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*Attorneys for Plaintiffs  
Teva Neuroscience, Inc.,  
Teva Pharmaceuticals USA, Inc. and  
Teva Pharmaceutical Industries Ltd.*

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

TEVA NEUROSCIENCE, INC., TEVA  
PHARMACEUTICALS USA, INC., and TEVA  
PHARMACEUTICAL INDUSTRIES LTD.,

Civil Action No.:

*Plaintiffs,*

v.

WATSON PHARMA, INC., WATSON  
LABORATORIES, INC., WATSON  
PHARMACEUTICALS, INC., WATSON  
PHARMA PRIVATE LTD. - UNIT IV,  
MYLAN PHARMACEUTICALS, INC.,  
MYLAN INC., MYLAN LLC, ORCHID  
CHEMICALS & PHARMACEUTICALS  
LTD., ORCHID HEALTHCARE (a division  
of Orchid Chemicals & Pharmaceuticals Ltd.),  
and ORGENUS PHARMA INC.

*Defendants.*

**COMPLAINT**

Teva Neuroscience, Inc., Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. (collectively, “Teva” or “Plaintiffs”) bring this action for patent infringement against Defendants Watson Pharma, Inc., Watson Laboratories, Inc., Watson Pharmaceuticals, Inc. and Watson Pharma Private Ltd. - Unit IV (collectively, “Watson”); Mylan Pharmaceuticals,

Inc., Mylan Inc. and Mylan LLC (collectively, “Mylan”); and Orgenus Pharma Inc., Orchid Chemicals & Pharmaceuticals Ltd. and Orchid Healthcare (a division of Orchid Chemicals & Pharmaceuticals Ltd.) (collectively “Orchid”). Watson, Mylan and Orchid collectively are referred to as “Defendants” herein.

1. This is an action by Teva against Defendants for infringement of United States Patent No. 5,453,446 (“’446 patent”). This action arises out of Defendants’ filing of Abbreviated New Drug Applications (“ANDAs”) seeking approval by the United States Food and Drug Administration (“FDA”) to sell generic versions of Azilect<sup>®</sup>, Teva’s innovative oral treatment for idiopathic Parkinson’s disease, prior to the expiration of the ’446 patent.

## **THE PARTIES**

### **Teva**

2. Teva Neuroscience, Inc. (“Teva Neuroscience”) is a Delaware corporation with its principal place of business at 901 E. 104<sup>th</sup> Street, Suite 900, Kansas City, Missouri 64131.

3. Teva Pharmaceuticals USA, Inc. (“Teva USA”) is a Delaware corporation with its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454.

4. Teva Pharmaceutical Industries Ltd. (“Teva Ltd.”) is an Israeli company with its principal place of business at 5 Basel Street, Petach Tikva, 49131, Israel.

### **Watson**

5. Watson Pharmaceuticals, Inc. (“Watson Pharmaceuticals”) is a Nevada corporation with its principal place of business at 311 Bonnie Circle, Corona, California 92880. Upon information and belief, Watson Pharmaceuticals conducts business at 360 Mt. Kemble Avenue, Morristown, New Jersey 07962.

6. Watson Pharma, Inc. (“Watson Pharma”) is a Delaware corporation with its principal place of business at 360 Mt. Kemble Avenue, Morristown, New Jersey 07962. Upon information and belief, Watson Pharma is a wholly-owned subsidiary of Watson Pharmaceuticals.

7. Upon information and belief, the offices of Watson Pharma in Morristown, New Jersey, are Watson’s executive offices and commercial headquarters.

8. Watson Laboratories, Inc. (“WLI - NV”) is a Nevada corporation with its principal place of business at 311 Bonnie Circle, Corona, California 92880. Upon information and belief, WLI – NV is a wholly-owned subsidiary of Watson Pharmaceuticals.

9. Watson Laboratories, Inc. (“WLI – FL”) is a Florida corporation with its principal place of business at 4955 Orange Drive, Davie, Florida 33314. Upon information and belief, WLI – FL is a wholly-owned subsidiary of Watson Pharmaceuticals.

10. Watson Laboratories, Inc. (“WLI – DE”) is a Delaware corporation with its principal place of business at 577 Chipeta Way, Salt Lake City, Utah 84108. Upon information and belief, WLI – DE is a wholly-owned subsidiary of Watson Pharmaceuticals.

11. Watson Laboratories, Inc. (“WLI – NY”) is a New York corporation with its principal place of business at 1033 Stoneleigh Avenue, Carmel, New York 10512 and/or 26 Bethpage Road, Copiague, NY 11726. Upon information and belief, WLI – NY is a wholly-owned subsidiary of Watson Pharmaceuticals.

12. Watson Laboratories, Inc. (“WLI – CT”) is a Connecticut corporation with its principal place of business at 131 West Street, Danbury, Connecticut 06810. Upon information and belief, WLI – CT is a wholly-owned subsidiary of Watson Pharmaceuticals.

13. “WLI” hereafter collectively refers to each and every individual WLI entity identified above that submitted, or collaborated or acted in concert with Watson in the preparation or submission of, Watson’s ANDA Number 201823 (“Watson ANDA”).

14. WLI conducts business at 360 Mt. Kemble Avenue, Morristown, New Jersey 07960.

15. Watson Pharma Private Ltd. - Unit IV (“WPP”) is an Indian company with its principal place of business at 201/301, HDO Building, Corporate Enclave, B Wing, 100 Link Road, Chakla, Andheri (E), Mumbai, Maharashtra 400 099 India. Upon information and belief, WPP is a subsidiary of Watson Pharmaceuticals.

16. WLI submitted the Watson ANDA No. 201823 to the FDA.

17. Upon information and belief, WLI’s preparation and submission of the Watson ANDA was done collaboratively with, and at least in part for the benefit of, Watson Pharmaceuticals, Watson Pharma and WPP.

18. Upon information and belief, Watson Pharmaceuticals, Watson Pharma, WLI and WPP collaborate or act in concert in the development, manufacturing, testing, packaging, marketing, promoting, selling and distributing of generic pharmaceutical products in the United States, including this Judicial District, for the benefit of Watson.

### **Mylan**

19. Mylan Inc. (“Mylan Inc.”) is a Pennsylvania corporation with its principal place of business at 1500 Corporate Drive, Canonsburg, Pennsylvania 15317. Upon information and belief, Mylan Inc. conducts business in Liberty Corner, New Jersey.

20. Mylan Pharmaceuticals, Inc. (“Mylan Pharmaceuticals”) is a West Virginia corporation with its principal place of business at 781 Chestnut Ridge Road, Morgantown, West

Virginia 26505. Upon information and belief, Mylan Pharmaceuticals is a wholly-owned subsidiary of Mylan Inc.

21. Mylan LLC (“Mylan LLC”) is a Delaware corporation with its principal place of business at Lot 24, Caguas West Industrial Parkway 156, Caguas, Puerto Rico 00725. Upon information and belief, Mylan LLC is a subsidiary of Mylan Inc. Upon information and belief, Mylan LLC was formerly known as Mylan Inc. (Puerto Rico).

22. Mylan Pharmaceuticals submitted ANDA No. 201971 (“Mylan ANDA”) to the FDA.

23. Upon information and belief, Mylan Pharmaceuticals’ preparation and submission of the Mylan ANDA on was done collaboratively with, and at least in part for the benefit of, Mylan Inc. and Mylan LLC.

24. Upon information and belief, Mylan Pharmaceuticals, Mylan Inc. and Mylan LLC collaborate or act in concert in the development, manufacturing, testing, packaging, marketing, promoting, selling and distributing of generic pharmaceutical products in the United States, including this Judicial District, for the benefit of Mylan.

### **Orchid**

25. Orchid Chemicals & Pharmaceuticals Ltd. (“Orchid Ltd.”) is an Indian company with its principal place of business at Orchid Towers, 313 Valluvar Kottam High Road, Nungambakkam, Chennai – 600 034, Tamil Nadu, India.

26. Orchid Ltd. has a division doing business as Orchid Healthcare (“Orchid d/b/a Orchid Healthcare”) with a principal place of business at Plot Nos. B5(Pt) & B6 (Pt), SIPCOT Industrial Park, Irungattukottai, Sriperumbudur – 602 105, Kancheepuram Dist., Tamil Nadu, India.

27. Orgenus Pharma Inc. (“Orgenus”) is a New Jersey corporation with its principal place of business at 700 Alexander Park, Suite 104, Princeton, New Jersey 08540. Upon information and belief, Orgenus is a wholly-owned subsidiary of Orchid Pharmaceuticals, Inc., which is a wholly-owned subsidiary of Orchid Ltd.

28. Orgenus is Orchid Ltd.’s “Primary Business Contact for US and Canada” and Orchid Ltd.’s website directs the public to Orgenus and its Executive Vice President – Business Development & Operations, Mr. Satish Srinivasan, concerning Orchid Ltd.’s business matters in the United States.

29. Orchid d/b/a Orchid Healthcare submitted ANDA No. 201970 (“Orchid ANDA”) to the FDA.

30. Orgenus is the authorized U.S. agent for the Orchid ANDA.

31. Upon information and belief, Orchid d/b/a Orchid Healthcare’s preparation and submission of the Orchid ANDA was done collaboratively with, and at least in part for the benefit of, Orchid Ltd. and Orgenus.

32. Upon information and belief, Orgenus supports, collaborates or acts in concert with Orchid Ltd. and Orchid d/b/a Orchid Healthcare in obtaining regulatory approval for and the sales and distribution of Orchid products in the United States.

33. Orchid Ltd., Orchid d/b/a Orchid Healthcare and Orgenus collaborate or act in concert in the development, manufacturing, testing, packaging, marketing, promoting, selling and distributing of generic pharmaceutical products in the United States, including this Judicial District, for the benefit of Orchid.

## **JURISDICTION AND VENUE**

### **Subject Matter Jurisdiction**

34. This action for patent infringement arises under 35 U.S.C. § 271.

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

### **Personal Jurisdiction Over Watson**

36. Upon information and belief, this Court has personal jurisdiction over Watson Pharma at least because Watson Pharma: (1) has its principal place of business in New Jersey and conducts business in this Judicial District; and (2) has engaged in continuous and systematic contacts with New Jersey and/or purposefully availed itself of this forum by, among other things, making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, Watson generic pharmaceutical products in this Judicial District, and deriving substantial revenue from such activities.

37. Upon information and belief, this Court has personal jurisdiction over Watson Pharmaceuticals at least because Watson Pharmaceuticals: (1) has a place of business and conducts business in this Judicial District; (2) directly and through its wholly-owned subsidiaries, including but not limited to Watson Pharma, manufactures, markets, distributes and/or sells generic Watson pharmaceuticals throughout the United States, including this Judicial District; (3) directly and through its wholly-owned subsidiaries, including but not limited to Watson Pharma, has engaged in continuous and systematic contacts with New Jersey and/or purposefully availed itself of this forum by, among other things, making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, Watson generic pharmaceutical products in this Judicial District, and deriving substantial revenue from such

activities; and (4) has previously consented to personal jurisdiction and filed claims in this Judicial District.

38. Upon information and belief, this Court has personal jurisdiction over WLI at least because WLI: (1) has a place of business in New Jersey and conducts business in this Judicial District; (2) develops, manufactures, sells and/or distributes generic Watson pharmaceutical products for the U.S. market, including this Judicial District; (3) has engaged in continuous and systematic contacts with New Jersey and/or purposefully availed itself of this forum by, among other things, making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, pharmaceutical products in this Judicial District, and deriving substantial revenue from such activities; and (4) has previously consented to personal jurisdiction and filed claims in this Judicial District.

39. Upon information and belief, this Court has personal jurisdiction over WPP at least because: (1) the generic pharmaceutical products that Watson distributes, markets and sells in this Judicial District for the benefit of Watson include products manufactured by WPP and (2) WPP has engaged in continuous and systematic contacts with New Jersey and/or purposefully availed itself of this forum by, among other things, assisting, collaborating or acting in concert with Watson Pharmaceuticals, Watson Pharma and/or WLI to make, use, offer to sell or sell generic Watson pharmaceutical products in this Judicial District, and deriving substantial revenue from such activities.

**Personal Jurisdiction Over Mylan**

40. Upon information and belief, this Court has personal jurisdiction over Mylan Pharmaceuticals at least because Mylan Pharmaceuticals: (1) is registered to do business in New Jersey and has appointed as its agent for receipt of service of process Corporate Service



Company, 830 Bear Tavern Road, West Trenton, New Jersey 08628; (2) markets, distributes and sells generic pharmaceutical products in the United States and in this Judicial District; (3) has engaged in continuous and systematic contacts with New Jersey and/or purposefully availed itself of this forum by, among other things, making, shipping, using, importing, offering to sell or selling, or causing others to ship, use, import, offer to sell, or sell, pharmaceutical products in this Judicial District, and deriving substantial revenue from such activities, and by filing claims in this Judicial District; and (4) has previously consented to personal jurisdiction in this Judicial District.

41. Upon information and belief, this Court has personal jurisdiction over Mylan Inc. at least because Mylan Inc.: (1) has a place of business in Liberty Corner, New Jersey; (2) is registered to do business in New Jersey and has appointed as its agent for receipt of service of process Corporate Service Company, 830 Bear Tavern Road, West Trenton, New Jersey 08628; (3) develops, manufactures, markets, promotes, sells and/or distributes generic pharmaceutical products in the United States and this Judicial District directly and/or through Mylan Pharmaceuticals, Mylan LLC and/or other agents or subsidiaries; (4) maintains and benefits from a distribution network in the United States, directly and indirectly through its agents and subsidiaries, including Mylan Pharmaceuticals, that results in the distribution and sale of Mylan products in the United States and in this Judicial District, and generates substantial revenue to the benefit of Mylan; (5) has engaged in continuous and systematic contacts with New Jersey and/or purposefully availed itself of this forum by, among other things, making, shipping, using, importing, offering to sell or selling, or causing others to ship, use, import, offer to sell, or sell, pharmaceutical products in this Judicial District, and deriving substantial revenue from such

activities, and by filing claims in this Judicial District; and (6) has previously consented to personal jurisdiction in this Judicial District.

42. Upon information and belief, this Court has personal jurisdiction over Mylan LLC at least because Mylan LLC has engaged in continuous and systematic contacts with New Jersey and/or purposefully availed itself of this forum by, among other things, making, shipping, using, importing, offering to sell or selling, or causing others to ship, use, import, offer to sell, or sell, Mylan generic pharmaceutical products in the United States, including in this Judicial District, either directly and/or through at least Mylan Inc. and/or Mylan Pharmaceuticals.

**Personal Jurisdiction Over Orchid**

43. Upon information and belief, this Court has personal jurisdiction over Orchid Ltd. at least because Orchid Ltd.: (1) is registered to do business in New Jersey and has designated an agent to accept service of process in New Jersey; (2) has designated Mr. Sathish Srinivasan of Orgenus, a New Jersey company, to accept service of process on its behalf in connection with this law suit, through its division d/b/a Orchid Healthcare; (3) is in the business of developing, manufacturing, marketing and/or selling generic pharmaceuticals for the global market, including the United States and is doing business in this Judicial District, directly and/or through its division d/b/a Orchid Healthcare and through Orgenus; (4) maintains and benefits from a distribution network in the United States, directly and indirectly through Orgenus, that results in the distribution and sale of Orchid products in the United States and in this Judicial District, and generates substantial revenue to the benefit of Orchid; (5) has engaged in continuous and systematic contacts with New Jersey and/or purposefully availed itself of this forum directly, through its division, Orchid Healthcare, and through Orgenus, by, among other things, making, shipping, using, offering to sell or selling, or causing others to ship, use, offer to sell, or sell,

pharmaceutical products in this Judicial District, and deriving substantial revenue from such activities; and (6) has previously consented to personal jurisdiction in this Judicial District and has filed claims in this Judicial District.

44. Upon information and belief, this Court has jurisdiction over Orchid d/b/a Orchid Healthcare at least because Orchid d/b/a Orchid Healthcare: (1) develops, manufactures, markets, distributes and/or sells generic pharmaceutical formulations for the U.S. market and markets, distributes and/or sells generic pharmaceutical products in the United States and in this Judicial District directly and indirectly through Orgenus; (2) has designated Mr. Sathish Srinivasan of Orgenus, a New Jersey company, to accept service of process on its behalf in connection with this law suit; (3) maintains and benefits from a distribution network in the United States, directly and indirectly through Orgenus, that results in the distribution and sale of Orchid products in the United States and in this Judicial District, and generates substantial revenue to the benefit of Orchid; (4) has engaged in continuous and systematic contacts with New Jersey and/or purposefully availed itself of this forum directly and through Orgenus, by, among other things, making, shipping, using, offering to sell or selling, or causing others to ship, use, offer to sell, or sell, pharmaceutical products in this Judicial District, and deriving substantial revenue from such activities; and (5) has previously consented to personal jurisdiction in this Judicial District.

45. Upon information and belief, this Court has personal jurisdiction over Orgenus at least because Orgenus: (1) has its principal place of business in Princeton, New Jersey and conducts business in this Judicial District; (2) is incorporated in New Jersey; (3) has engaged in continuous and systematic contacts with New Jersey and/or purposefully availed itself of this forum by, among other things, making, shipping, using, importing, offering to sell or selling, or

causing others to ship, use, import, offer to sell, or sell, pharmaceutical products in this Judicial District, and deriving substantial revenue from such activities, and by filing claims in this Judicial District; and (4) has previously admitted personal jurisdiction in this Judicial District.

### **Venue**

46. Venue is proper in this Judicial District under 28 U.S.C. § 1391 and 1400(b).

## **BACKGROUND**

### **The Patent-in-Suit**

47. The '446 patent, entitled "Use of the R-Enantiomers of N-Propargyl 1-Aminoindan Compounds for Treating Parkinson's Disease," was duly and lawfully issued on September 26, 1995 to inventors Moussa B.H. Youdim, John P. M. Finberg, Ruth Levy, Jeffrey Sterling, David Lerner, Tirtsah Berger-Paskin and Haim Yellin. The named inventors assigned the '446 patent to Teva Ltd. and the Technion Research and Development Foundation Ltd. ("Technion"). The Technion subsequently assigned to Teva Ltd. its rights in the '446 patent. Accordingly, Teva Ltd. is the sole owner by assignment of all rights, title and interest in the '446 patent. The '446 patent is listed in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly referred to as "The Orange Book" ("Orange Book") with respect to Azilect<sup>®</sup>. The '446 patent will expire on February 7, 2017. A true and accurate copy of the '446 patent is attached hereto as Exhibit A.

### **The Azilect<sup>®</sup> Drug Product**

48. Plaintiffs researched, developed, applied for and obtained approval to make, sell, promote and/or market rasagiline mesylate tablet products known as Azilect<sup>®</sup>.

49. Teva Neuroscience and/or Teva USA have been selling, promoting, distributing and marketing Azilect<sup>®</sup> in the United States since July 2006.

50. Azilect<sup>®</sup> is indicated to treat idiopathic Parkinson's disease, as both monotherapy and adjunct therapy with levodopa.

51. Teva Ltd. holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(a), for 0.5 and 1.0 mg Azilect<sup>®</sup> tablets for the use in treating Parkinson's disease. Teva Neuroscience is Teva Ltd.'s authorized U.S. agent for the NDA.

### **The Watson ANDA**

52. WLI filed with the FDA in Rockville, Maryland, an ANDA under 21 U.S.C. § 355(j) seeking approval to manufacture, use, offer for sale, sell in and import into the United States 0.5 and 1.0 mg rasagiline mesylate tablets that WLI asserts are generic copies of Azilect<sup>®</sup> ("Watson's generic Azilect<sup>®</sup> products") prior to the expiration of the '446 patent.

53. The FDA assigned the Watson ANDA the number 201823.

54. WLI also filed with the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the claims of the '446 patent are invalid, unenforceable and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Watson's generic Azilect<sup>®</sup> products ("Watson's Paragraph IV Certification").

55. By letter dated September 1, 2010, WLI notified Plaintiffs that it had filed an ANDA seeking approval to market Watson's generic Azilect<sup>®</sup> products prior to the expiration of the '446 patent ("Watson Notice Letter").

56. This action is being commenced before the expiration of forty-five days from the date of receipt of the Watson Notice Letter.

### **The Mylan ANDA**

57. Mylan Pharmaceuticals filed with the FDA in Rockville, Maryland, an ANDA under 21 U.S.C. § 355(j) seeking approval to manufacture, use, offer for sale, sell in and import into the United States 0.5 and 1.0 mg rasagiline mesylate tablets that Mylan Pharmaceuticals asserts are generic copies of Azilect<sup>®</sup> (“Mylan’s generic Azilect<sup>®</sup> products”) prior to the expiration of the ’446 patent.

58. The FDA assigned the Mylan ANDA the number 201971.

59. Mylan Pharmaceuticals also filed with the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the claims of the ’446 patent are invalid, unenforceable and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Mylan’s generic Azilect<sup>®</sup> products (“Mylan’s Paragraph IV Certification”).

60. By letter dated August 27, 2010, Mylan Pharmaceuticals notified Plaintiffs that it had filed an ANDA seeking approval to market Mylan’s generic Azilect<sup>®</sup> products prior to the expiration of the ’446 patent (“Mylan Notice Letter”).

61. This action is being commenced before the expiration of forty-five days from the date of receipt of the Mylan Notice Letter.

### **The Orchid ANDA**

62. Upon information and belief, Orchid d/b/a Orchid Healthcare filed with the FDA in Rockville, Maryland, an ANDA under 21 U.S.C. § 355(j) seeking approval to manufacture, use, offer for sale, sell in and import into the United States 0.5 and 1.0 mg rasagiline mesylate tablets that Orchid d/b/a Orchid Healthcare asserts are generic copies of Azilect<sup>®</sup> (“Orchid’s generic Azilect<sup>®</sup> products”) prior to the expiration of the ’446 patent.

63. Upon information and belief, the FDA assigned the Orchid ANDA the number 201970.

64. Upon information and belief, Orchid d/b/a Orchid Healthcare also filed with the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the claims of the '446 patent are invalid, unenforceable and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Orchid's generic Azilect<sup>®</sup> products ("Orchid's Paragraph IV Certification").

65. By letter dated August 18, 2010, Orchid d/b/a Orchid Healthcare notified Plaintiffs that it had filed an ANDA seeking approval to market Orchid's generic Azilect<sup>®</sup> products prior to the expiration of the '446 patent ("Orchid Notice Letter").

66. This action is being commenced before the expiration of forty-five days from the date of receipt of the Orchid Notice Letter.

**COUNT I FOR INFRINGEMENT OF U.S. PATENT NO. 5,453,446 BY WATSON**

67. The allegations of paragraphs 1-66 are realleged and incorporated herein by reference.

68. The use of Watson's generic Azilect<sup>®</sup> products is covered by one or more claims of the '446 patent.

69. The commercial manufacture, use, offer for sale, sale, marketing, distribution and/or importation of Watson's generic Azilect<sup>®</sup> products would infringe one or more claims of the '446 patent.

70. WLI infringed the '446 patent by submitting the Watson ANDA to the FDA seeking approval to market Watson's generic Azilect<sup>®</sup> products containing rasagiline mesylate before the expiration of the '446 patent.

71. Upon information and belief, Defendants Watson Pharmaceuticals, Watson Pharma, WPP and WLI acted in concert and actively and knowingly caused to be submitted, assisted with, participated in, encouraged, contributed to, aided and abetted and/or directed the submission of the Watson ANDA to the FDA.

72. Defendants Watson Pharmaceuticals, Watson Pharma and WPP induced the infringement of the '446 patent by actively and knowingly aiding and abetting the preparation and submission of the Watson ANDA and in the preparation to sell Watson's generic Azilect<sup>®</sup> products in the United States.

73. Watson was aware of the '446 patent when engaging in these knowing and purposeful activities and was aware that filing the Watson ANDA with Watson's Paragraph IV Certification with respect to the '446 patent constituted an act of infringement of the '446 patent.

74. Use of Watson's generic Azilect<sup>®</sup> products in accordance with and as directed by Watson's proposed labeling for that product would infringe one or more claims of the '446 patent.

75. Upon information and belief, Watson intends to engage in the manufacture, use, offer for sale, sale, marketing, distribution and/or importation of Watson's generic Azilect<sup>®</sup> products with its proposed labeling immediately and imminently upon approval of the Watson ANDA.

76. Upon information and belief, Watson plans and intends to, and will, actively induce infringement of the '446 patent when the Watson ANDA is approved, and plans and intends to, and will, do so immediately and imminently upon approval.

77. Upon information and belief, Watson knows that Watson's generic Azilect<sup>®</sup> products and the proposed labeling for Watson's generic Azilect<sup>®</sup> products are especially made



or adapted for use in infringing the '446 patent and that Watson's generic Azilect<sup>®</sup> products and the proposed labeling are not suitable for substantial noninfringing use. Upon information and belief, Watson plans and intends to, and will, contribute to the infringement of the '446 patent immediately and imminently upon approval of the Watson ANDA.

78. The foregoing actions by Watson constitute and/or would constitute infringement of the '446 patent, active inducement of infringement of the '446 patent and/or contribution to the infringement by others of the '446 patent.

79. Upon information and belief, Watson acted without a reasonable basis for believing that it would not be liable for infringing the '446 patent, actively inducing infringement of the '446 patent and/or contributing to the infringement by others of the '446 patent.

80. Plaintiffs will be substantially and irreparably harmed by Watson's infringing activities unless the Court enjoins those activities. Plaintiffs will have no adequate remedy at law if Watson is not enjoined from the commercial manufacture, use, offer to sell, sale in and importation into the United States of Watson's generic Azilect<sup>®</sup> products.

81. Watson's activities render this case an exceptional one, and Plaintiffs are entitled to an award of their reasonable attorney fees under 35 U.S.C. § 285.

**COUNT II FOR INFRINGEMENT OF U.S. PATENT NO. 5,453,446 BY MYLAN**

82. The allegations of paragraphs 1-66 are realleged and incorporated herein by reference.

83. The use of Mylan's generic Azilect<sup>®</sup> products is covered by one or more claims of the '446 patent.

84. The commercial manufacture, use, offer for sale, sale, marketing, distribution and/or importation of Mylan's generic Azilect<sup>®</sup> products would infringe one or more claims of the '446 patent.

85. Mylan Pharmaceuticals infringed the '446 patent by submitting the Mylan ANDA to the FDA seeking approval to market Mylan's generic Azilect<sup>®</sup> products containing rasagiline mesylate before the expiration of the '446 patent.

86. Upon information and belief, Defendants Mylan Inc., Mylan LLC and Mylan Pharmaceuticals acted in concert and actively and knowingly caused to be submitted, assisted with, participated in, encouraged, contributed to, aided and abetted and/or directed the submission of the Mylan ANDA to the FDA.

87. Defendants Mylan Inc. and Mylan LLC induced the infringement of the '446 patent by actively and knowingly aiding and abetting the preparation and submission of the Mylan ANDA and in the preparation to sell Mylan's generic Azilect<sup>®</sup> products in the United States.

88. Mylan was aware of the '446 patent when engaging in these knowing and purposeful activities and was aware that filing the Mylan ANDA with Mylan's Paragraph IV Certification with respect to the '446 patent constituted an act of infringement of the '446 patent.

89. Use of Mylan's generic Azilect<sup>®</sup> products in accordance with and as directed by Mylan's proposed labeling for that product would infringe one or more claims of the '446 patent.

90. Upon information and belief, Mylan intends to engage in the manufacture, use, offer for sale, sale, marketing, distribution and/or importation of Mylan's generic Azilect<sup>®</sup> products with its proposed labeling immediately and imminently upon approval of the Mylan ANDA.

91. Upon information and belief, Mylan plans and intends to, and will, actively induce infringement of the '446 patent when the Mylan ANDA is approved, and plans and intends to, and will, do so immediately and imminently upon approval.

92. Upon information and belief, Mylan knows that Mylan's generic Azilect<sup>®</sup> products and the proposed labeling for Mylan's generic Azilect<sup>®</sup> products are especially made or adapted for use in infringing the '446 patent, and that Mylan's generic Azilect<sup>®</sup> products and the proposed labeling are not suitable for substantial noninfringing use. Upon information and belief, Mylan plans and intends to, and will, contribute to the infringement of the '446 patent immediately and imminently upon approval of the Mylan ANDA.

93. The foregoing actions by Mylan constitute and/or would constitute infringement of the '446 patent, active inducement of infringement of the '446 patent and/or contribution to the infringement by others of the '446 patent.

94. Upon information and belief, Mylan acted without a reasonable basis for believing that it would not be liable for infringing the '446 patent, actively inducing infringement of the '446 patent and/or contributing to the infringement by others of the '446 patent.

95. Plaintiffs will be substantially and irreparably harmed by Mylan's infringing activities unless the Court enjoins those activities. Plaintiffs will have no adequate remedy at law if Mylan is not enjoined from the commercial manufacture, use, offer to sell, sale in, and importation into the United States of Mylan's generic Azilect<sup>®</sup> products.

96. Mylan's activities render this case an exceptional one and Plaintiffs are entitled to an award of their reasonable attorney fees under 35 U.S.C. § 285.

**COUNT III FOR INFRINGEMENT OF U.S. PATENT NO. 5,453,446 BY ORCHID**

97. The allegations of paragraphs 1-66 are realleged and incorporated herein by reference.

98. The use of Orchid's generic Azilect<sup>®</sup> products is covered by one or more claims of the '446 patent.

99. The commercial manufacture, use, offer for sale, sale, marketing, distribution and/or importation of Orchid's generic Azilect<sup>®</sup> products would infringe one or more claims of the '446 patent.

100. Orchid d/b/a Orchid Healthcare infringed the '446 patent by submitting the Orchid ANDA to the FDA seeking approval to market Orchid's generic Azilect<sup>®</sup> products containing rasagiline mesylate before the expiration of the '446 patent.

101. Upon information and belief, Defendants Orchid Ltd., Orchid d/b/a Orchid Healthcare and Orgenus acted in concert and actively and knowingly caused to be submitted, assisted with, participated in, encouraged, contributed to, aided and abetted and/or directed the submission of the Orchid ANDA to the FDA.

102. Defendants Orchid Ltd. and Orgenus induced the infringement of the '446 patent by actively and knowingly aiding and abetting the preparation and submission of the Orchid ANDA and in the preparation to sell Orchid's generic Azilect<sup>®</sup> products in the United States.

103. Orchid was aware of the '446 patent when engaging in these knowing and purposeful activities and was aware that filing the Orchid ANDA with Orchid's Paragraph IV Certification with respect to the '446 patent constituted an act of infringement of the '446 patent.

104. Use of Orchid's generic Azilect<sup>®</sup> products in accordance with and as directed by Orchid's proposed labeling for that product would infringe one or more claims of the '446 patent.

105. Upon information and belief, Orchid intends to engage in the manufacture, use, offer for sale, sale, marketing, distribution and/or importation of Orchid's generic Azilect<sup>®</sup> products with its proposed labeling immediately and imminently upon approval of the Orchid ANDA.

106. Upon information and belief, Orchid plans and intends to, and will, actively induce infringement of the '446 patent when the Orchid ANDA is approved, and plans and intends to, and will, do so immediately and imminently upon approval.

107. Upon information and belief, Orchid knows that Orchid's generic Azilect<sup>®</sup> products and the proposed labeling for Orchid's generic Azilect<sup>®</sup> products are especially made or adapted for use in infringing the '446 patent and that Orchid's generic Azilect<sup>®</sup> products and the proposed labeling are not suitable for substantial noninfringing use. Upon information and belief, Orchid plans and intends to, and will, contribute to the infringement of the '446 patent immediately and imminently upon approval of the Orchid ANDA.

108. The foregoing actions by Orchid constitute and/or would constitute infringement of the '446 patent, active inducement of infringement of the '446 patent and/or contribution to the infringement by others of the '446 patent.

109. Upon information and belief, Orchid acted without a reasonable basis for believing that it would not be liable for infringing the '446 patent, actively inducing infringement of the '446 patent and/or contributing to the infringement by others of the '446 patent.

110. Plaintiffs will be substantially and irreparably harmed by Orchid's infringing activities unless the Court enjoins those activities. Plaintiffs will have no adequate remedy at law if Orchid is not enjoined from the commercial manufacture, use, offer to sell, sale in and importation into the United States of Orchid's generic Azilect<sup>®</sup> products.

111. Orchid's activities render this case an exceptional one and Plaintiffs are entitled to an award of their reasonable attorney fees under 35 U.S.C. § 285.

**PRAYER FOR RELIEF**

WHEREFORE, Teva respectfully requests the following relief:

a. a judgment that Watson's submission of the Watson ANDA No. 201823, Mylan's submission of the Mylan ANDA No. 201971 and Orchid's submission of the Orchid ANDA No. 201970 were acts of infringement of one or more claims of the '446 patent and that the making, using, offering to sell, selling, marketing, distributing, or importing of Watson's generic Azilect<sup>®</sup> products, Mylan's generic Azilect<sup>®</sup> products, or Orchid's generic Azilect<sup>®</sup> products (collectively, "Defendants' generic Azilect<sup>®</sup> products") prior to the expiration of the '446 patent will infringe, actively induce infringement and/or contribute to the infringement of one or more claims of the '446 patent;

b. an Order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any FDA approval of the Watson ANDA No. 201823, Mylan ANDA No. 201971 and Orchid ANDA No. 201970, or any product or compound the use of which infringes the '446 patent, shall be a date that is not earlier than the expiration of the '446 patent;

c. an Order permanently enjoining Defendants and all persons acting in concert with Defendants from commercially manufacturing, using, offering for sale, selling, marketing, distributing, or importing Defendants' generic Azilect<sup>®</sup> products, or any product or compound

the use of which infringes the '446 patent, or inducing or contributing to the infringement of the '446 patent until after the expiration of the '446 patent;

d. an Order enjoining Defendants and all persons acting in concert with Defendants from seeking, obtaining, or maintaining approval of the Watson ANDA No. 201823, Mylan ANDA No. 201971, or Orchid ANDA No. 201970 before the expiration of the '446 patent;

e. an award of Plaintiffs' damages or other monetary relief to compensate Plaintiffs if Defendants engage in the commercial manufacture, use, offer to sell, sale or marketing or distribution in, or importation into the United States of Defendants' generic Azilect<sup>®</sup> products, or any product or compound the use of which infringes the '446 patent, or the inducement or contribution of the foregoing, prior to the expiration of the '446 patent in accordance with 35 U.S.C. § 271(e)(4)(C);

f. a judgment that this is an exceptional case and awarding Plaintiffs their attorneys' fees under 35 U.S.C. § 285;

g. an award of Plaintiffs' reasonable costs and expenses in this action; and

h. an award of any further and additional relief to Plaintiffs as this Court deems just and proper.

Dated: October 1, 2010

**LITE DEPALMA GREENBERG, LLC**

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**LOCAL CIVIL RULE 11.2 CERTIFICATION**

Pursuant to Local Civil Rule 11.2, I hereby certify that the matter in controversy is not related to any other action, pending arbitration or administrative proceeding currently pending in any court.

Dated: October 1, 2010

**LITE DEPALMA GREENBERG, LLC**

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# Exhibit A



US005453446A

**United States Patent** [19]

[11] **Patent Number:** **5,453,446**

**Youdim et al.**

[45] **Date of Patent:** **\* Sep. 26, 1995**

[54] **USE OF THE R-ENANTIOMERS OF N-PROPARGYL 1-AMINOINDAN COMPOUNDS FOR TREATING PARKINSON'S DISEASE.**

4,826,875 5/1989 Chiesi ..... 514/534

**FOREIGN PATENT DOCUMENTS**

1003686 9/1965 United Kingdom .

**OTHER PUBLICATIONS**

Finberg and Youdim, Modification of blood pressure and nictitating membrane response to sympathetic amines by selective monoamine oxidase inhibitors, types A and B, in the cat *British J. Pharmac.* (Jun. 1985) 85(2):541-546.

Kabins and Gershon, Potential applications for monoamine oxidase B inhibitors *Dementia* (1990) 1:323-348.

The Merck Index (Tenth ed. 1983) pp. 149, 248-249.

The Parkinson Study Group, Effect of deprenyl on the progression of disability in early Parkinson's disease. *New England J. Med.* (1989) 321(20):1364-1371.

The Parkinson Study Group, Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease, *New England J. Med.* (Jan. 21, 1993) 328(3):176-183.

Riederer and Youdim, Monoamine oxidase activity and monoamine metabolism in brains of Parkinsonian patients treated with 1-deprenyl, *J. Neurochem.* (1986) 46(5):1359-1365.

Tekes, et al., Effect of MAO inhibitors on the uptake and metabolism of dopamine in rat and human brain, *Pol. J. Pharmacol. Pharm.* (1988) 40:653-658.

Youdim et al. in Handbook of Experimental Pharmacology vol. 90/I (1988) Chapter 3, Trendelenburg and Weiner, eds.

*Primary Examiner*—Allen J. Robinson

*Assistant Examiner*—Brian M. Burn

*Attorney, Agent, or Firm*—John P. White

[57] **ABSTRACT**

R(+)-N-p-opargyl-1-aminoindan, its preparation and use and pharmaceutical compositions containing it. The novel compound was found to be useful for the treatment of human patients for Parkinson's disease, memory disorders, dementia of the Alzheimer type (DAT), depression and the hyperactive syndrome.

**20 Claims, 17 Drawing Sheets**

[75] **Inventors:** **Moussa B. H. Youdim**, Haifa; **John P. M. Finberg**, Tivon; **Ruth Levy**, Tel-Aviv; **Jeffrey Sterling; David Lerner**, both of Jerusalem; **Tirtsah Berger-Paskin**, Raanana; **Haim Yellin**, Ramat-Gan, all of Israel

[73] **Assignees:** **Teva Pharmaceutical Industries, Ltd.**, Jerusalem; **Technion Research and Development Foundation Ltd.**, Haifa, both of Israel

[\*] **Notice:** The portion of the term of this patent subsequent to Feb. 7, 2012 has been disclaimed.

[21] **Appl. No.:** **255,046**

[22] **Filed:** **Jun. 7, 1994**

**Related U.S. Application Data**

[63] Continuation of Ser. No. 63,455, May 18, 1993, Pat. No. 5,387,612, which is a continuation of Ser. No. 632,184, Dec. 21, 1990, abandoned.

[30] **Foreign Application Priority Data**

Jan. 3, 1990 [IL] Israel ..... 92952

[51] **Int. Cl.<sup>6</sup>** ..... **A61K 31/135**

[52] **U.S. Cl.** ..... **514/647; 564/308**

[58] **Field of Search** ..... 514/647, 657; 564/308, 428

**References Cited**

**U.S. PATENT DOCUMENTS**

3,201,470 8/1965 Huebner ..... 260/577  
 3,253,037 5/1966 Huebner ..... 260/577  
 3,513,244 5/1970 Gittos et al. .... 424/320

FIGURE 1

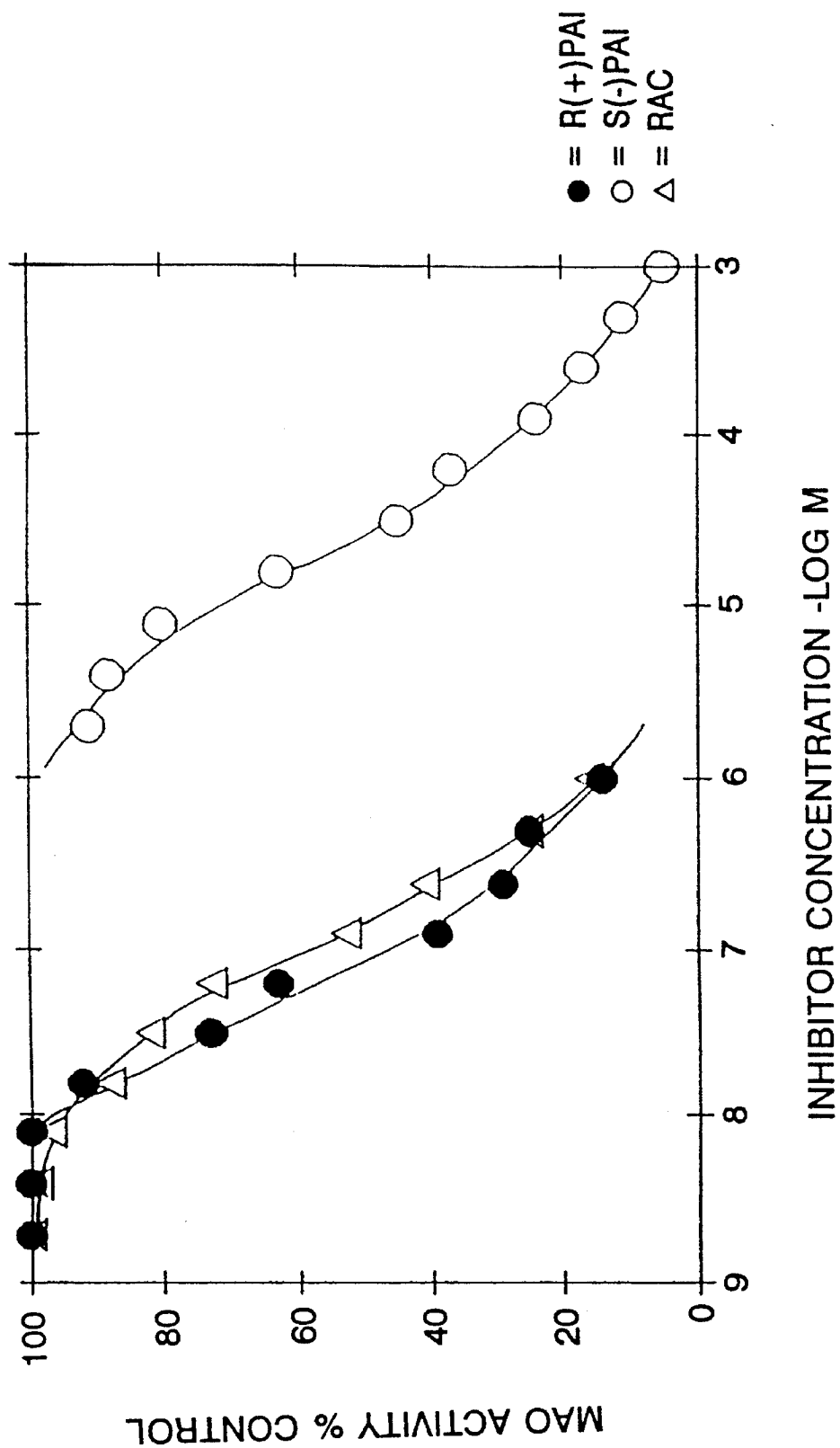


FIGURE 2

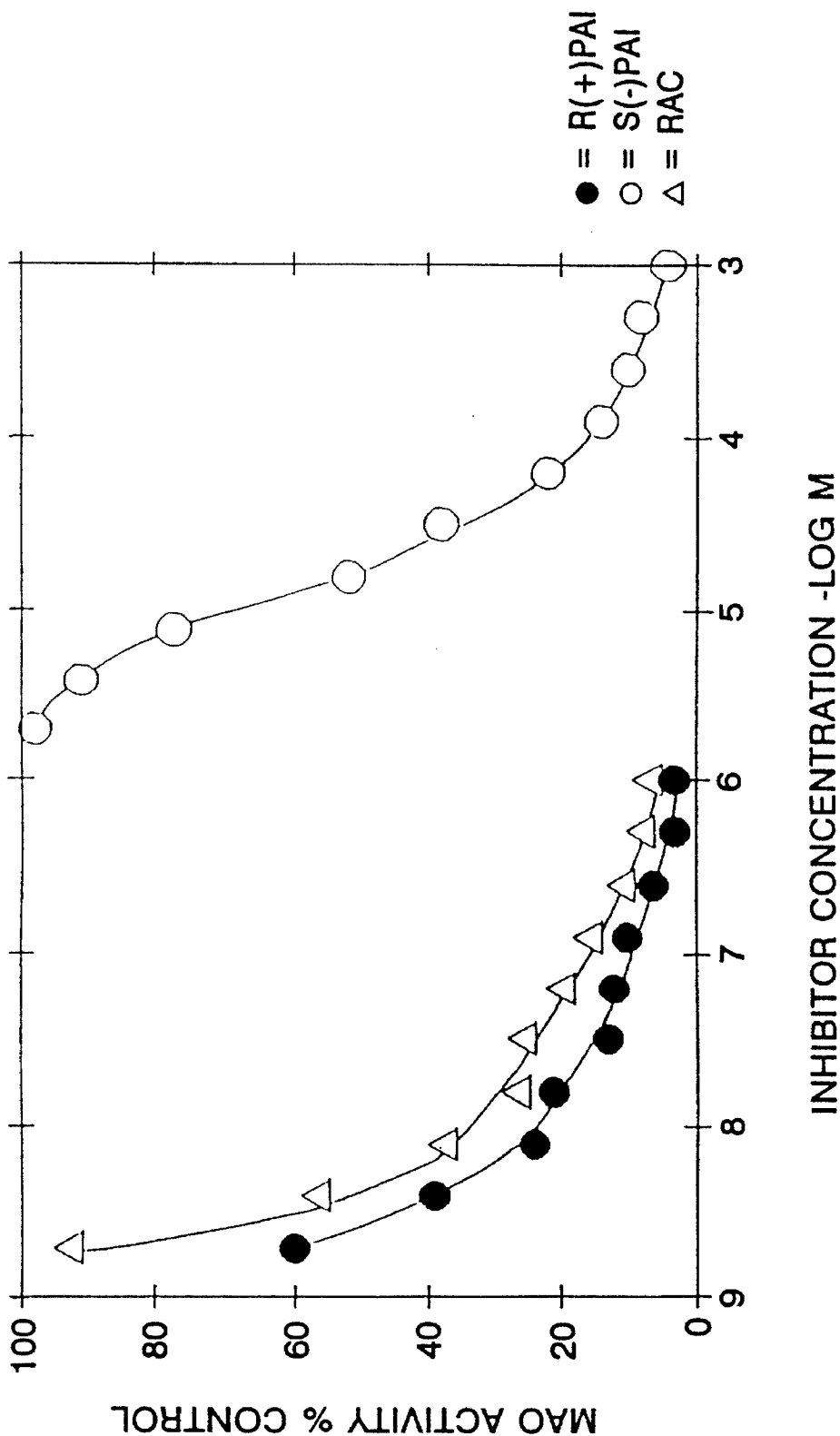
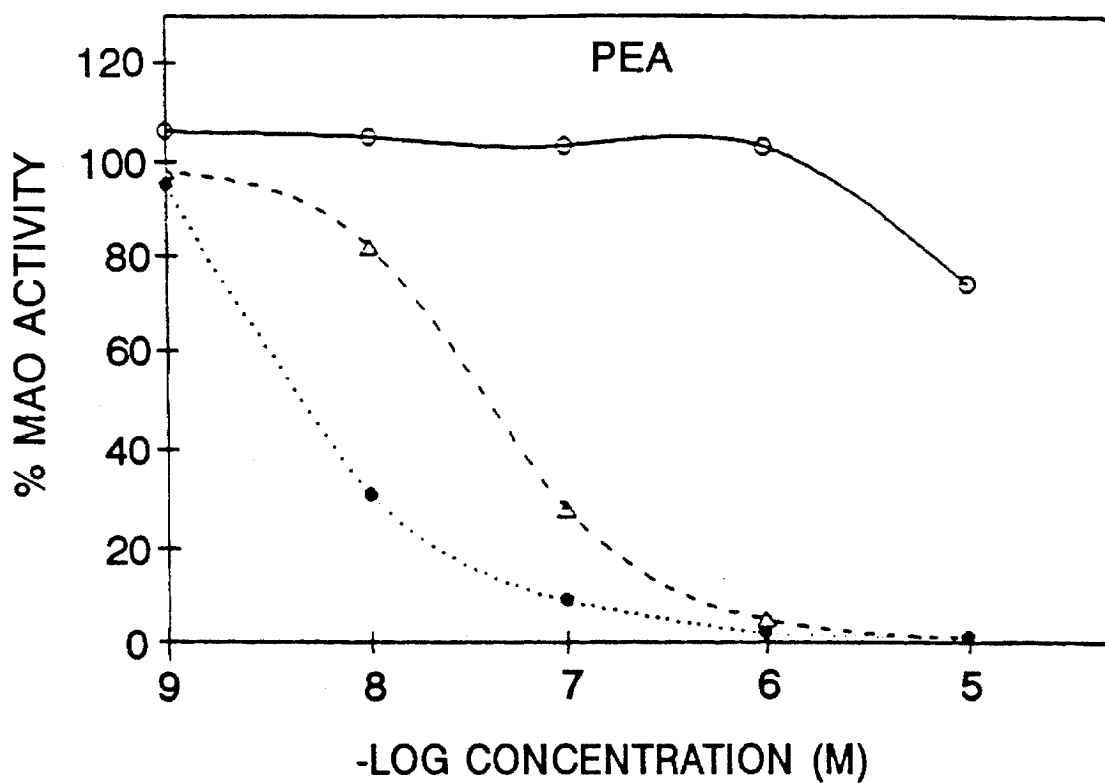
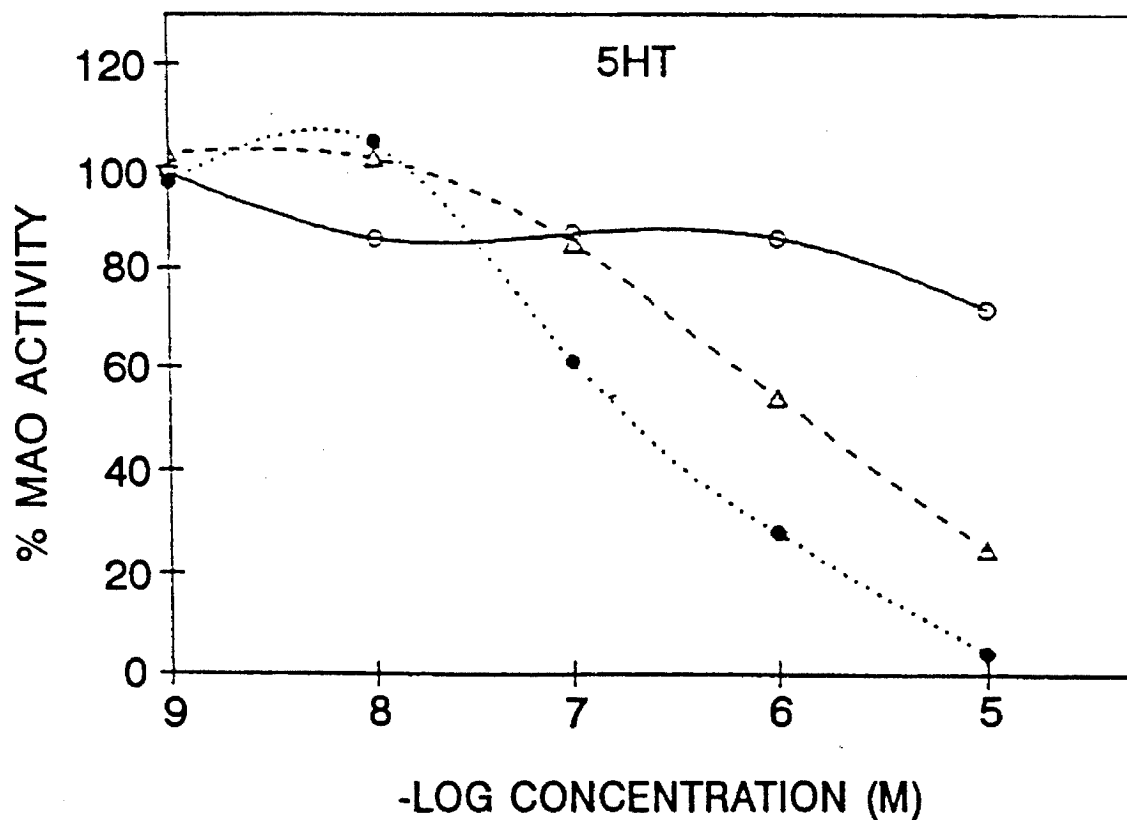


FIGURE 3A



- S(-)PAI
- .....● R(+)-PAI
- △---△ RAC

FIGURE 3B



- S(-)PAI
- .....● R(+)-PAI
- △---△ RAC

FIGURE 4

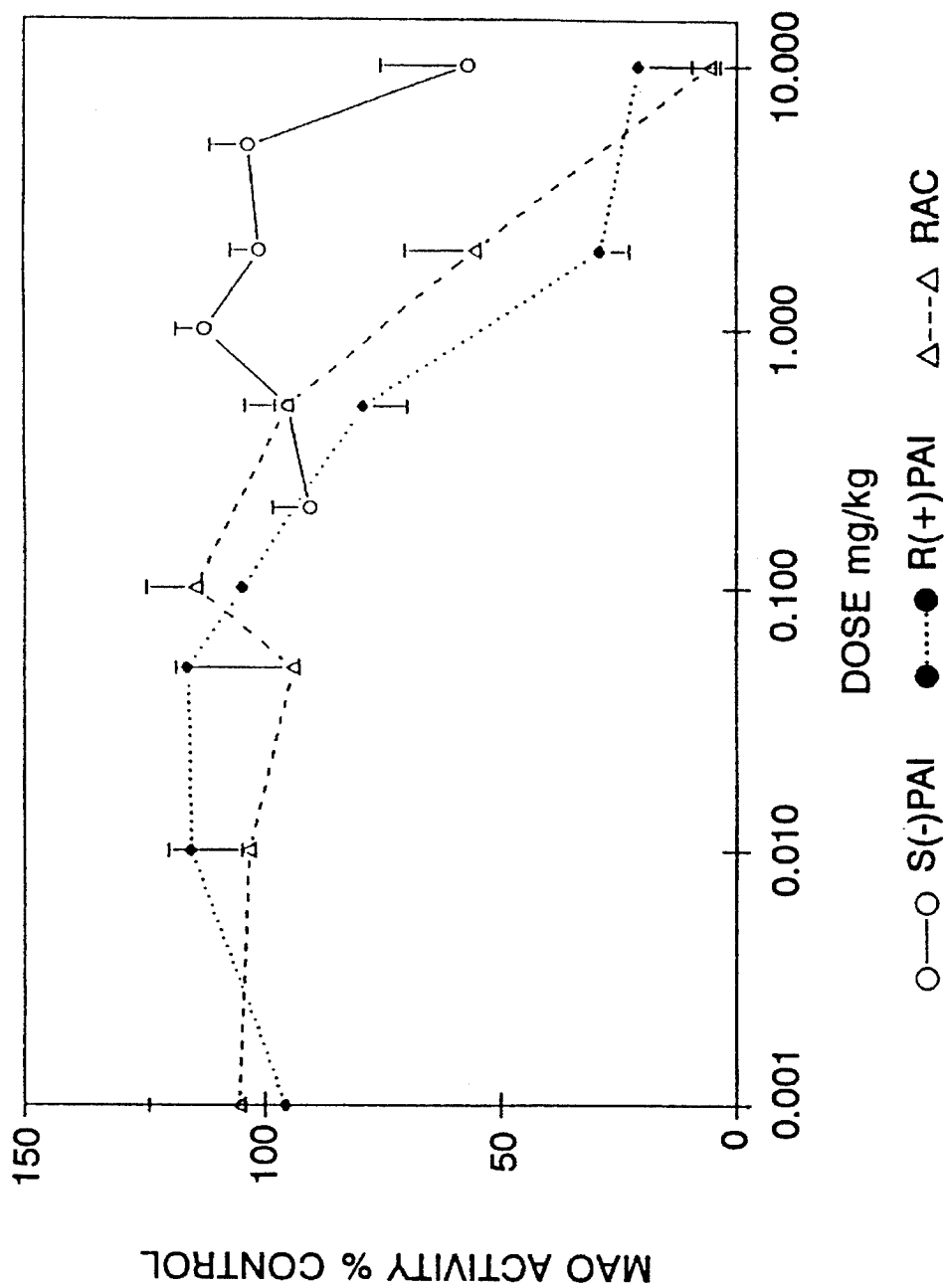




FIGURE 5

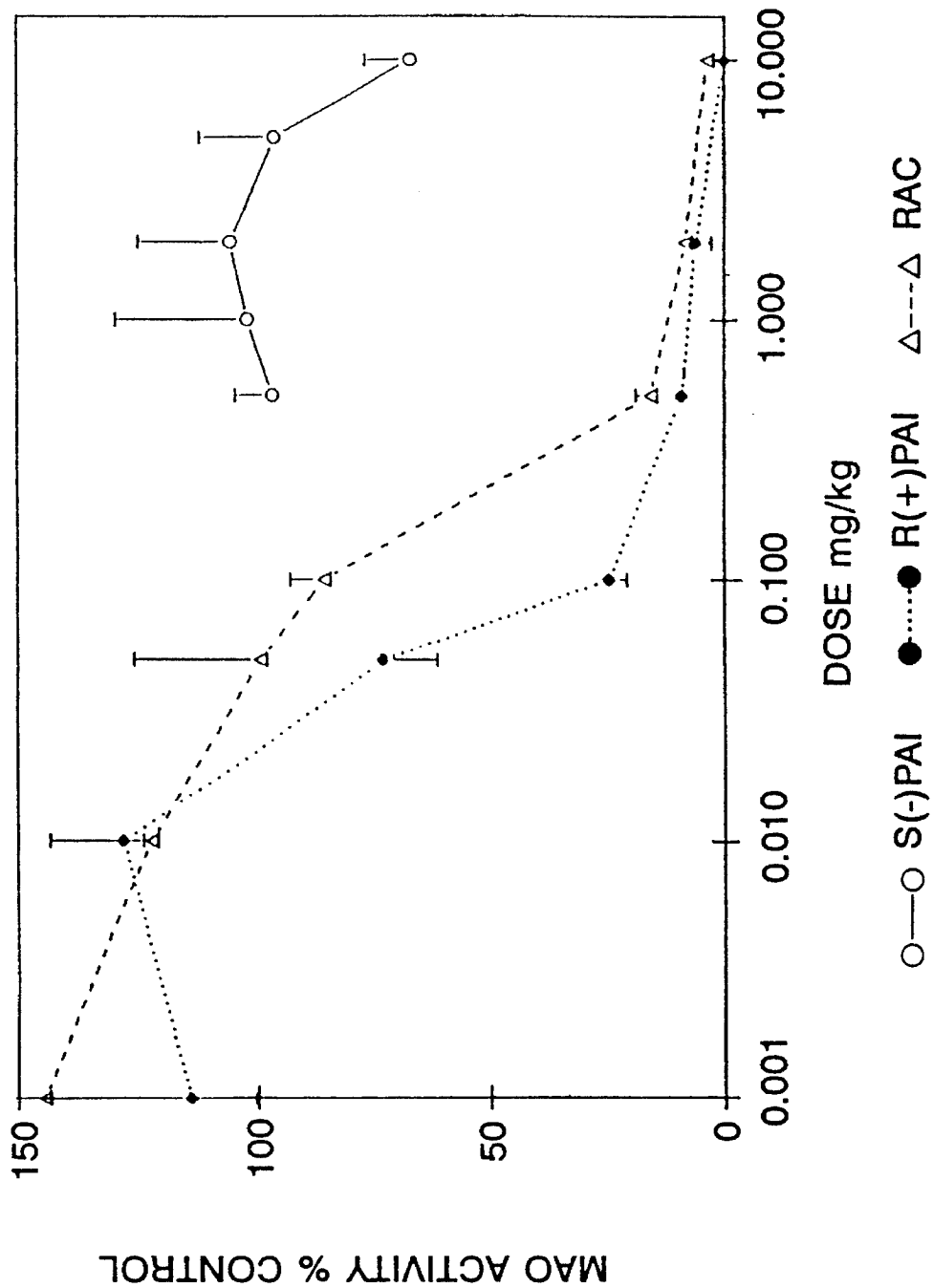


FIGURE 6

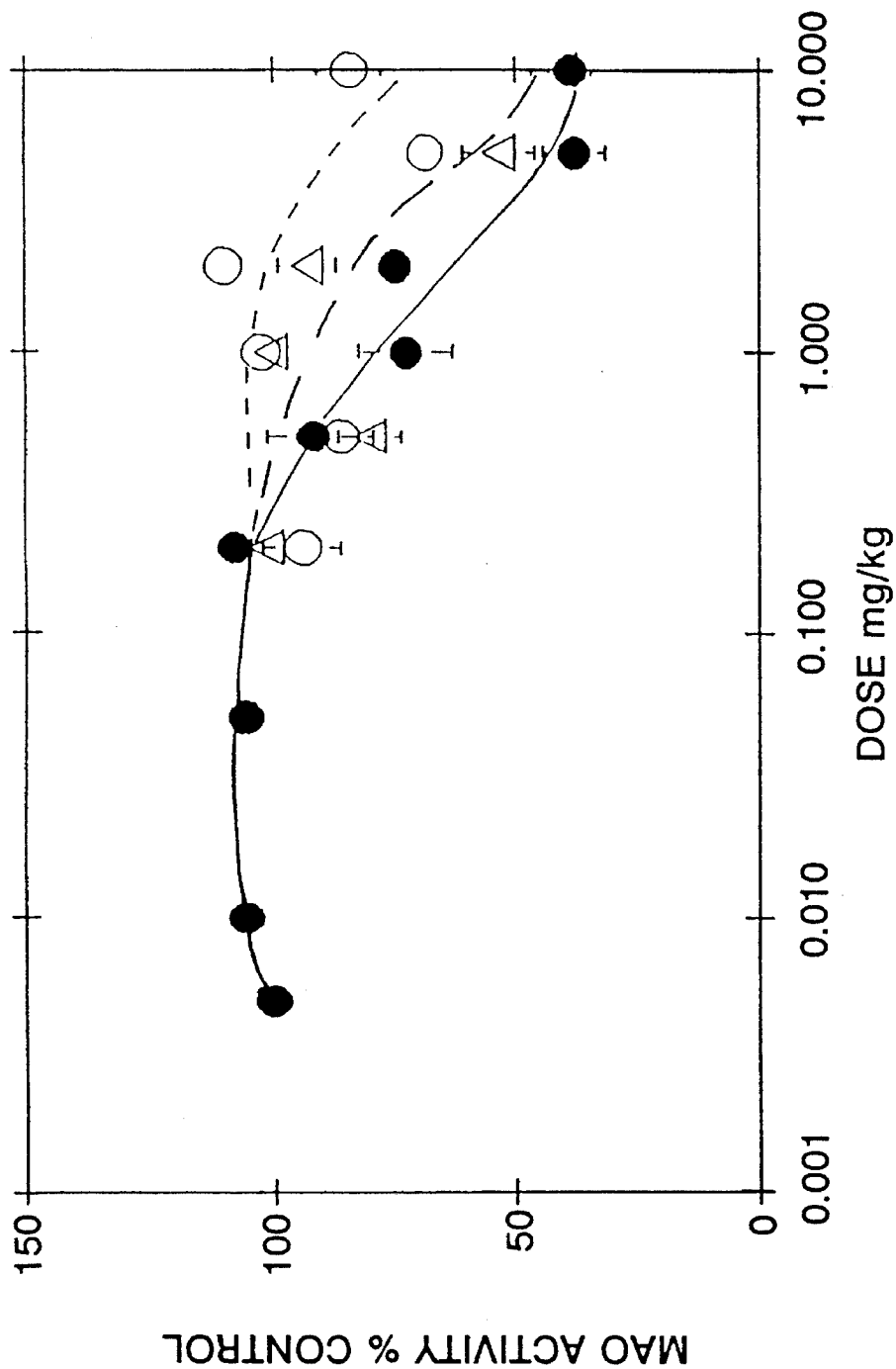


FIGURE 7

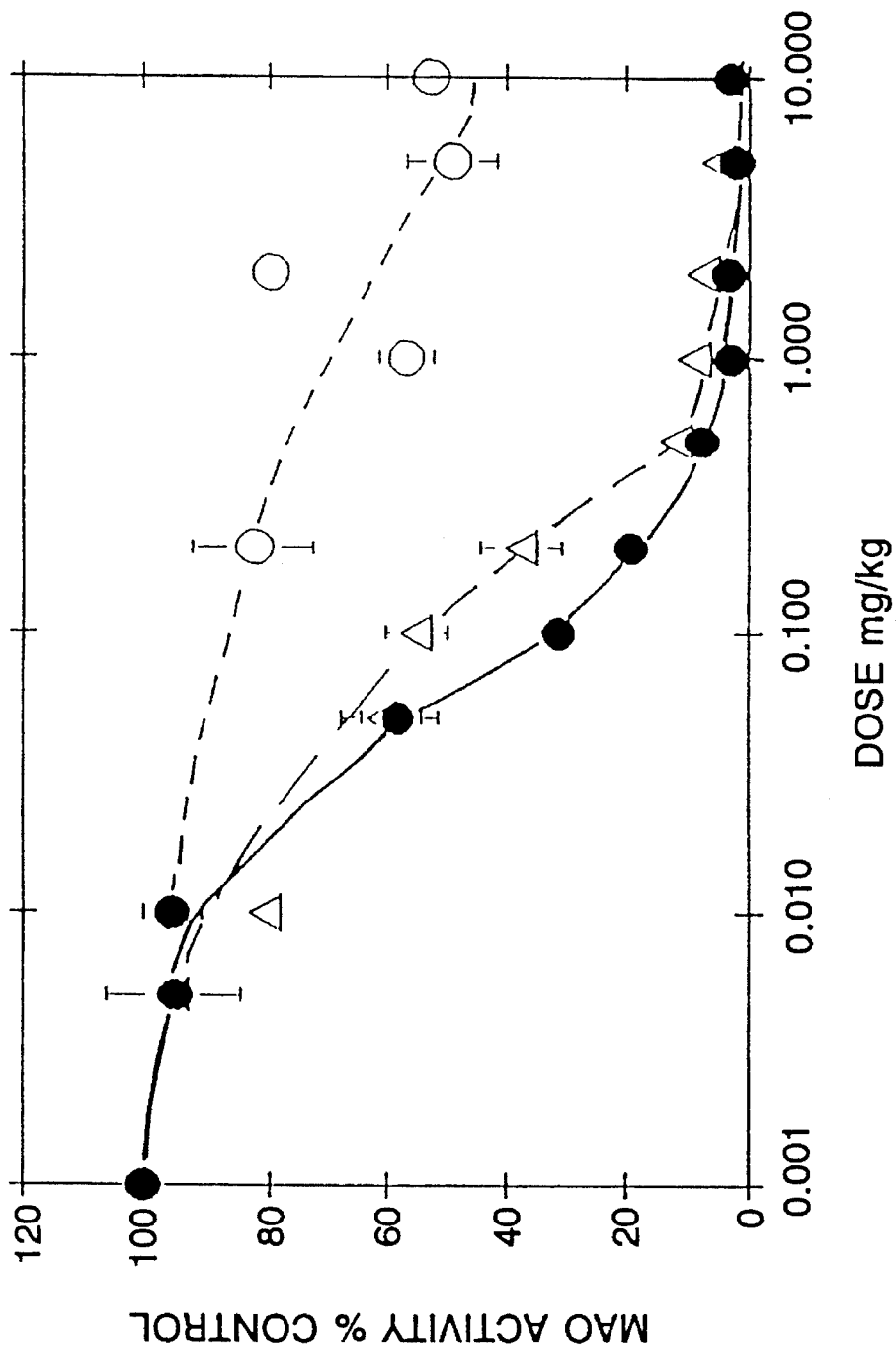


FIGURE 8

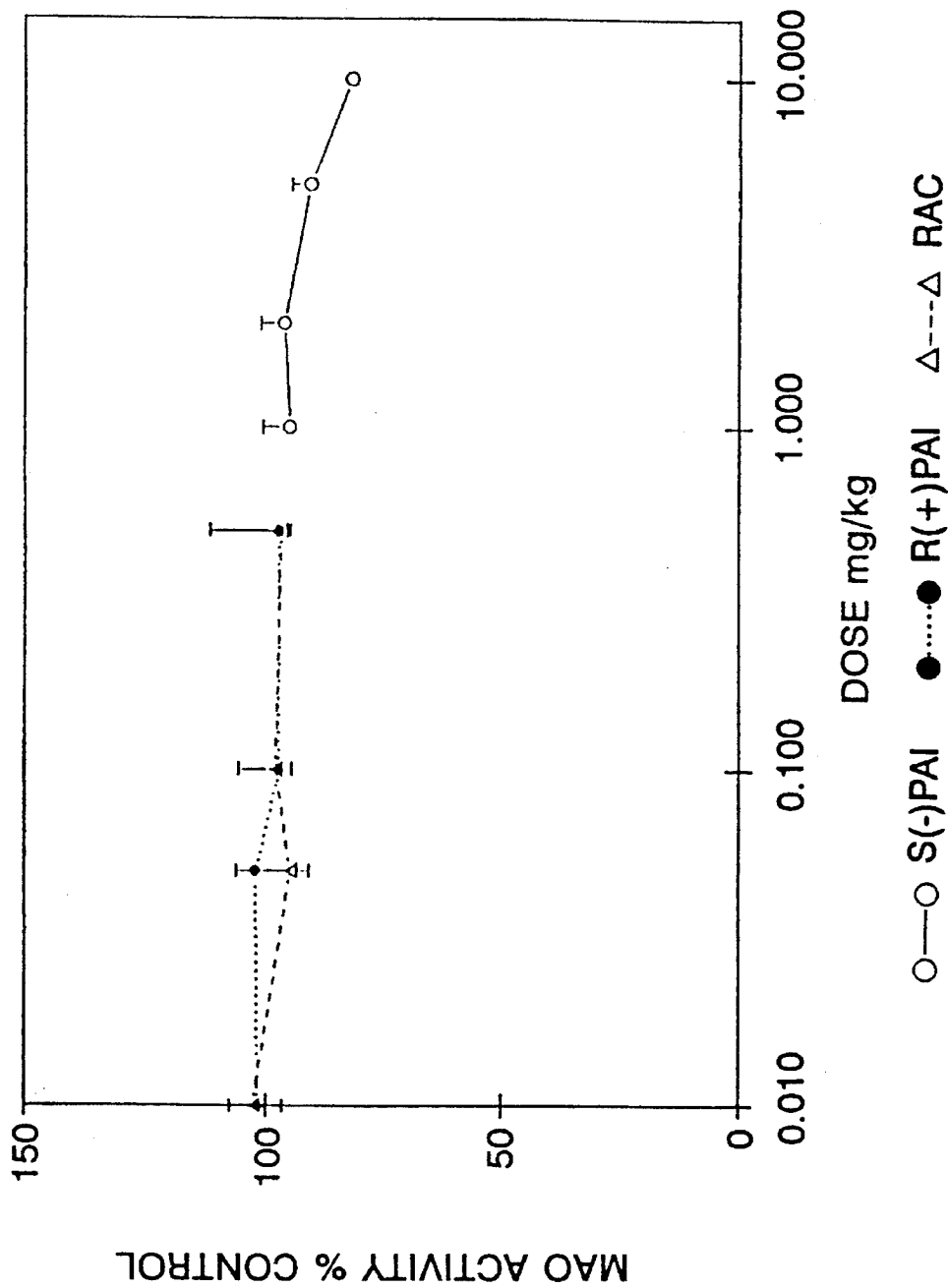


FIGURE 9

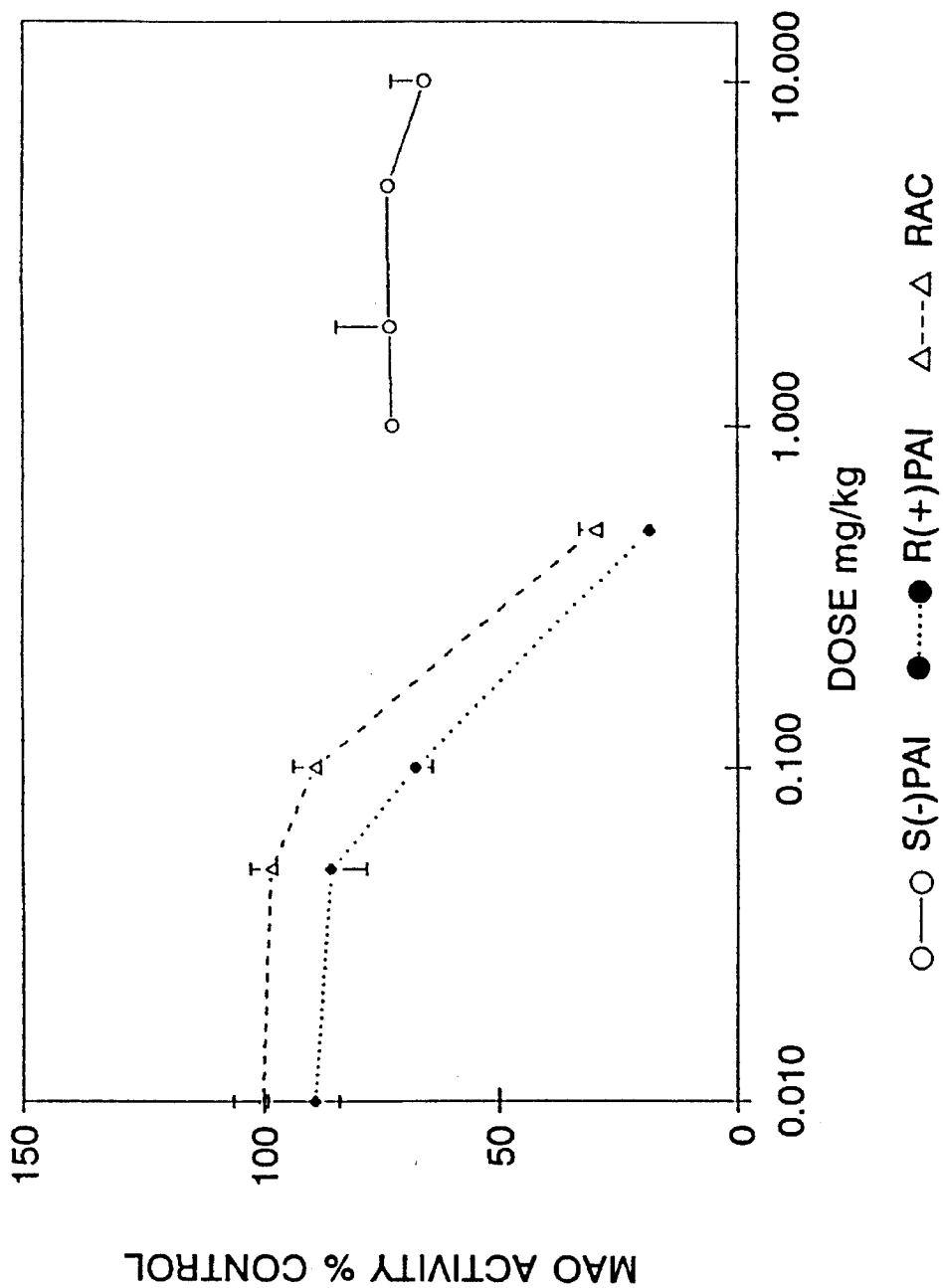


FIGURE 10

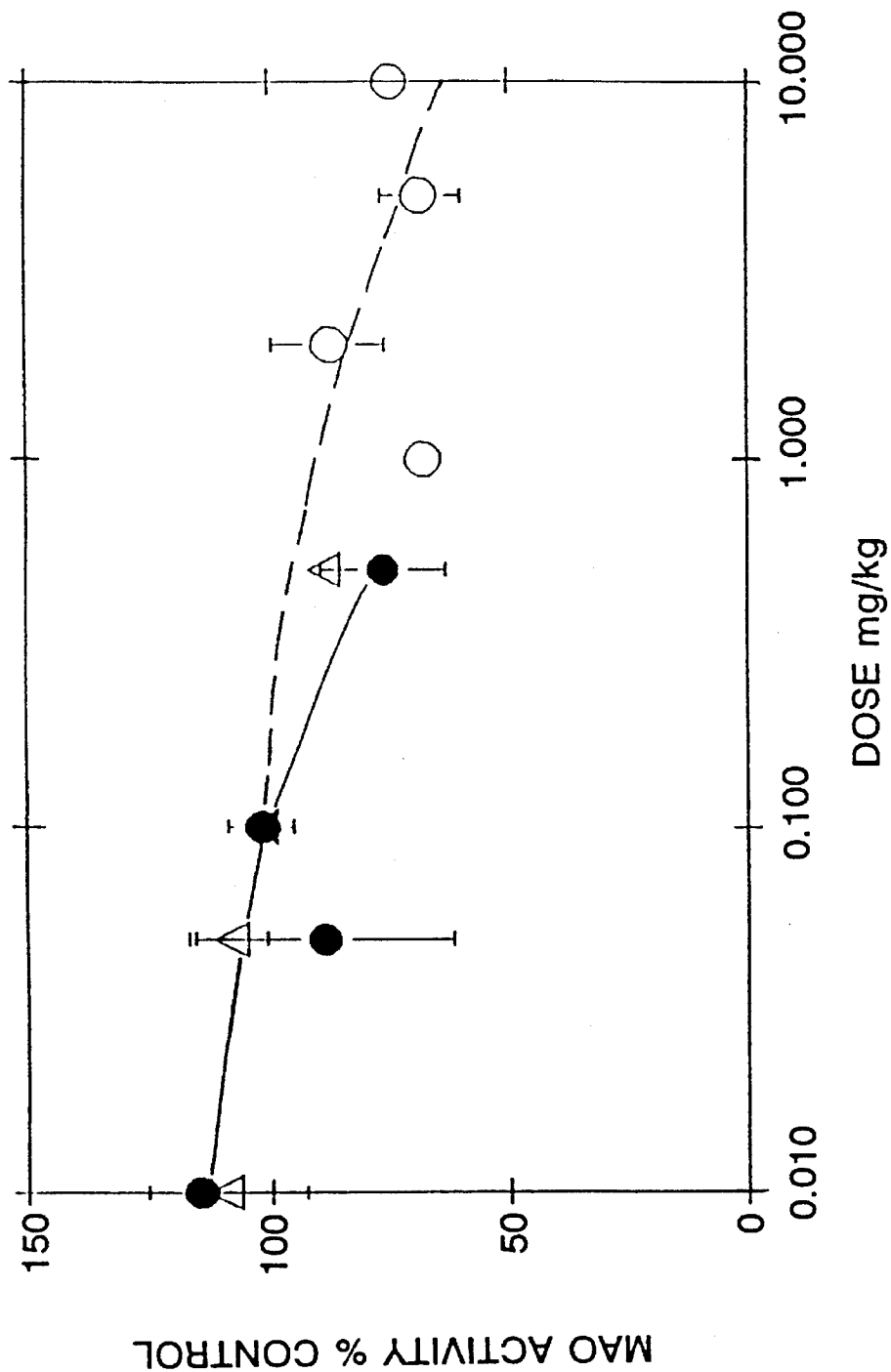


FIGURE 11

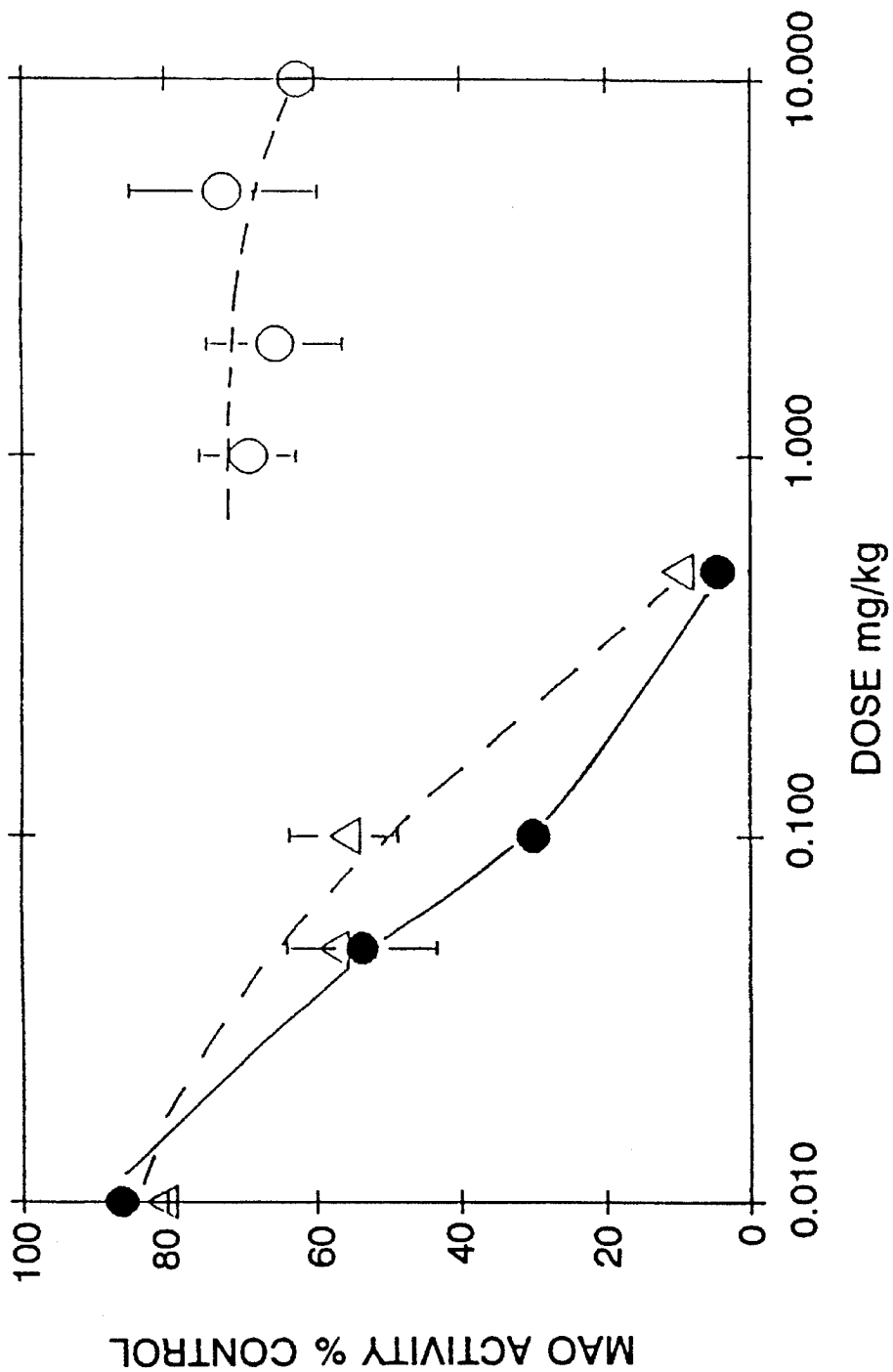


FIGURE 12

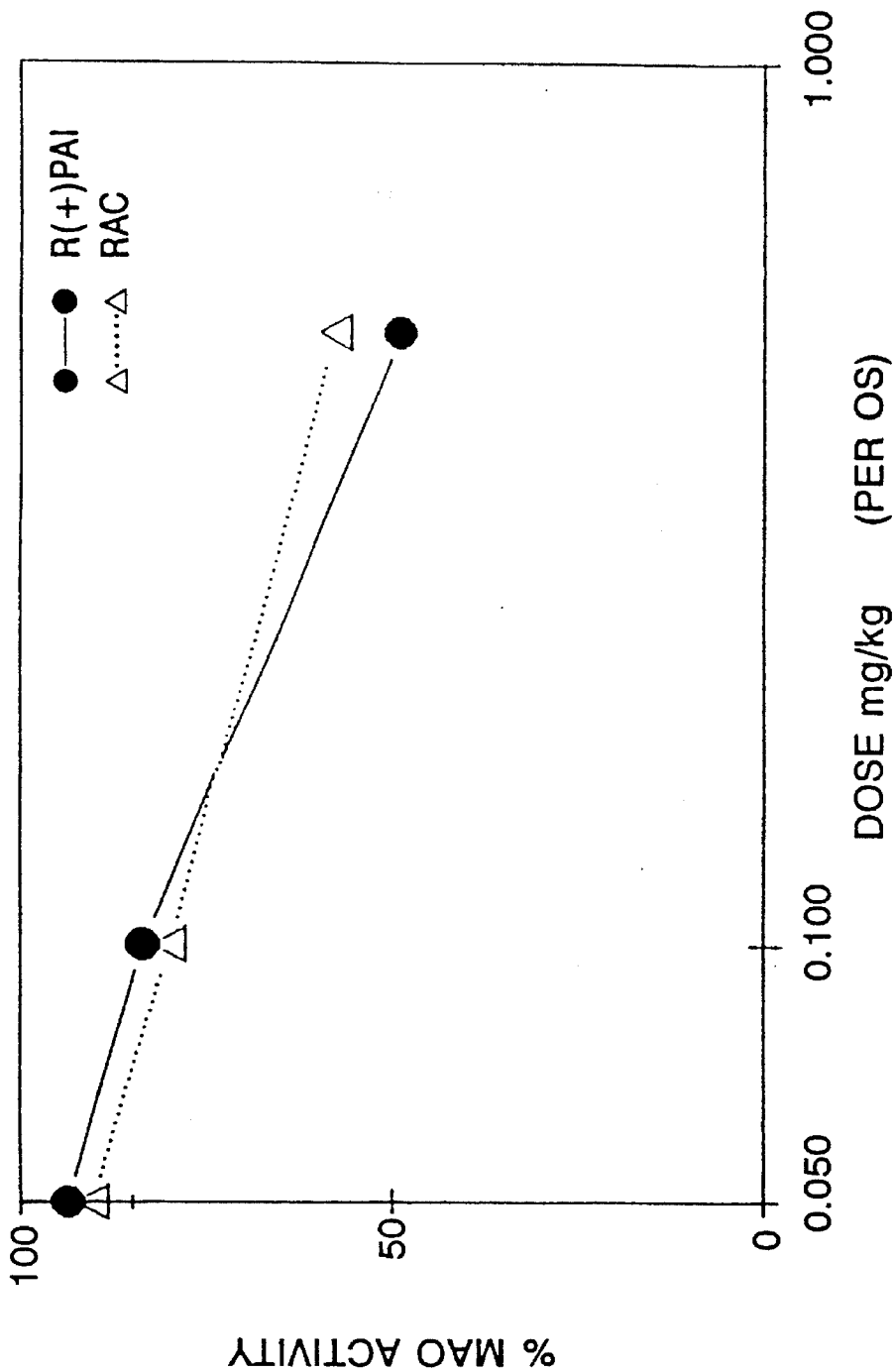




FIGURE 13

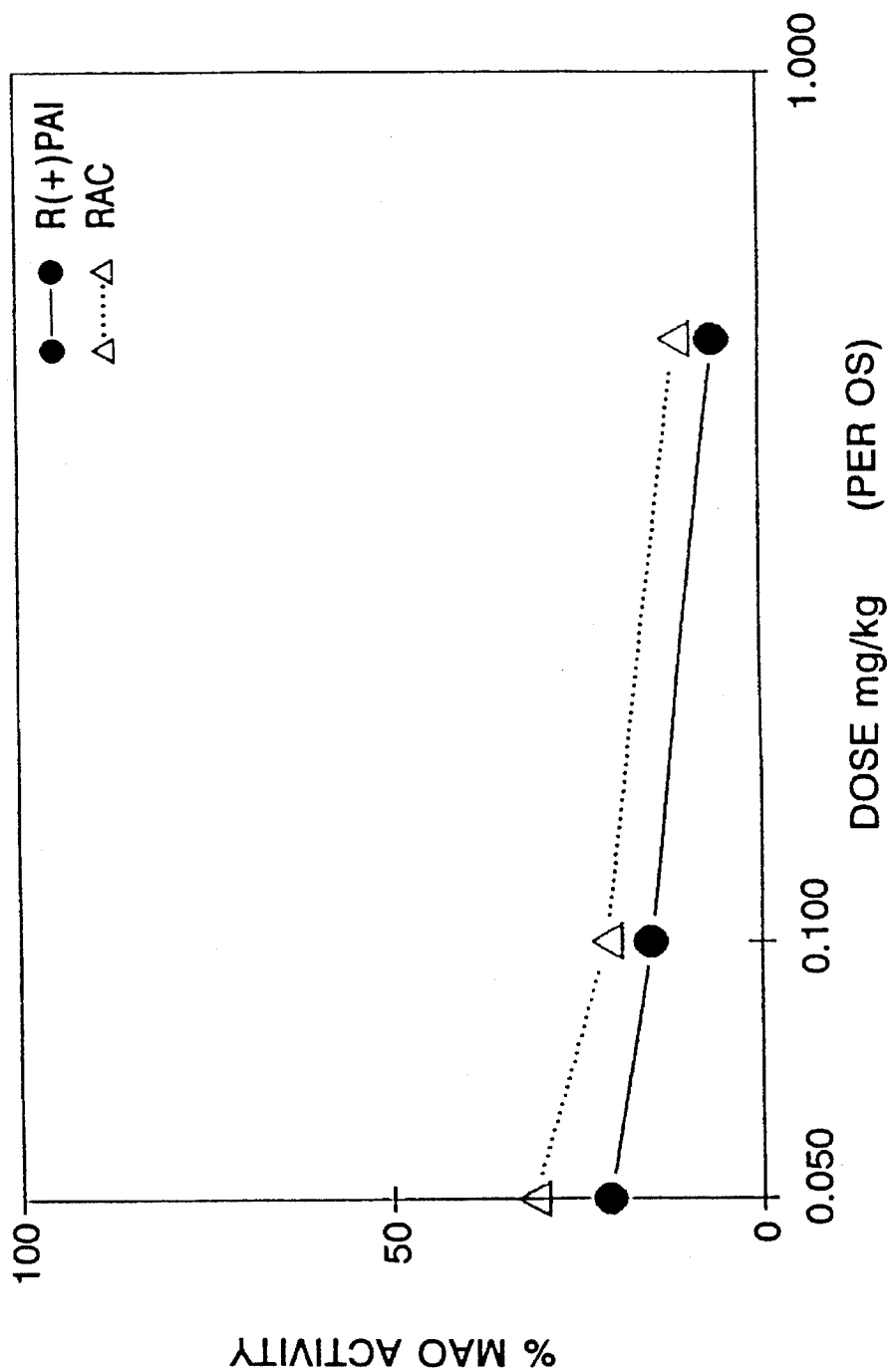


FIGURE 14

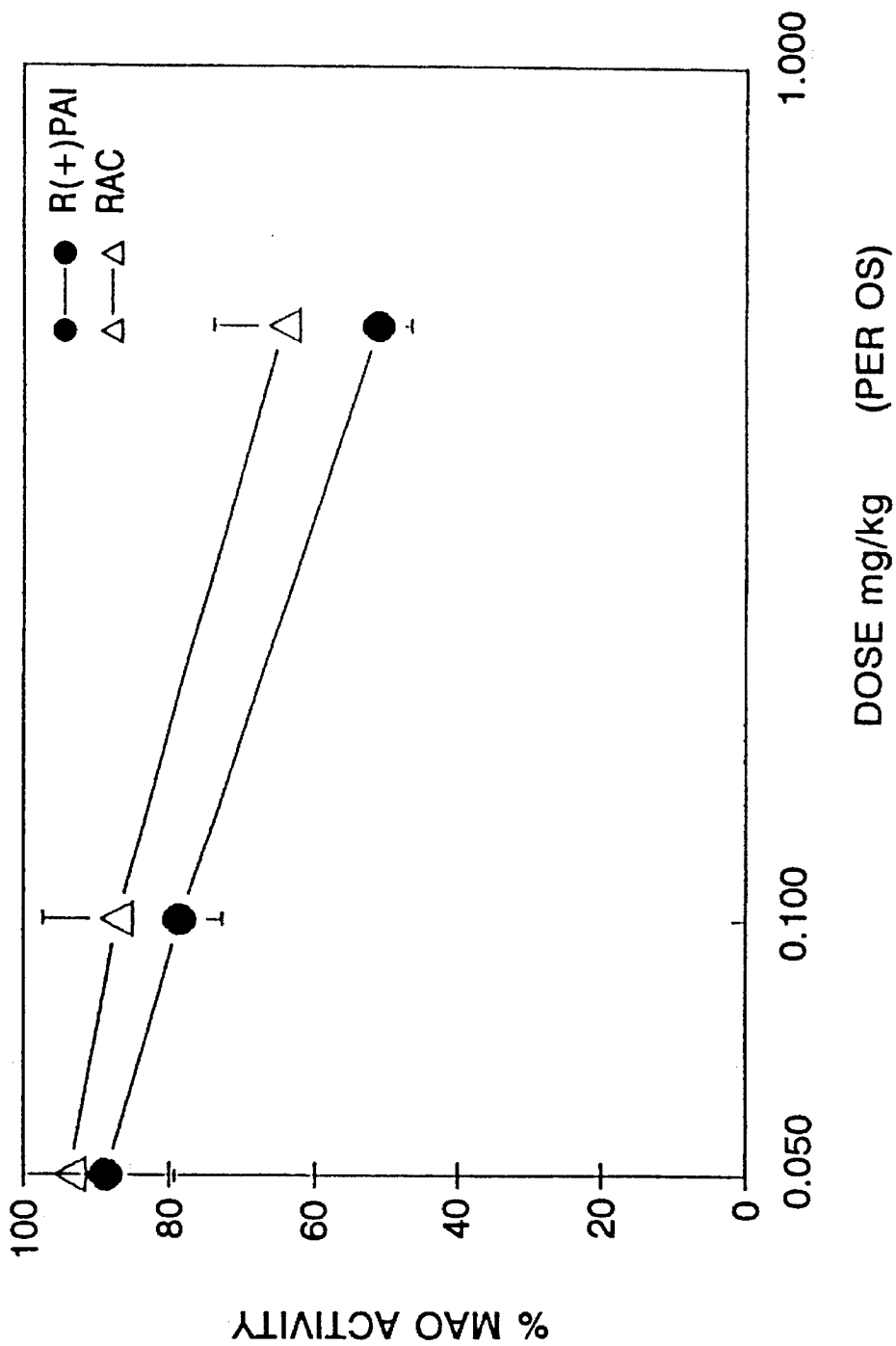


FIGURE 15

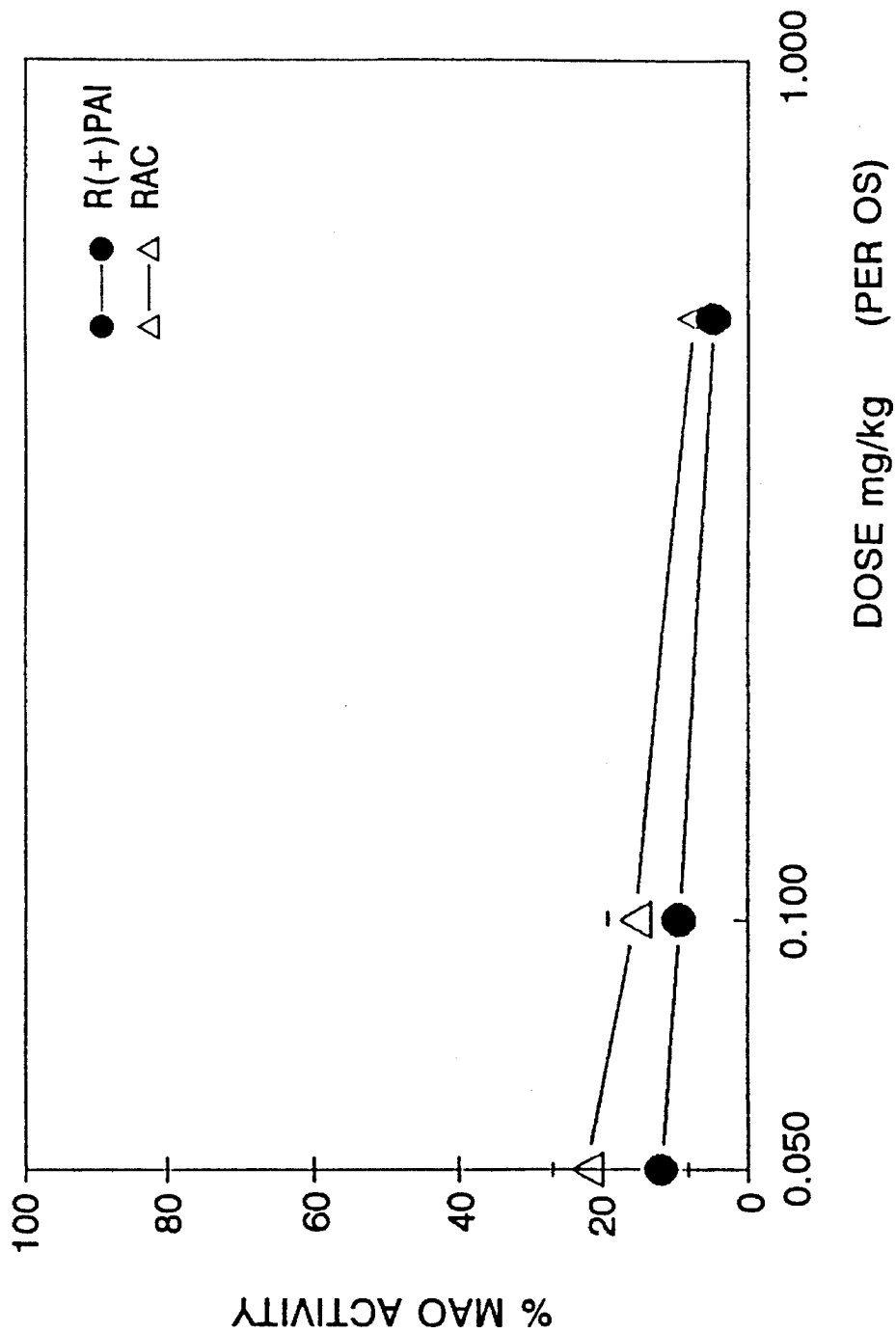
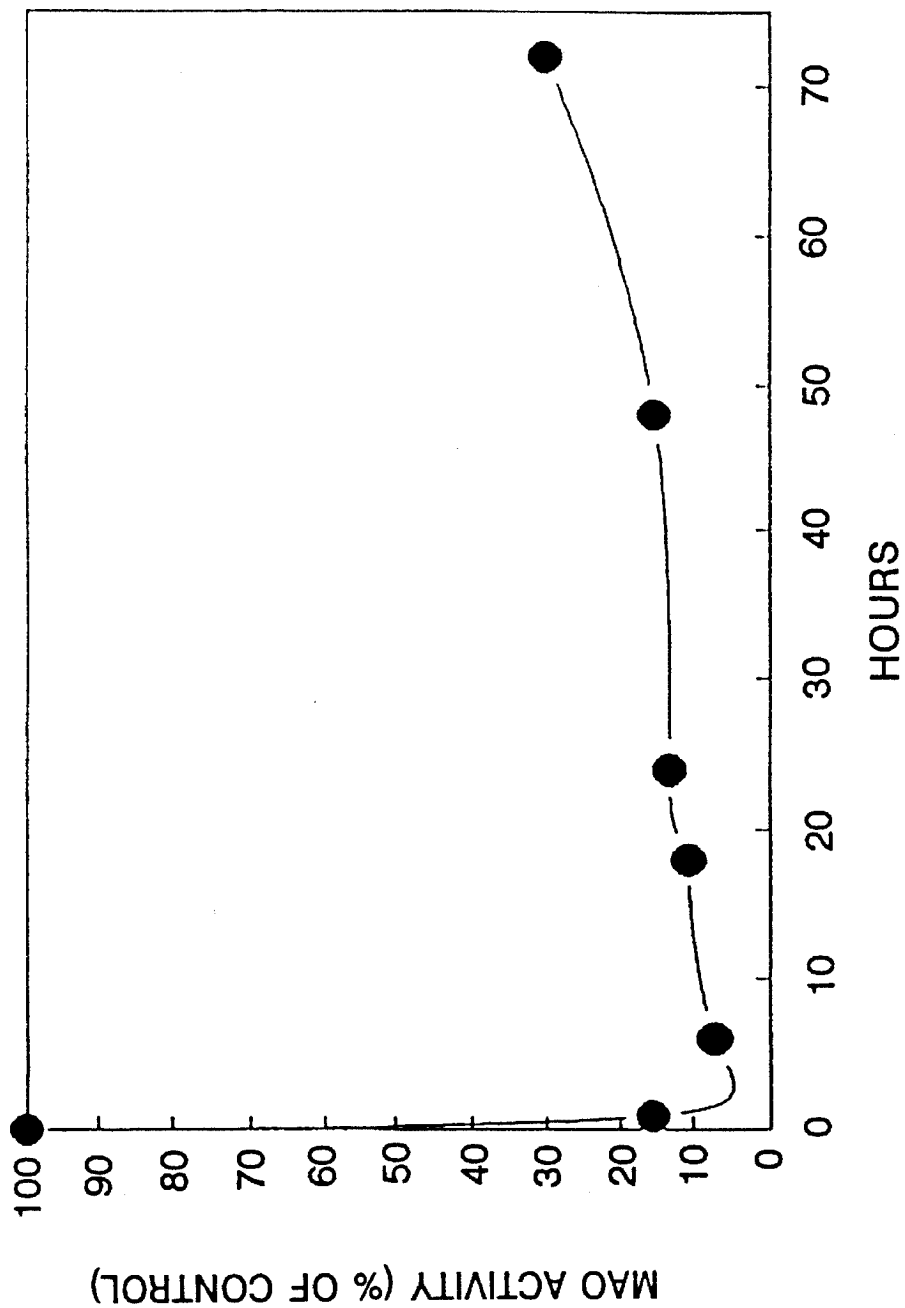


FIGURE 16



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**USE OF THE R-ENANTIOMERS OF  
N-PROPARGYL 1-AMINOINDAN  
COMPOUNDS FOR TREATING  
PARKINSON'S DISEASE.**

This application is a continuation of U.S. Ser. No. 08/063,455, (now U.S. Pat. No. 5,387,612) filed May 18, 1993, which is a continuation of U.S. Ser. No. 07/632,184, filed Dec. 21, 1990, abandoned.

**FIELD OF THE INVENTION**

The present invention is in the field of selective irreversible inhibitors of the enzyme monoamine oxidase (hereinafter MAO) and relates to the R(+) enantiomer of N-propargyl-1-aminoindan (hereinafter, PAI) which is a selective irreversible inhibitor of the B-form of the monoamine oxidase enzyme (hereinafter, MAO-B). The invention also relates to pharmaceutical compositions containing R(+) PAI which is particularly useful for the treatment of Parkinson's disease, memory disorders and dementia of the Alzheimer type (DAT), depression, and hyperactive syndrome in children.

**BACKGROUND OF THE INVENTION AND  
PRIOR ART**

Parkinson's disease is widely considered to be the result of degradation of the pre-synaptic dopaminergic neurons in the brain, with a subsequent decrease in the amount of the neurotransmitter dopamine, that is being released. Inadequate dopamine release, therefore, leads to the onset of voluntary muscle control disturbances symptomatic of Parkinson's disease.

Various procedures for treating Parkinson's disease have been established and are currently in widespread use, for example, the administration of L-Dopa together with a decarboxylase inhibitor, such as L-carbidopa or benzerazide. The decarboxylase inhibitor protects the L-Dopa molecule from peripheral decarboxylation and thus ensures L-Dopa uptake by the remaining dopaminergic neurons in the striatum of the brain. Here the L-Dopa is converted into dopamine resulting in increased levels of dopamine in these neurons. In response to physiological impulses these neurons are therefore capable of releasing larger amounts of dopamine, the quantity of which approximates the normal required levels. This treatment therefore alleviates the symptoms of the disease and contributes to the well-being of the patients.

However, this L-Dopa treatment has its drawbacks, the main one being that its effectiveness is optimal only in the first few years following the onset of treatment. After this initial period the clinical response is diminished and is accompanied by adverse side effects which include dyskinesia, fluctuation in efficacy throughout the day ("on-off effect") and psychiatric symptoms such as confusional states, paranoia and hallucinations. This fall-off in the effect of L-Dopa treatment is attributed to a number of factors, including the natural progression of the disease, alteration in dopamine receptors as a consequence of increased dopamine production or increased levels of dopamine metabolites, and pharmacokinetic problems of L-Dopa absorption (reviewed by Youdim et al., *Progress in Medicinal Chemistry*, Vol. 21, Chapter 4, pp. 138-167 (1984), Eds. Ellis and West, Elsevier, Amsterdam).

In order to overcome the drawbacks of the L-Dopa treatment, various treatments have been devised in which

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L-Dopa is combined with MAO inhibitors, with the aim of reducing the metabolic breakdown of the newly formed dopamine (see for example, U.S. Pat. No. 4,826,875).

MAO exists in two forms known as MAO-A and MAO-B which have selectivity for different substrates and inhibitors. For example, MAO-B metabolizes more efficiently substrates such as 2-phenylethylamine and is selectively and irreversibly inhibited by (-)-deprenyl (as described below).

It should be noted, however, that combining L-Dopa with an inhibitor of both MAO-A and MAO-B is undesirable leading to adverse side effects related to an increased level of catecholamines throughout the neuraxis. Furthermore, complete inhibition of MAO is also undesirable as it potentiates the action of sympathomimetic amines such as tyramine leading to the so-called "cheese effect" (reviewed by Youdim et al., *Handbook of Experimental Pharmacology*, Vol. 90, Chap. 3 (1988) Eds. Trendelenburg and Weiner, Springer-Verlag). As MAO-B was shown to be the predominant form of MAO in the brain, selective inhibitors for this form were thus considered to be a possible way for achieving a decrease in dopamine breakdown on the one hand, together with a minimization of the systemic effects of total MAO inhibition, on the other.

One of these selective MAO-B inhibitors, (-)-deprenyl, has been extensively studied and has been used as an MAO-B inhibitor to augment L-Dopa treatment. This treatment with (-)-deprenyl is generally favorable, not causing the "cheese effect" at doses causing nearly complete inhibition of MAO-B (Elsworth et al., *Psychopharmacology*, 57, 33 (1978). Furthermore, addition of (-)-deprenyl to a combination of L-Dopa and decarboxylase inhibitor to Parkinson's patients leads to improvements in akinesia and overall functional capacity as well as the elimination of "on-off" type fluctuations (reviewed by Birkmayer & Riederer in "Parkinson's Disease" pp. 138-149, Springer-Verlag (1983)).

Thus, (-)-deprenyl enhances and prolongs the effect of L-Dopa and permits a lowering of the dosage of L-Dopa whereby the adverse effects of L-Dopa treatment are limited.

However, (-)-deprenyl is not without its own adverse side effects which include activation of pre-existing gastric ulcers and occasional hypertensive episodes. Furthermore, (-)-deprenyl is an amphetamine derivative and is metabolized to yield amphetamine and methamphetamines which may lead to undesirable side effects associated with these substances, e.g. increased heart rate (Simpson, *Biochemical Pharmacology*, 27, 1591 (1978); Finberg et al., in "Monoamine Oxidase Inhibitors—The State of the Art", pp. 31-43, Eds. Youdim and Paykel, (1981) Wiley).

Other compounds that are selective irreversible inhibitors of MAO-B but which are free of the undesirable effects associated with (-)-deprenyl have been described. One such compound, namely N-propargyl-1-aminoindan. HCl (racemic-PAI.HCl) was described in GB 1,003,686, GB 1,037,014 and U.S. Pat. No. 3,513,244. It is a potent, selective, irreversible inhibitor of MAO-B, is not metabolized to amphetamines and does not give rise to unwanted sympathomimetic effects.

In comparative animal tests racemic PAI was shown to have considerable advantages over (-)-deprenyl, for example, racemic PAI produced no significant tachycardia, did not increase blood pressure (effects produced by doses of 5 mg/kg of (-)-deprenyl), and did not lead to contraction of nictitating membrane nor to an increase in heart rate at doses up to 5 mg/kg (effects caused by (-)-deprenyl at doses over

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0.5 mg/kg). Furthermore, racemic PAI.HCl does not potentiate the cardiovascular effects of tyramine (Finberg et al. in "Enzymes and Neurotransmitters in Mental Disease", pp. 205-219, (1980), Eds. Usdin et al., Pub. John Wiley and sons, N.Y.; Finberg et al. (1981) in "Monoamine Oxidase Inhibitors—The State of the Art", *ibid*; Finberg and Youdim, *British Journal Pharmacol.* 85 451, (1985).

One object of this invention is to separate the racemic PAI compounds and to produce an enantiomer with MAO-B inhibition activity.

Since deprenyl has a similar structure to PAI and it is known that the (-)-enantiomer of deprenyl, i.e. (-)-deprenyl, is considerably more pharmaceutically active than the (+)-enantiomer, it was expected, by those skilled in the art, that only the (-) enantiomer of PAI would be the active MAO-B inhibitor.

However, contrary to such expectations, upon resolution of the enantiomers, it was found, in accordance with the present invention that the (+)-PAI enantiomer was in fact the active MAO-B inhibitor while the (-)enantiomer showed extremely low MAO-B inhibitory activity. Furthermore, the (+)PAI enantiomer surprisingly also had a higher degree of selectivity for MAO-B inhibition than the corresponding racemic form and may thus have less undesirable side effects in the treatment of the indicated disease. These findings are based on both in vitro and in vivo experiments as presented hereinafter in greater detail.

It was subsequently shown that (+)-PAI has the R absolute configuration. This was also surprising based on the expected structural analogy with deprenyl and the amphetamines.

The high degree of stereoselectivity of pharmacological activity between R(+)-PAI and the S(-) enantiomer is also remarkable. The compounds R(+)-PAI is nearly four orders of magnitude more active than the S(-) enantiomer in MAO-B inhibition. This ratio is significantly higher than that observed between the two deprenyl enantiomers (Knoll and Magyar, *Adv. Biochem. Psychopharmacol.*, 5, 393 (1972); Magyar, et al., *Acta Physiol. Acad. Sci. Hung.*, 32, 377 (1967). Furthermore, in some physiological tests, (+) deprenyl was reported to have equal or even higher activity than the (-) enantiomer (Tekes, et al., *Pol. J. Pharmacol. Pharm.* 40, 653 (1988).

N-methyl-N-propargylaminoindan (MPAI) is a more potent inhibitor of MAO activity, but with lower selectivity for MAO-B over A (Tipton, et al., *Biochem. Pharmacol.*, 31, 1250 (1982)). Surprisingly, in this case we have found only small degree of difference in the relative activities of the two resolved enantiomers thus further emphasising the remarkable difference of the case of R(+)-PAI. (See Table 1A).

Another object of the present invention is to provide for the first time use of the pharmaceutically active PAI-enantiomer alone (without L-Dopa) for treatment of Parkinson's disease, dementia and depression (see review by Youdim et al. in *Handbook of Experimental Pharmacology*, Vol. 90/I, (1988), chap.3, Eds. Trendelenberg and Wiener).

It is yet another object of the invention to provide for the use of the pharmaceutically active PAI-enantiomer for pre-treatment alone or together with synergistic agents, of Parkinson's disease in order to delay the L-Dopa treatment and its associated adverse side effects. This approach has been studied with respect to (-)-deprenyl which was shown to be effective when administered alone to early Parkinsonism patients, and may also have a synergistic effect in these patients when administered together with  $\alpha$ -tocopherol (a

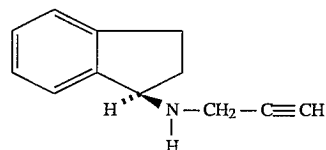
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vitamin E derivative), (The Parkinson's Study Group, *New England J. Med.*, 321 (20), 1364-1371, (1989)).

In addition to its usefulness in treating Parkinson's disease, (-)-deprenyl has also been shown to be useful in the treatment of patients with dementia of the Alzheimer type (DAT) (Tarlott et al., *Psychopharmacology*, 91, 489-495, 1987), and in the treatment of depression (Mendelewicz and Youdim, *Brit. J. Psychiat.* 142, 508-511, 1983). Thus, the R(+)-PAI compound of this invention has been shown to possess activity in restoration of memory, thus having potential for treatment of memory disorders, dementia and especially useful in Alzheimer's disease and for the treatment of the hyperactive syndrome in children.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention thus provides as a novel compound the R(+)-enantiomer of N-propargyl-1-aminoindan [R(+)-PAI] of the formula (I):



(I)

and pharmaceutically acceptable acid addition salts thereof. The present invention also relates to the preparation of R(+)-PAI, to pharmaceutical compositions comprising the compound R(+)-PAI together with suitable carriers and to the use of R(+)-PAI for the treatment of human patients for Parkinson's disease, memory disorders, dementia of the Alzheimer type and hyperactive syndrome.

The R(+)-PAI may be obtained by optical resolution of racemic mixtures of R and S-enantiomer of PAI. Such a resolution can be accomplished by any conventional resolution method, well known to a person skilled in the art, such as those described in "Enantiomers, Racemates and Resolutions" by J. Jacques, A. Collet and S. Wilen, Pub. John Wiley & Sons, N.Y., 1981. For example, the resolution may be carried out by preparative chromatography on a chiral column. Another example of a suitable resolution method is the formation of diastereomeric salts with a chiral acid such as tartaric, malic, mandelic acid or N-acetyl derivatives of amino acids, such as N-acetyl leucine, followed by recrystallisation to isolate the diastereomeric salt of the desired R enantiomer.

The racemic mixture of R and S enantiomers of PAI may be prepared, e.g. as described in GB 1,003,676 and GB 1,037,014. The racemic mixture of PAI can also be prepared by reacting 1-chloroindan or 1-bromoindan with propargylamine. Alternatively, this racemate may be prepared by reacting propargylamine with 1-indanone to form the corresponding imine, followed by reduction of the carbon-nitrogen double bond of the imine with a suitable agent, such as sodium borohydride.

In accordance with this invention, the R enantiomer of PAI, can also be prepared directly from the optically active R-enantiomer of 1-aminoindan by reaction with propargyl bromide or propargyl chloride in the presence of an organic or inorganic base and optionally in the presence of a suitable solvent.

Suitable organic or inorganic bases for use in the above reaction are, e.g., triethylamine, pyridine, alkali metal carbonates or bicarbonates etc. If the reaction is conducted in

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the presence of a solvent, this may be chosen from, e.g., toluene, methylene chloride and acetonitrile. A preferred method of preparation of the aforementioned compound is the reaction between R-1-aminoindan with propargyl chloride using potassium bicarbonate as a base and acetonitrile as solvent.

The above described reaction of 1-aminoindan generally results in a mixture of unreacted primary amine, the desired secondary amine and the tertiary amine N,N-bispropargylamino product. The desired secondary amine, i.e. N-propargyl-1-aminoindan, can be separated from this mixture by any conventional separation method, such as chromatography, distillation, selective extraction, etc.

The R-1-aminoindan starting material can be prepared by methods known from the literature, for example Lawson and Rao, *Biochemistry* (1980) 19, 2133 and the references cited therein, and European Patent No. 235,590.

The R-1-aminoindan can also be prepared by resolution of a racemic mixture of the R and S enantiomers, e.g. by formation of diastereomeric salts with chiral acids, or by any other known method, such as those reported in the above mentioned "Enantiomers, Racemates and Resolutions" by J. Jacques et al, Pub. John Wiley & Sons, N.Y., 1981. Alternatively, the R-1-aminoindan starting material may be prepared by reacting 1-indanone with an optically active amine, followed by reduction of the carbon-nitrogen double bond of the resulting imine by hydrogenation over a suitable catalyst, such as palladium on carbon, platinum oxide, Raney-nickel etc. Suitable optically active amines are, for example, one of the antipodes of phenethylamine or an ester of an amino acid, such as valine or phenylalanine. The benzylic N—C bond may be cleaved subsequently, by hydrogenation under non-vigorous conditions.

Additional methods for preparing R-1-aminoindan are the hydrogenation, as described above, of indan-1-one oxime ethers, wherein the alkyl portion of the ether contains an optically pure chiral center. Alternatively, a non-chiral derivative of indan-1-one containing a carbon-nitrogen double bond, such as an imine or oxime, can be reduced with a chiral reducing agent, e.g. a complex of lithium aluminium-hydride and ephedrine.

For the preparation of pharmaceutically acceptable acid addition salts of the compound of R(+)-PAI, the free base can be reacted with the desired acids in the presence of a suitable solvent by conventional methods. Similarly, an acid addition salt may be converted to the free base form in a known manner.

In accordance with the present invention, the compound R(+)-PAI may be prepared as pharmaceutical compositions particularly useful for the treatment of Parkinson's disease, dementia of the Alzheimer type (DAT) or depression. Such compositions may comprise the compound of R(+)-PAI or pharmaceutically acceptable acid addition salts thereof, together with pharmaceutically acceptable carriers and/or excipients. For example, these compositions may be prepared as medicaments to be administered orally, parenterally, rectally or transdermally. Suitable forms for oral administration include tablets, compressed or coated pills, dragées, sachets, hard or soft gelatin capsules, sub-lingual tablets, syrups and suspensions; for parenteral administration the invention provides ampoules or vials that include an aqueous or non-aqueous solution or emulsion; for rectal administration there are provided suppositories with hydrophilic or hydrophobic vehicles; and for topical application as ointments and transdermal delivery there are provided suitable delivery systems as known in the art.

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These above compositions may be used alone to treat Parkinson's disease, Alzheimer's disease or depression, or alternatively, in the case of Parkinson's disease, they may be used as an adjunct to the conventional L-Dopa treatments. A composition may comprise 2–10 mg of R(+)-N-propargyl-1-aminoindan, 50–200 mg of Levodopa, and 12.5–50 mg of benserazide.

The preferred dosages of the active ingredient, i.e., R-PAI compounds, in the above compositions are within the following ranges: for oral or suppository formulations 2–20 mg per dosage unit to be taken daily and more preferably 5–10 mg per dosage unit to be taken daily may be used; and for injectable formulations 1–10 mg/ml per dosage unit to be taken daily and more preferably 2–5 mg/ml per dosage unit to be taken daily may be used.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graphic representation of the results according to Example 19.

FIG. 2 is a graphic representation of the results according to Example 19.

FIG. 3A is a graphic representation of the results according to Example 19.

FIG. 3B: See description of FIG. 3A

FIG. 4 is a graphic representation of the results according to Example 20.

FIG. 5 is a graphic representation of the results according to Example 20.

FIG. 6 is a graphic representation of the results according to Example 20.

FIG. 7 is a graphic representation of the results according to Example 20.

FIG. 8 is a graphic representation of the results according to Example 20.

FIG. 9 is a graphic representation of the results according to Example 20.

FIG. 10 is a graphic representation of the results according to Example 20.

FIG. 11 is a graphic representation of the results according to Example 20.

FIG. 12 is a graphic representation of the results according to Example 21.

FIG. 13 is a graphic representation of the results according to Example 21.

FIG. 14 is a graphic representation of the results according to Example 21.

FIG. 15 is a graphic representation of the results according to Example 21.

FIG. 16 is a graphic representation of the results according to Example 22.

The invention will now be described in more detail in the following non-limiting examples and their accompanying Tables and Figures.

#### EXAMPLE 1

##### Racemic N-propargyl-1-aminoindan hydrochloride

Racemic 1-aminoindan (10.0 g) and 10.4 g of potassium carbonate were added to 75 ml of acetonitrile. The resulting suspension was heated to 60° C. and 4.5 g of propargyl chloride were added dropwise.

The mixture was stirred at 60° C. for 16 hours, whereafter most of the volatiles were removed by distillation in vacuo.

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The residue was partitioned between 10% aqueous sodium hydroxide and methylene chloride.

The organic phase was dried and the solvent removed by distillation. The residue was flash chromatographed on silica gel, eluting with 40% ethyl acetate/60% hexane. The fractions containing the title compound as a free base were combined and the eluant replaced by ether. The ethereal solution was treated with gaseous HCl, the precipitate formed was isolated by suction filtration and recrystallized from isopropanol to yield 7.3 g of the title compound, m.p. 182°–4° C.

Chromatographic and spectroscopic data were in accordance with the literature (U.S. Pat. No. 3,513,244) and an authentic sample.

NMR ( $\delta$ , CDCl<sub>3</sub>): 2.45 (2H, m), 2.60 (1H, t), 2.90 (1H, m), 3.45 (1H, m), 3.70 (2H, d), 4.95 (1H, t), 7.5 (4H, m) ppm.

## EXAMPLE 2

## S-(–)-N-Propargyl-1-aminoindan hydrochloride

The title compound in free base form was isolated by resolving the racemic mixture of the free base of Example 1 on a Chiracel OJ (cellulose tris[p-methylbenzoate]) preparative HPLC column eluting with 10% isopropanol/90% hexane and collecting the first eluted major peak. The resulting oil was converted to the title compound (hydrochloride) by treatment of a 10% diethyl ether solution of the oil with gaseous HCl and the resulting precipitate was collected by suction filtration.

[ $\alpha$ ]<sub>D</sub>–29.2° (1%, ethanol), m.p. 182°–184° C. Other chromatographic and spectroscopic properties were identical with the hydrochloride salt of Example 1.

## EXAMPLE 3

## R-(+)-N-Propargyl-1-aminoindan hydrochloride

The title compound was prepared as in Example 2 above, except that the second eluted peak from the preparative HPLC was collected: [ $\alpha$ ]<sub>D</sub>+29.1° (0.8%, ethanol), m.p. 179°–181° C. Other chromatographic and spectroscopic properties were identical with the hydrochloride salt of Example 1.

## EXAMPLE 4

## R-(+)-N-propargyl-1-aminoindan hydrochloride

R-(–)-1-aminoindan (12.4 g) and 12.9 g of potassium carbonate were added to 95 ml of acetonitrile. The resulting suspension was heated to 60° and 5.6 g of propargyl chloride were added dropwise. The mixture was stirred at 60° C. for 16 hours, whereafter most of the volatiles were removed by distillation in vacuo. The residue was partitioned between 10% aqueous sodium hydroxide and methylene chloride.

The organic phase was dried and the solvent removed in vacuo, the residue was flash chromatographed on silica gel eluting with 40% ethyl acetate/60% hexane. Fractions containing the free base of the title compound were combined and the solvent replaced by ether. The ethereal solution was treated with gaseous HCl and the resulting precipitate was isolated by suction filtration and recrystallized from isopropanol to yield 6.8 g of the title compound, m.p. 183°–185° C., [ $\alpha$ ]<sub>D</sub>+30.90 (2%, ethanol). Spectral properties were identical to those reported for the compound of Example 1.

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## EXAMPLE 5

## S-(–)-N-propargyl-1-aminoindan hydrochloride

The title compound was prepared by the method of Example 4, except that S-(+)-1-aminoindan was used as starting material. The product exhibited [ $\alpha$ ]<sub>D</sub>–30.3 (2%, ethanol), m.p. 183°–5° C. Spectral properties were identical to those reported for the compound of Example 1.

## EXAMPLE 6

## Di (R-(+)-N-propargyl-1-aminoindan)L-tartrate

To a solution of L-Tartaric acid (4.4 g) in 48 ml of boiling methanol was added a solution of R-(+)-N-propargyl-1-aminoindan free base (5.0 g) in methanol (48 ml). The solution was heated to reflux and 284 ml of *t*-butylmethyl ether was added over 20 minutes. The mixture was heated for an additional 30 minutes, cooled, and the resulting precipitate was isolated by suction filtration to yield 6.7 g of the title compound, m.p. 175°–177° C. [ $\alpha$ ]<sub>D</sub> (1.5, H<sub>2</sub>O)=+34.3; Anal. calcd. for C<sub>28</sub>H<sub>32</sub>O<sub>6</sub>N<sub>2</sub>; C, 68.26, H, 6.56, N, 5.69. Found: C, 68.76; H, 6.57; N, 5.61.

## EXAMPLE 7

## R-(+)-N-Methyl-N-propargyl-1-aminoindan hydrochloride

The free base form of R-(+)-N-propargyl-1-aminoindan from Example 4 (1.2 grams), potassium carbonate (0.97 grams) and methyl iodide (1 gram) were added to 15 ml of acetone and the resulting suspension heated to reflux under a nitrogen atmosphere for 8 hrs. Thereafter the volatiles were removed under reduced pressure and the residue partitioned between 10% aqueous sodium hydroxide (30 ml) and methylene chloride (30 ml). The organic phase was dried and the solvent removed in vacuo. The residue was flash chromatographed on silica gel eluting with 40% ethyl acetate/60% hexane. Fractions containing the title compound as a free base were combined and the solvent replaced by diethyl ether. The ethereal solution was treated with gaseous HCl, the volatiles removed in vacuo and the residue recrystallized from isopropanol to yield 400 mg of the title compound as a white crystalline solid, m.p.: 134°–136° C. [ $\alpha$ ]<sub>D</sub>+31.40 (ethanol). NMR( $\delta$ CDCl<sub>3</sub>):2.55 (2H, m); 2.7 (1H, br.s); 2.8 (3H, s); 3.0 (1H, m); 3.4 (1H, m); 3.9 (2H, br.s); 5.05 (1H, m) 7.7 (4H, m) ppm.

## EXAMPLE 8

## S-(–)-N-methyl-N-propargyl-1-aminoindan hydrochloride

The title compound was prepared as in Example 7 above, except that S-(–)-N-propargyl-1-aminoindan (free base) from Example 5 was used as starting material. All of the physical and spectral properties of the title compound were identical to those in Example 7 except for the [ $\alpha$ ]<sub>D</sub> –34.9° (ethanol).

## EXAMPLE 9

## Tablet Composition

R-(+)-N-propargyl-1-aminoindan hydrochloride	5.0mg
Pregelatinized starch	47.0mg
Lactose hydrous	66.0mg



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-continued

Tablet Composition	
Microcrystalline cellulose	20.0mg
Sodium starch glycolate	3.0mg
Talc	1.5mg
Magnesium stearate	0.7mg
Purified water added as required for granulation.	

## EXAMPLE 10

Tablet Composition	
R(+)-N-propargyl-1-aminoindan hydrochloride	1.0mg
Lactose hydrous	50.0mg
Pregelatinized starch	36.0mg
Microcrystalline cellulose	14.0mg
Sodium starch glycolate	2.2mg
Talc	1.0mg
Magnesium stearate	0.5mg
Purified water added as required for granulation.	

## EXAMPLE 11

Capsule Composition	
R(+)-N-propargyl-1-aminoindan hydrochloride	5.0mg
Pregelatinized starch	10.0mg
Starch	44.0mg
Microcrystalline cellulose	25.0mg
Ethylcellulose	1.0mg
Talc	1.5mg
Purified water added as required for granulation.	

## EXAMPLE 12

Injection Composition	
R(+)-N-propargyl-1-aminoindan hydrochloride	5.0mg
Dextrose anhydrous	44.0mg
HCl added to pH 5	
Purified water added as required for 1 ml	

## EXAMPLE 13

Injection Composition	
R(+)-N-propargyl-1-aminoindan hydrochloride	1.0mg
Sodium chloride	8.9mg
HCl added to pH 5	
Purified water added as required to 1 ml	

## EXAMPLE 14

Injection Composition	
R(+)-N-propargyl-1-aminoindan hydrochloride	2.0mg
Sodium chloride	8.9mg

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-continued

Injection Composition	
HCl added to pH 5	
Purified water added as required to 1 ml	

## EXAMPLE 15

Syrup Composition	
R(+)-N-propargyl-1-aminoindan hydrochloride	5.0 mg
Sucrose	2250.0 mg
Saccharin sodium	5.0 mg
Methylparaben	6.0 mg
Propylparaben	1.0 mg
Flavor	20.0 mg
Glycerin USP	500 mg
Alcohol 95% USP	200 mg
Purified water as required to 5.0 ml	

## EXAMPLE 16

Sublingual Tablets	
R(+)-N-propargyl-1-aminoindan hydrochloride	2.5 mg
Microcrystalline cellulose	20.0 mg
Lactose hydrous	5.0 mg
Pregelatinized starch	3.0 mg
Povidone	0.3 mg
Coloring agent	q.s.
Flavor	q.s.
Sweetener	q.s.
Talc	0.3 mg

Blend the excipients and the active and granulate with an ethanol solution of Povidone. After drying and weighing, it is blended with the talc and compressed.

## EXAMPLE 17

PAI Sublingual Tablets	
R(+)-N-propargyl-1-aminoindan hydrochloride	5.0mg
Microcrystalline cellulose	15.0mg
Pregelatinized starch	12.0mg
Ethyl cellulose	0.3mg
Talc	0.3mg
Purified water added as required for granulation.	

## EXAMPLE 18

Tablet Composition	
R(+)-N-propargyl-1-aminoindan hydrochloride	5.0 mg
Levodopa	100.0 mg
Carbidopa	25.0 mg
Pregelatinized starch	24.0 mg
Starch	40.0 mg
Microcrystalline cellulose	49.5 mg
Col. D & C Yellow No. 10	0.5 mg
Col. D & C Yellow No. 6	0.02 mg
Alcohol USP added as required for granulation.	

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The following Examples and their accompanying Tables and Figures relate to the Biological Experiments carried out in accordance with this invention.

## EXAMPLE 19

## Inhibition of MAO Activity In Vitro

## Experimental Protocol

The MAO enzyme source was a homogenate of rat brain in 0.3M sucrose, which was centrifuged at 600g for 15 min. The supernatant was diluted appropriately in 0.05M phosphate buffer, and pre-incubated with serial dilutions of compounds of general formula I: R(+)-PAI, S(-)-PAI and racemic-PAI (wherein A is hydrogen) for 20 min at 37° C. <sup>14</sup>C-labelled substrates (2-phenylethylamine, hereinafter PEA; 5-hydroxytryptamine, hereinafter 5-HT) were then added, and the incubation continued for a further 20 min (PEA), or 30–45 min (5-HT). Substrate concentrations used were 50uM (PEA), and 1 mM (5-HT). In the case of PEA, enzyme concentration was chosen so that not more than 10% of the substrate was metabolized during the course of the reaction. The reaction was then stopped by addition of tranlycypromine (to final concentration 1 mM), and the incubate filtered over a small column of Amberlite CG-50, buffered to pH 6.3. The column was washed with 1.5 ml water, the eluates pooled and the radioactive content determined by liquid scintillation spectrometry. Since the amine substrates are totally retained on the column, radioactivity in the eluate indicates the production of neutral and acidic metabolites formed as a result of MAO activity. Activity of MAO in the sample was expressed as a percentage of control activity in the absence of inhibitors, after subtraction of appropriate blank values. The activity determined using PEA as substrate is referred to as MAO-B, and that determined using 5-HT as MAO-A.

## Results

Inhibitory activity of the R(+)-PAI, S(-)-PAI and racemic-PAI compounds of formula I were examined separately in vitro, and the results of typical experimental runs are shown in FIGS. 1 and 2. The entire experiment was repeated three times. Concentration of inhibitor producing 50% inhibition of substrate metabolism (IC-50) was calculated from the inhibition curves, and is shown in Table 1. From this data it can be seen that:

- the R(+)-PAI is twice as active as the racemate for inhibition of MAO-B;
- the R(+)-PAI is 29 times more active for inhibition of MAO-B than MAO-A;
- the S(-)-PAI is only 1/6,800 as active as the R(+)-PAI for inhibition of MAO-B, and shows little or no selec-

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tivity between MAO-B and MAO-A.

TABLE 1

IC-50 (nM) VALUES FOR INHIBITION OF MAO-A AND MAO-B BY RACEMIC-PAI AND THE R(+) AND S(-) ENANTIOMERS THEREOF IN RAT BRAIN HOMOGENATE IN VITRO						
IC-50 (nM)						
Compound:	MAO-A			MAO-B		
	S(-)PAI	R(+)-PAI	Rac	S(-)PAI	R(+)-PAI	Rac
26000	73	140	17000	2.5	5	

The results of the same experiment using R(+) and S(-) MPAI (N-methyl-N-propargyl-1-aminoindan) are reported in Table 1A. Each of the enantiomers of MPAI is less selective between MAO-B and MAO-A inhibition than R(+)-PAI. Furthermore, R(+)-MPAI is only five times as active as S(-)-MPAI in MAO-B inhibition, in contrast to R(+)-PAI which is about 7000 times as active as S(-)-PAI in this assay.

TABLE 1A

IC-50 (nM) VALUES FOR INHIBITION OF MAO-A AND MAO-B BY THE R(+) AND S(-) ENANTIOMERS OF MPAI IN RAT BRAIN HOMOGENATE IN VITRO				
IC-50 (nM)				
Compound:	MAO-A		MAO-B	
	S(-)MPAI	R(+)-MPAI	S(-)MPAI	R(+)-MPAI
70	3	50	10	

Some experiments were also carried out with human cerebral cortical tissues, obtained 6 hours post-mortem, and treated as described above. The results of such an experiment are shown in FIG. 3 (where the R(+)-PAI, S(-)-PAI and racemic PAI compounds were those equivalent to formula I).

## EXAMPLE 20

## Inhibition of MAO Activity In Vivo: Acute Treatment

## Experimental Protocol

Rats (male Sprague-Dawley derived) weighing 250±20 g were treated with one of the enantiomers or the racemic form of PAI by intraperitoneal injection (ip) or oral gavage (po) and decapitated 1 h or 2 h later respectively. Groups of three rats were used for each dose level of inhibitor, and MAO activity determined in brain and liver using the general technique described above. The amount of protein in each incubation was determined using the Folin-Lowry method, and enzyme activity calculated as nmol substrate metabolized per hour incubation for each mg protein. Activity of MAO in tissues from animals treated with inhibitors was expressed as a percentage of the enzyme activity in a group of control animals, administered vehicle (water for oral administration; 0.9% saline for ip injection) and killed as above.

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**13****Results**

None of the dose levels used with the inhibitor drugs produced any obvious behavioural alteration. The results are depicted in FIGS. 4 to 11. Following ip administration, compound R(+)-PAI produced 90% inhibition of brain MAO-B activity at a dose of 0.5 mg/kg. The same dose produced only 20% inhibition of MAO-A activity. By oral administration, the same dose of R(+)-PAI produced 80% inhibition of MAO-B with no detectable inhibition of MAO-A. Essentially similar results were seen for inhibition of hepatic MAO, as for brain MAO. The doses producing 50% inhibition of MAO-A and MAO-B (IC-50) were calculated from the inhibition curves, and are shown in Table 2. These data show:

- (a) that MAO inhibitory activity of compound R(+)-PAI is maintained in vivo in the rat;
- (b) that selectivity for inhibition of MAO-B, as opposed to MAO-A, by R(+)-PAI is maintained in vivo;
- (c) that the much greater activity of the (+)-as opposed to (-)-enantiomer, is maintained in vivo;
- (d) that the compounds are effectively absorbed after oral administration; and
- (e) that the compounds effectively pass the blood-brain barrier, and effectively inhibit brain MAO. The fact that R(+)-PAI was about twice as active as the racemic compound for inhibition of MAO-B is a reflection of the extremely low activity of S(-)-PAI for inhibition of MAO-B.

TABLE 2

IC-50 VALUES (mg/kg) FOR INHIBITION OF MAO-A AND MAO-B BY R(+)-PAI, S(-)-PAI OR RACEMIC-PAI, IN THE RAT FOLLOWING INTRAPERITONEAL (IP) INJECTION OR ORAL ADMINISTRATION (PO)						
	IC-50 (mg/kg)					
	MAO-A			MAO-B		
Compound:	S(-)PAI	R(+)-PAI	Rac	S(-)PAI	R(+)-PAI	Rac
IP BRAIN	>10	1.2	2.5	>10	0.07	0.22
IP LIVER	>10	5	5	>10	0.06	0.11
PO BRAIN	>10	>5	>5	>10	0.17	0.29
PO LIVER	>10	>5	>5	>10	0.05	0.09

**EXAMPLE 21****Inhibition of MAO Activity In Vivo: Chronic Treatment****Experimental Protocol**

Rats (specification as in Example 20:4 animals for each dose level) were treated with compound R(+)-PAI or racemic form at three dose levels (0.05, 0.1 and 0.5 mg/kg) by oral administration, one dose daily for 21 days, and decapitated 2 hours after the last dose. The activity of MAO types A and B was determined in brain and liver as described in Example 20.

**Results**

A dose of 0.1 mg/kg daily of compound R(+)-PAI produced a good degree of selective inhibition, with more than 80% inhibition of brain MAO-B and 20% or less inhibition of brain MAO-A. At the higher dose of 0.5 mg/kg daily, MAO-A was still inhibited by less than 50% (FIGS. 12 and 13). Hepatic MAO showed a similar degree of selective

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inhibition (FIGS. 14 and 15). Compound R(+)-PAI was again more potent than the racemic form of the inhibitor, by a factor of about twofold. In the case of brain MAO, R(+)-PAI had a better degree of selectivity for inhibition of MAO-B than the racemic form.

These results show that selectivity of MAO-B inhibition can be maintained following chronic treatment with the compounds. As with other irreversible inhibitors, the degree of enzyme inhibition is greater with chronic treatments than following a single dose of the drug. Compound R(+)-PAI shows a better degree of selectivity for inhibition of brain MAO-B than the racemic compound.

**EXAMPLE 22****Irreversible Nature of MAO Inhibition****Experimental Protocol**

A single dose of compound R(+)-PAI (1 mg/kg) was administered by ip injection to groups of 4 rats, and the animals killed 2,6,18,24,48 and 72 hours later. Activity of MAO-B was determined in whole brain tissues as described herein before.

**Results**

The results are shown in FIG. 16. Maximal inhibition of MAO-B was attained at 6 hours after the injection. MAO activity had only returned to 30% control activity at 72 hours after the injection. This experiment demonstrates the irre-

versible nature of the MAO inhibition by compound R(+)-PAI.

**EXAMPLE 23****Potentiation of Tyramine Pressor Effect in Conscious Rats****Experimental Protocol**

Rats were anaesthetised with a mixture of pentobarbital (30 mg/kg) and chloral hydrate (120 mg/kg) by intraperitoneal injection. The left carotid artery and jugular vein were cannulated with fine polythene tubing (artery) or fine silicone rubber tubing connected to polyethylene tubing (vein), the distal end of which was brought under the skin to an anchor point behind the neck. The tubing was filled with heparinised saline solution, and plugged with a fine steel rod. The animals were treated with 20 mg chloramphenicol by intramuscular injection and allowed to recover from the operation overnight. The following day, the rats were placed

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in a high-walled container permitting free movement- The arterial catheter was connected to a pressure transducer via a 100 cm length of saline-filled, fine-bore polyethylene tubing, and the venous catheter connected to a 1 ml syringe via a similar length of tubing, which, together with the syringe, contained a solution of tyramine hydrochloride in saline (1 mg/ml).

Following an equilibration period of 30 to 40 min, tyramine injections (50 or 100 µg) were given, and blood pressure responses recorded. At least 15 min was maintained between injections, after return of blood pressure to control values. Control pressor responses were established, and then one of the drugs injected intra-peritoneally, and tyramine responses repeated over the next 4 hours. Area under the blood pressure response curve was estimated, and the ratio of this area after treatment to before treatment determined, using the average off 3 to 4 values obtained in control period, and 1 to 3 hours after injection of the compounds.

## Results

The results are shown in Table 3. Compound R(+)-PAI at a dose of 1 mg/kg, (which causes complete inhibition of MAO-B in brain and liver, and 40 to 50% inhibition of MAO-A in these tissues) caused no significant potentiation of tyramine pressor response. At the higher R(+)-PAI dose of 5 mg/kg, (which causes more extensive inhibition of MAO-A in brain and periphery), there was a significant potentiation of the tyramine pressor response, which was similar in extent to that produced by the same dose of deprenyl, and less than that produced by clorgyline (at a dose which inhibits hepatic MAO-A activity by over 85%).

TABLE 3

POTENTIATION OF TYRAMINE PRESSOR EFFECT IN CONSCIOUS RATS BY MAO INHIBITORS				
Inhibitor	Dose (mg/kg)	No. of rats (n)	Ratio Area Under Pressor Response Curve; After/Before	SEM
Saline		12	1.25	0.28
Clorgyline	2	6	10.39	2.13
(-)Deprenyl	1	2	1.15	
(-)Deprenyl	5	3	2.36	0.16
R(+)-PAI	1	3	1.38	0.7
R(+)-PAI	5	3	3.49	0.98

From this experiment it can be concluded that compound R(+)-PAI causes no potentiation of the tyramine pressor effect at a dose which effectively inhibits MAO-B.

## EXAMPLE 24

## Suppression of MPTP-induced Dopaminergic Toxicity by R(+)-PAI

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a neurotoxin that damages nigrostriatal dopaminergic neurons in several mammalian species including mice and produces a parkinsonian syndrome in humans and primates. A crucial initial step in the mechanism of its neurotoxicity involves conversion of MPTP to its toxic metabolite 1-methyl-4-phenyl pyridinium ion (MPP+). This reaction is catalyzed by the enzyme MAO-B and probably takes place outside of dopaminergic neurons, mainly in glia. It is known that MPTP is both a substrate and an irreversible inhibitor of MAO-B. Pretreatment of experimental animals with

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MAO-B inhibitors such as deprenyl or pargyline protects against and prevents the MPTP-induced damage to nigrostriatal neurons because the oxidative conversion of MPTP to MPP+ is blocked. One of the major current hypotheses suggests that the progressive nigrostriatal degeneration in Parkinson's may be due to exposure to environmentally-derived exogenous MPTP-like neurotoxins. In such case, there is an additional strong indication to initiation of sustained treatment with an MAO-B inhibitor from the very early stages of Parkinson's disease in the hope that it will neutralize the damaging effects of such yet putative MPTP-like toxins and thus arrest or slow down the progression of the illness. A successful MAO-B inhibitor drug is currently judged by its ability to block MPTP-induced damage to nigrostriatal dopaminergic neurons in vivo. We therefore tested the (-) and (+) enantiomers of PAI for their potency in preventing or attenuating the MPTP-induced striatal dopamine depletions in mice.

## Experimental Protocol

Male C57 black mice (20-25 g weight) were injected with MPTP.HCl (30 mg/kg dissolved in distilled water, s.c.) or vehicle alone or one hour after pretreatment with the (-) or (+) isomers of PAI (2.5 mg/kg, i.p.) or with deprenyl (5 mg/kg, i.p.) and decapitated 5 days later. Brains were removed and corpora striata dissected on an ice-cold glass plate and frozen on dry ice. Striatal tissues were homogenized in 0.1M perchloric acid, and deproteinized aliquots containing dihydroxybenzylamine as an internal standard were assayed for dopamine and its major metabolite 3,4-dihydroxy-phenylacetic acid (DOPAC) using HPLC with electro-chemical detection.

## Results

Table 4 shows the results of this experiment. Treatment with MPTP alone produced marked striatal dopamine (DA) and DOPAC depletions. Treatment with the (-) and (+) enantiomers of PAI or with (-) deprenyl did not affect striatal DA concentrations. Pretreatment with the (-) isomer of PAI did not affect the MPTP-induced DA and DOPAC levels in striatum. The (+)-isomer of PAI given before MPTP, completely abolished the reduction in striatal DA and DOPAC levels produced by the toxin. At a dose of 2.5 mg/kg it was equipotent to (-) deprenyl (5 mg/kg) in its protective effect.

TABLE 4

EFFECT OF PRETREATMENT WITH THE (-) AND (+) ENANTIOMERS OF THE MAO-B INHIBITOR PAI ON THE STRIATAL DA AND DOPAC DEPLETIONS INDUCED BY MPTP IN MICE IN VIVO.			
		DA	DOPAC
(ng/mg protein)			
Control		162.8 ± 7.2	8.4 ± 0.5
MPTP		53.1 ± 6.2	3.2 ± 0.3
(-)-PAI		174.0 ± 4.8	7.5 ± 0.2
(-)-PAI	+ MPTP	53.4 ± 6.9	7.0 ± 0.6
(+)-PAI		185.0 ± 6.9	3.3 ± 0.3
(+)-PAI	+ MPTP	177.8 ± 14.4	6.0 ± 0.3
(-)Deprenyl		170.6 ± 7.1	5.6 ± 0.3
(-)Deprenyl	+ MPTP	197.0 ± 8.0	6.4 ± 0.5

Above values for DA and DOPAC expressed as Mean ± S.E.M., and No. of rats, n = 7-11 in each group.

These results indicate that the R(+)-PAI is an excellent

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MAO-B inhibitor in vivo, and is of especially great potential for the treatment of Parkinson's disease.

While the invention has been described with reference to the aforementioned Examples and their accompanying Tables and Figures, it is not restricted thereto. various modifications and applications of the invention are possible, for example, compounds of Formula I may be combined, in a synergistic way, with  $\alpha$ -tocopherol (Vit. E. deriv.) for the treatment of Parkinson's disease.

EXAMPLE 25

Effect of PAI Enantiomers on Amphetamine Induced Stereotype Behavior in Senescent Rats

Amphetamine is known to induce stereotypic behaviour (Sulser, F. & Sanders-Bush, E. *Ann. Rev. Pharmacol.* 11:209-230 (1971)) by the mobilization of endogenous dopamine. Amphetamine is not metabolized by MAO-B. Inhibition of MAO-B by an effective inhibitor and administration of amphetamine cause release of dopamine which will not undergo degradation by the inhibited MAO-B. Thus, an increase of synaptic dopamine is expected after administration of amphetamine and effective MAO-B inhibitor leading to an increase in stereotype behavior—potentiation of the amphetamine effect. The extent of this behavior is rated in accordance with the number of lateral head movements over a period of 1 minute.

Experimental Protocol

The test compound was administered at a dose of 0.5 mg/kg/day in drinking water, 24 hours before the infliction of hypoxia (92% nitrogen+8% oxygen for 6 hours). Following that, amphetamine was injected s.c. at a dose of 0.5 mg/kg 45 min. later, lateral head movements were counted.

Results

The results of these experiments are shown in Table 5.

TABLE 5

EFFECT OF PAI ISOMERS ON AMPHETAMINE-INDUCED STEREOTYPE BEHAVIOUR IN SENESCENT RATS (CONTROL AND HYPOXIALESIONED)		
Group	Treatment	Stereotype Behavior Rating
Control (6)	—	87 ± 10
Control (5)	(+)PAI	126 ± 16-
Control (4)	(-)PAI	94 ± 18
Hypoxia lesioned (5)	—	93 ± 12
Hypoxia lesioned (6)	(+)PAI	143 ± 6-

Numbers in parenthesis are numbers of animals tested  
 P < 0.001 with respect to untreated hypoxia group or untreated control group correspondingly

The results in Table 5 indicate that (+)PAI caused significant potentiation of the amphetamine-induced stereotype behavior in both hypoxia-lesioned and control rats. (-)PAI was totally inactive in this respect. These behavioral in vivo results corroborate previous biochemical findings that (+)PAI is an active inhibitor of MAO-B in the brain while (-)PAI is inactive in this respect.

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EXAMPLE 26

Effect on R(+)-PAI on the Improvement or Restoration of Memory

Newborn rat pups subjected to a brief episode of anoxia and then allowed to resume their growth in a normal way, develop a long-lasting impairment of memory (Speiser, et al. *Behav. Brain Res.* 30:89-94, 1988). This memory impairment is expressed as an inferior performance in the passive avoidance test.

The effect of R(+)-PAI and S(-)-PAI on the improvement or restoration of memory was investigated in the passive avoidance test. If the drug is effective it increases the latency of response to enter a dark compartment or chamber where an electroshock has been experienced earlier by the rat being tested. The latency of the maximal response is 300 seconds.

Experimental Protocol

Young rats were subjected to post-natal anoxia as described in Example 27. R(+)-PAI or S(-)-PAI were administered according to one of the following protocols:

Protocol A—Nursing mothers were given a dose of either isomer of 1-1.5 mg/kg/day, in drinking water until weaning at 21 days. Following that the weaned offsprings were directly dosed with the same dose for 20 days. Treatment was terminated at 40 days and the test was performed at 60 days, that is 20 days after the last dose of the drug.

Protocol B—The dose was reduced to 0.5 mg/kg/day administered to the nursing mother till weaning at 21 days than directly to the young rats to 60 days at which time the test was performed.

Passive Avoidance Test—The apparatus consisted of a lit chamber adjoining a dark chamber and a sliding door separating the two. At training, a rat was placed in the lit chamber for 30 sec. then the door was opened. The rat moved to the dark chamber with a latency that was recorded. Upon entry of the rat into the dark compartment, the door was closed and a 0.3 mA foot-shock was delivered for 3 sec.

Retention (memory) after 48 hours was determined by repeating the test and recording the latency to step through from light to darkness to an arbitrary maximum of 300 sec.

Results

The results of these experiments are shown in Table 6.

TABLE 6

EFFECT OF PAI ISOMERS ON PASSIVE AVOIDANCE RESPONSE IN YOUNG RATS (60-DAYS OLD)			
Group	Treatment	Response	
		Before Electroshock	After Electroshock
<b>PROTOCOL A</b>			
Control	—	49 ± 13	201 ± 111
Control	(+)PAI	49 ± 19	220 ± 100(+9%)*
Control	(-)PAI	48 ± 13	192 ± 116
Anoxia-lesioned	—	45 ± 11	183 ± 109
Anoxia-lesioned	(+)PAI	49 ± 10	239 ± 99(+19%)*
Anoxia-lesioned	(-)PAI	55 ± 27	179 ± 123
<b>PROTOCOL B</b>			
Control	—	53 ± 20	104 ± 101
Control	(+)PAI	48 ± 11	128 ± 119(+23%)*
Anoxia-lesioned	—	45 ± 8	119 ± 105

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TABLE 6-continued

EFFECT OF PAI ISOMERS ON PASSIVE AVOIDANCE RESPONSE IN YOUNG RATS (60-DAYS OLD)			
Group	Treatment	Before Electroshock	After Electroshock
Anoxia-lesioned	(+)PAI	52 ± 12	137 ± 126(+15%)*
Anoxia-lesioned	(-)PAI	48 ± 19	112 ± 112

— Figures represent the latency in seconds for entering a dark compartment where an electroshock had been first experienced by the rat tested.

\*The indicated percent increases are with respect to the anoxia or control groups correspondingly.

The experimental results indicated that (+)PAI but not (-)PAI is effective in improving the memory of anoxia-lesioned and control rats. Drugs active in this test are considered to be potentially useful for treatment of various memory impairment disorders, dementia and especially senile dementia of the Alzheimer's type.

## EXAMPLE 27

## Effect of R(+)-PAI on the Anoxia-induced Hyperactive Syndrome in Juvenile Rats

Rats that had been exposed postnatally to anoxia and then left to grow under normal conditions show increased motor activity in the open field at the age of 10–42 days (Hertshkowitz et al., *Dev. Brain Res.* 7: 145–155 (1983)).

The effect of R(+)-PAI and R(-)-PAI on such hyperactive syndrome was investigated.

## Experimental Protocol

Anoxia was performed on rat pups on the first postnatal day. They were placed in a glass chamber and exposed to 100% nitrogen for 25 min. They were resuscitated by intermittent massage softly applied to the chest and then returned to their respective mothers. Control rats received the same treatment but with air instead of nitrogen.

The R(+)-PAI or S(-)-PAI (0.5 mg/kg/day) was administered to the nursing mothers in drinking water, thereby transferred to the sucklings through milk.

Locomotion was measured in 6 fully computerized cages (28×28 cm) by recording the number of crossing over a given period of time. Crossings of grid infrared beams at 4-cm intervals initiated electrical impulses which fed a counter. Recordings of motor activity were made at the ages of 15 and 20 days, over a period of 15 min.

## Results

The experimental results are given in Table 7.

TABLE 7

EFFECT OF EACH OF THE TWO ENANTIOMERS ON THE ANOXIA-INDUCED HYPERACTIVE SYNDROME			
Group	Treatment	15-day old rats	20-day old rats
Control	—	414 ± 192(11)	808 ± 212(12)
Control	(+)PAI	254 ± 149(11)c	719 ± 110(13)
Anoxia-lesioned	—	482 ± 119(7)	858 ± 96(9)
Anoxia-lesioned	(+)PAI	276 ± 186(15)a	737 ± 150(16)c
Anoxia-lesioned	(-)PAI	334 ± 196(5)	778 ± 232(6)

Numbers in parenthesis are numbers of animals tested.

TABLE 7-continued

EFFECT OF EACH OF THE TWO ENANTIOMERS ON THE ANOXIA-INDUCED HYPERACTIVE SYNDROME			
Group	Treatment	15-day old rats	20-day old rats

— The figures are the number of crossings of infrared beam grid in the activity cage over a period of 15 minutes.

a P < 0.001 compared to anoxia untreated group.

b P < 0.05 compared to anoxia untreated group.

c P < 0.05 compared to control group.

These results indicate that chronic oral treatment with R(+)-PAI at dose of 0.5 mg/kg administered to the nursing mother and reaching the milk-fed offspring, significantly improved the hyperactive syndrome. Consequently, R(+)-PAI is a potentially useful drug for the treatment of the hyperactive syndrome in children.

We claim:

1. A method of treating a subject for Parkinson's disease which comprises administering to the subject an amount of R(+)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof effective to treat the subject.

2. The method of claim 1, wherein R(+)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof is administered orally.

3. The method of claim 2, wherein the amount of R(+)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof administered is 2 to 20 mg per daily dosage unit.

4. The method of claim 2, wherein the amount of R(+)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof administered is 5 to 10 mg per daily dosage unit.

5. The method of claim 1, wherein R(+)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof is administered rectally.

6. The method of claim 5, wherein the amount of R(+)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof administered is 2 to 20 mg per daily dosage unit.

7. The method of claim 5, wherein the amount of R(+)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof administered is 5 to 10 mg per daily dosage unit.

8. The method of claim 1, wherein R(+)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof is administered transdermally.

9. The method of claim 8, wherein the amount of R(+)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof administered is 2 to 20 mg per daily dosage unit.

10. The method of claim 8, wherein the amount of R(+)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof administered is 5 to 10 mg per daily dosage unit.

11. The method of claim 1, wherein R(+)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof is administered parenterally.

12. The method of claim 11, wherein the amount of R(+)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof administered is 1 to 10 mg per mL per daily dosage unit.

13. The method of claim 12, wherein the amount of R(+)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof administered is 2 to 5 mg per mL per daily dosage unit.

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14. The method of claim 13 which further comprises administering to the subject a decarboxylase inhibitor in an amount effective to ensure L-Dopa uptake.

15. The method of claim 14, wherein the decarboxylase inhibitor is Carbidopa.

16. The method of claim 15, wherein the decarboxylase inhibitor is benserazide.

17. The method of claim 1 which further comprises administering to the subject Levodopa in an amount relative to the amount of R(+)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof effective to treat the disease.

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18. The method of claim 1 which further comprises administering to the subject a decarboxylase inhibitor in an amount effective to ensure L-Dopa uptake.

19. The method of claim 18, wherein the decarboxylase inhibitor is Carbidopa.

20. The method of claim 18, wherein the decarboxylase inhibitor is benserazide.

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