

4. The method of claim **1** wherein Z is a cyclic polyamine that contains 10–24 members and contains 4 nitrogen atoms.

5. The method of claim **3** wherein Z and Z' are both 1,4,8,11-tetraazocyclotetradecane.

6. The method of claim **1** wherein the linker comprises an aromatic ring bracketed by two methylene moieties.

7. The method of claim **6** wherein the linker is 1,4-phenylene-bis-methylene.

8. The method of claim **7** wherein the compound of formula (1) is 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane.

9. The method of claim **1** wherein

Z is of the formula

wherein A comprises a monocyclic or bicyclic fused ring system containing at least one N and B is H or an organic moiety of 1–20 atoms.

10. The method of claim **1** wherein formula (1) is in the form of its acid addition salt.

11. The method of claim **10** wherein the acid addition salt is hydrochloride.

12. The method of claim **1** wherein the compound is administered to said subject by an intravenous or subcutaneous route.

13. The method of claim **1** wherein the compound of formula (1) is administered to said subject in the dosage range of about 0.1 μg/kg–5 mg/kg of body weight.

14. The method of claim **1** which further comprises administering macrophage inflammatory protein to said subject.

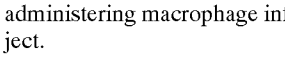
15. The method of claim **1** which further comprises administering G-CSF to said subject prior to performing said method.

16. A method to obtain progenitor and/or stem cells from a subject which method comprises

(a) administering to said subject an amount of a compound that binds to the chemokine receptor CXCR4 sufficient to mobilize said progenitor and/or stem cells into the peripheral blood of said subject; followed by

(b) harvesting said progenitor and/or stem cells by apheresis.

17. The method of claim **4** wherein Z' is



wherein each R, N and X are as defined in claim **1**.

18. The method of claim **17** wherein the linker is 1,4-phenylene-bis-(methylene).

19. The method of claim **18** wherein Z' is 2-aminomethyl-pyridine.

20. The method of claim **19** wherein the compound of formula (1) is N[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylene-bis-(methylene)]-2-aminomethyl-pyridine.

21. The method of claim **1** wherein the subject is human.

22. The method of claim **16** wherein the subject is human.

* * * * *