CAVELIER ABOGADOS COLO 14656-841-006-3 ID-129572

1959

1995

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 05-129098- -00004-0000
Fecha: 2008-07-04 16:56:02 Dep: 2020 NUEVACREACIONE
Tra: 11 PATENTESYII Eve: 379 FASENACIONALII
Act: 329 CTOINFORMACION Folios: 13

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1 **SOLICITUD DE:**

☐ Corrección de Error Material ☒ Modificación a una solicitud

2 **SOLICITANTE**

Nombre: ***TAKEDA PHARMACEUTICAL COMPANY LIMITED***
Sociedad constituida y existente bajo las leyes de Japón.

Dirección: 1-1,Doshomachi, 4-chome, Chuo-ku, Osaka-shi, Osaka 5410045, Japón

Domicilio: Osaka, Japón

Teléfono: 546 09 70 **Fax:** 249 40 70
E-mail: clientes@camyp.com

IDENTIFICACION

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐

Número: _____

3 **REPRESENTANTE O APODERADO**

Nombre: Emilio FERRERO
Dirección: Carrera 4ª No. 72-35
Teléfono: 347 36 11 **Fax:** 217 92 11
E-mail: cavelier@cavelier.com

IDENTIFICACION

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐

Número: 438.019 TP 31.929

4 **Número de expediente:** 05.129.098

5 **Descripción de la corrección o modificación solicitada:**

Presento nuevo capítulo reivindicatorio compuesto por 55 reivindicaciones y solicito respetuosamente a Su Despacho que sean tenidas en cuenta al momento de efectuar el examen de patentabilidad de la presente Solicitud de Patente.

6 **Comprobante de pago No.** 08-48.140 **Fecha:** 17 de junio de 2008

7 **Anexos**

☒ Comprobante de pago de la tasa por $103.000, por concepto de modificaciones.
☐ Poderes, si fuere el caso
☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

8 **NOMBRE:** EMILIO FERRERO **FIRMA:** _____

C.C. 438.019 de Usaquén **T.P.A.** 31.929

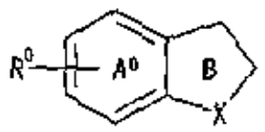
LMA

1960
1996

REIVINDICACIONES

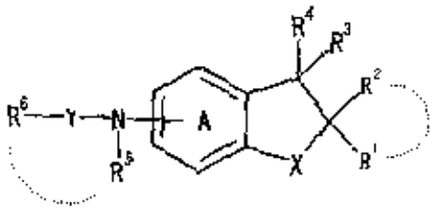
Habiéndose descrito la invención como antecede, se reclama como propiedad lo contenido en las siguientes reivindicaciones.

1. Un modulador del receptor canabinoide, caracterizado porque contiene un compuesto representado por la fórmula (I_0)



en donde, X es un átomo de oxígeno, un átomo de azufre opcionalmente substituido o un grupo imino opcionalmente substituido, R^0 es un grupo acilamino opcionalmente substituido, el anillo A^0 es un anillo de benceno el cual puede además tener un substituyente además de R^0, y el anillo B es un heterociclo de 5 miembros opcionalmente substituido, o una sal del mismo o un profármaco del mismo.

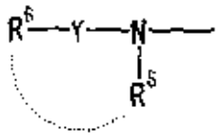
2. El modulador de conformidad con la reivindicación 1, caracterizado porque el compuesto representado por la Fórmula (I_0) o una sal del mismo o un profármaco del mismo es un compuesto representado por la fórmula (I)



en donde, X es un átomo de oxígeno, un átomo de azufre opcionalmente substituido o un grupo imino opcionalmente substituido, R^1, R^2, R^3 y R^4 son independientemente un átomo de hidrógeno, un grupo hidrocarburo opcionalmente substituido, un grupo heterocíclico opcionalmente substituido, un grupo hidroxilo opcionalmente substituido, un grupo mercapto opcionalmente substituido o un grupo amino opcionalmente substituido, o R^2 y R^3 pueden tomarse juntos para formar un enlace, o R^1 y R^2 pueden tomarse con el átomo de carbono adyacente para formar un anillo opcionalmente substituido, Y es -CO-, -SO-, ó $-SO_2-$, R^5 es un átomo de hidrógeno o un grupo hidrocarburo opcionalmente substituido, R^6 es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente substituido, un grupo hidroxilo opcionalmente substituido o un grupo amino

1961
1997

opcionalmente substituido, o R^5 y R^6 pueden tomarse con el átomo de carbono o átomo de azufre adyacente y átomo de nitrógeno para formar un anillo opcionalmente substituido, y el anillo A es un anillo de benceno el cual puede además tener un substituyente además de un grupo representado por la siguiente fórmula



en donde, cada uno de los símbolos tiene el mismo significado como se describe arriba, o una sal del mismo o un profármaco del mismo.

3. El modulador de conformidad con la reivindicación 2, caracterizado porque R^1 y R^2 son un átomo de hidrógeno.

4. El modulador de conformidad con la reivindicación 2, caracterizado porque R^1 y R^2 son respectivamente un átomo de hidrógeno o un grupo alquilo C_{1-4}, con la condición de que R^1 y R^2 no son un átomo de hidrógeno al mismo tiempo.

5. El modulador de conformidad con la reivindicación 1, caracterizado porque el compuesto representado por la fórmula (I_0) o la sal del mismo es un agonista del receptor canabinoide.

6. El modulador de conformidad con la reivindicación 5, caracterizado porque el receptor canabinoide es receptor canabinoide de tipo 1.

7. El modulador de conformidad con la reivindicación 1, caracterizado porque el compuesto representado por la fórmula (I_0) o la sal del mismo es un antagonista del receptor canabinoide.

8. El modulador de conformidad con la reivindicación 7, caracterizado porque el receptor canabinoide es receptor canabinoide de tipo 1.

9. El modulador de conformidad con la reivindicación 1, caracterizado porque el compuesto representado por la fórmula (I_0) o una sal del mismo es un agonista del receptor canabinoide de tipo 2.

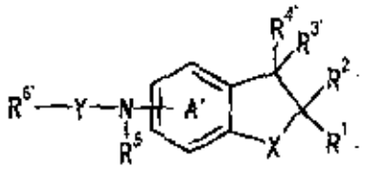
1962
1998

10. El modulador de conformidad con la reivindicación 1, caracterizado porque es un agente para prevenir, tratar o aliviar dolor agudo, trastornos cerebrovasculares, daño en la medula espinal, lesión en la cabeza, esclerosis múltiple, glaucoma, depresión, vómito, artritis, o asma.

11. El modulador de conformidad con la reivindicación 1, caracterizado porque es un agente para prevenir o tratar trastornos de la memoria, enfermedades psiquiatrías, obesidad, enfermedades mentales, ansiedad, depresión, fármaco dependencia, Alzheimer, demencia o enfermedad de Parkinson, o una ayuda para dejar de fumar.

12. El modulador de conformidad con la reivindicación 1, caracterizado porque es un agente para prevenir o tratar esclerosis múltiple, enfermedades neurodegenerativas, síndrome de intestino irritable, enfermedad de Crohn, oesofagitis de reflujo, COPD, psoriasis, enfermedades autoinmunes, rechazo al injerto, enfermedades alérgicas, dolor psicogénico, virus de hepatitis o hipertensión, o un agente de inmunidad regulada.

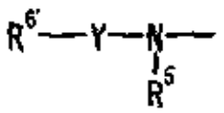
13. Un compuesto representado por la fórmula (I')



caracterizado porque, X es un átomo de oxígeno, un átomo de azufre opcionalmente substituido o un grupo imino opcionalmente substituido, R^1 y R^2 son independientemente un átomo de hidrógeno, un grupo hidrocarburo opcionalmente substituido, un grupo heterocíclico opcionalmente substituido, un grupo hidroxilo opcionalmente substituido, un grupo mercapto opcionalmente substituido o un grupo amino opcionalmente substituido, o R^1 y R^2 pueden tomarse con el átomo de carbono adyacente para formar un anillo opcionalmente substituido, $R^{3'}$ es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente substituido, un grupo hidroxilo opcionalmente substituido, un grupo mercapto opcionalmente substituido o un grupo amino opcionalmente substituido, $R^{4'}$ es un átomo de hidrógeno, un grupo alquilo opcionalmente substituido, un grupo arilo opcionalmente substituido, o un grupo

1963
1999

heterocíclico opcionalmente substituido, Y es -CO-, -SO-, ó $-SO_2-$, R^5 es un átomo de hidrógeno o un grupo hidrocarburo opcionalmente substituido, $R^{6'}$ es un grupo hidrocarburo opcionalmente substituido (con la condición de que ambos de R^1 y R^2 no son un átomo de hidrógeno, $R^{6'}$ no es un anillo de benceno), un grupo hidroxilo opcionalmente substituido o un grupo amino opcionalmente substituido, y el anillo A' es un anillo de benceno el cual puede además tener un substituyente en adición a un grupo representado por la siguiente fórmula



en donde, cada uno de los símbolos tiene el mismo significado como se describe arriba,
o una sal del mismo.

14. El compuesto de conformidad con la reivindicación 13, caracterizado porque R^1 y R^2 son independientemente un átomo de hidrógeno, un grupo hidrocarburo opcionalmente substituido, un grupo heterocíclico opcionalmente substituido, un grupo hidroxilo opcionalmente substituido, un grupo mercapto opcionalmente substituido o un grupo amino opcionalmente substituido.

15. El compuesto de conformidad con la reivindicación 13, caracterizado porque R^1 y R^2 son un átomo de hidrógeno.

16. El compuesto de conformidad con la reivindicación 13, caracterizado porque R^1 y R^2 son respectivamente un átomo de hidrógeno o un grupo alquilo C_{1-4}, con la condición de que R^1 y R^2 no son un átomo de hidrógeno al mismo tiempo.

17. El compuesto de conformidad con la reivindicación 13, caracterizado porque $R^{3'}$ es un átomo de hidrógeno.

18. El compuesto de conformidad con la reivindicación 13, caracterizado porque $R^{4'}$ es un grupo arilo C_{6-14} opcionalmente substituido o un grupo heterocíclico de 5 a 14 miembros opcionalmente substituido.

19. El compuesto de conformidad con la reivindicación 13,

1964
2000

caracterizado porque $R^{4'}$ es un grupo fenilo opcionalmente substituido.

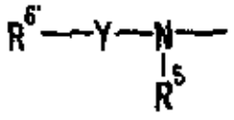
20. El compuesto de conformidad con la reivindicación 19, caracterizado porque $R^{4'}$ es un grupo fenilo el cual puede ser substituido con un grupo alquilo C_{1-4} opcionalmente substituido o un grupo alcoxi C_{1-4} opcionalmente substituido.

21. El compuesto de conformidad con la reivindicación 13, caracterizado porque Y es -CO-.

22. El compuesto de conformidad con la reivindicación 13, caracterizado porque R^5 es un átomo de hidrógeno.

23. El compuesto de conformidad con la reivindicación 13, caracterizado porque X es un átomo de oxígeno.

24. El compuesto de conformidad con la reivindicación 13, caracterizado porque la posición 5 del heterociclo fusionado en la fórmula (I') está substituida por un grupo representado por la siguiente fórmula



en donde, cada uno de los símbolos tiene el mismo significado como se describe arriba.

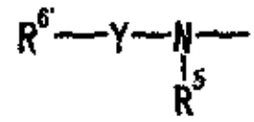
25. El compuesto de conformidad con la reivindicación 24, caracterizado porque la posición 7 del heterociclo fusionado en la fórmula (I') está además substituida por un grupo arilo C_{6-14}-alquilo C_{1-4} opcionalmente substituido.

26. El compuesto como se describe de conformidad con la reivindicación 25, caracterizado porque el grupo arilo C_{6-14}-alquilo C_{1-4} opcionalmente substituido es un grupo bencilo opcionalmente substituido.

27. El compuesto de conformidad con la reivindicación 13, caracterizado porque el anillo A' es un anillo de benceno el cual puede además tener 1 a 3 substituyentes seleccionados de un grupo

1965
2001

alquilo C_{1-6} opcionalmente substituido, un grupo arilo C_{6-12} opcionalmente substituido, un grupo heterocíclico de 5 ó 6 miembros opcionalmente substituido y un grupo acilo además de un grupo representado por la siguiente fórmula



en donde, cada uno de los símbolos tiene el mismo significado como se describe arriba.

28. El compuesto de conformidad con la reivindicación 27, caracterizado porque la posición 7 del heterociclo fusionado en la fórmula (I_0) es substituido por un grupo alquilo C_{1-4} opcionalmente substituido, un grupo arilo C_{6-12} opcionalmente substituido, un grupo heterocíclico de 5 ó 6 miembros opcionalmente substituido, o un grupo acilo.

29. El compuesto de conformidad con la reivindicación 27, caracterizado porque la posición 7 del heterociclo fusionado en la fórmula (I_0) está substituida por un grupo fenilo, un grupo furanilo, un grupo tienilo, un grupo piridilo, un grupo acetilo, un grupo propionilo, un grupo butirilo, o un grupo benzoilo, los cuales pueden ser substituidos, respectivamente.

30.N-(3-(4-isopropilfenil)-4,6,7-trimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

(+)-N-((3R)-3-(4-isopropilfenil)-4,6,7-trimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

N-(7-acetil-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

N-(3-(4-isopropilfenil)-7-metoxi-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

(+)-N-((3R)-7-acetil-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

(+)-N-(tert-butil)-N'-((3R)-3-(4-isopropilfenil)-4,6,7-trimetil-

1966
2002

2,3-dihidro-1-benzofuran-5-il}urea,

N-(3-(4-isopropilfenil)-4,6-dimetil-7-fenil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

N-(7-(3-dimetilaminofenil)-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

N-(3-hidroxipropil)-N'-(3-(4-isopropilfenil)-4,6,7-trimetil-2,3-dihidro-1-benzofuran-5-il)urea,

N-((4-isopropil-3-(2-metoxietoxi)fenil)-4,6,7-trimetil-2,3-dihidro-1-benzofuran-5-il))-3,3-dimetilbutanamida,

N-(7-(4-isopropilbencil)-3,4,6-trimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

N-(3-(4-tert-butilfenil)-2,2,4,6,7-pentametil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

N-(3-(4-isopropilfenil)-4,6,7-trimetil-3H-espiro(1-benzofuran-2,1'-ciclopentan)-5-il)-3,3-dimetilbutanamida,

N-(3-(4-isopropilfenil)-4,6-dimetil-7-propil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

(+)-N-((3R)-7-(1-hidroxietil)-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

N-(7-(6-fluoropiridin-3-il)-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

N-(7-(3-furil)-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida,

N-(7-hidroxi-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida, o
N-(7-etoxi-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida.

1967
2003

31. N-(3-(4-isopropilfenil)-4,6,7-trimetil-2,3-dihidro-1-benzofuran -5-il)-3,3-dimetilbutanamida o una sal del mismo.

32. (+)-N-((3R)-3-(4-isopropilfenil)-4,6,7-trimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

33. N-(7-acetil-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

34. N-(3-(4-isopropilfenil)-7-metoxi-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

35. (+)-N-((3R)-7-acetil-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

36. (+)-N-(tert-butil)-N'-((3R)-3-(4-isopropilfenil)-4,6,7-trimetil-2,3-dihidro-1-benzofuran-5-il)urea o una sal del mismo.

37. N-(3-(4-isopropilfenil)-4,6-dimetil-7-fenil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

38. N-(7-(3-dimetilaminofenil)-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

39. N-(3-hidroxipropil)-N'-(3-(4-isopropilfenil)-4,6,7-trimetil-2,3-dihidro-1-benzofuran-5-il)urea o una sal del mismo.

40. N-((4-isopropil-3-(2-metoxietoxi)fenil)-4,6,7-trimetil-2,3-dihidro -1-benzofuran-5-il))-3,3-dimetilbutanamida o una sal del mismo.

41. N-(7-(4-isopropilbencil)-3,4,6-trimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

42. N-(3-(4-tert-butilfenil)-2,2,4,6,7-pentametil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

43. N-(3-(4-isopropilfenil)-4,6,7-trimetil-3H-espiro(1-benzofuran-

2,1'-ciclopentan)-5-il)-3,3-dimetilbutanamida o una sal del mismo.

44. N-(3-(4-isopropilfenil)-4,6-dimetil-7-propil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

45. (+)-N-((3R)-7-(1-hidroxietil)-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

46. N-(7-(6-fluoropiridin-3-il)-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

47. N-(7-(3-furil)-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

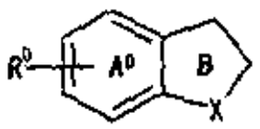
48. N-(7-hidroxi-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

49. N-(7-etoxi-3-(4-isopropilfenil)-4,6-dimetil-2,3-dihidro-1-benzofuran-5-il)-3,3-dimetilbutanamida o una sal del mismo.

50. Un profármaco del compuesto de conformidad con la reivindicación 13.

51. Un fármaco, caracterizado porque comprende el compuesto como se describe de conformidad con la reivindicación 13, o un profármaco del mismo.

52. El uso de un compuesto representado por la fórmula (I_0)

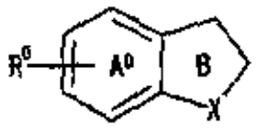


en donde, X es un átomo de oxígeno, un átomo de azufre opcionalmente substituido o un grupo imino opcionalmente substituido, R^0 es un grupo acilamino, el anillo A^0 es un anillo de benceno el cual puede además tener un substituyente además de R^0, y el anillo B es un heterociclo de 5 miembros opcionalmente substituido, o una sal del mismo o un profármaco del mismo, para la manufactura de un agente para prevenir o tratar enfermedades

1969
2005

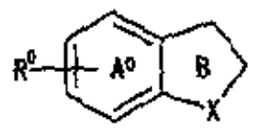
cerebrovasculares agudas, daño en la medula espinal, lesión en la cabeza, esclerosis múltiple, glaucoma, depresión, vómito, artritis, o asma; o para la manufactura de un agente analgésico.

53. El uso de un compuesto representado por la fórmula (I_0)



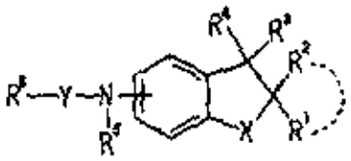
en donde, X es un átomo de oxígeno, un átomo de azufre opcionalmente substituido o un grupo imino opcionalmente substituido, R^0 es un grupo acilamino, el anillo A^0 es un anillo de benceno el cual puede además tener un substituyente además de R^0, y el anillo B es un heterociclo de 5 miembros opcionalmente substituido, o una sal del mismo o un profármaco del mismo, para la manufactura de un agente para prevenir o tratar trastornos de la memoria, enfermedades psiquiátricas, obesidad, enfermedades mentales, ansiedad, depresión, farmacodependencia, Alzheimer, demencia o enfermedad de Parkinson, o una ayuda para dejar de fumar.

54. El uso de un compuesto representado por la fórmula (I_0)

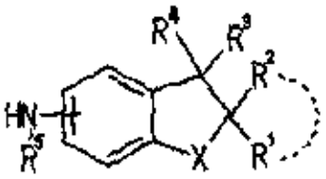


en donde, X es un átomo de oxígeno, un átomo de azufre opcionalmente substituido o un grupo imino opcionalmente substituido, R^0 es un grupo acilamino, el anillo A^0 es un anillo de benceno el cual puede además tener un substituyente además de R^0, y el anillo B es un heterociclo de 5 miembros opcionalmente substituido, o una sal del mismo o un profármaco del mismo, para la manufactura de un agente para prevenir o tratar esclerosis múltiple, enfermedades neurodegenerativas, síndrome de intestino irritable, enfermedad de Crohn, oesofagitis de reflujo, COPD, psoriasis, enfermedades autoinmunes, rechazo al injerto, enfermedades alérgicas, dolor psicogénico, virus de hepatitis o hipertensión, o un agente de inmunidad regulada.

55. Un método para preparar un compuesto representado por la siguiente fórmula



en donde, cada uno de los símbolos tiene el mismo significado como se describe a continuación, o una sal del mismo, caracterizado porque comprende hacer reaccionar un compuesto representado por la siguiente fórmula



en donde, X es un átomo de oxígeno, un átomo de azufre opcionalmente substituido o un grupo imino opcionalmente substituido,

R^1, R^2, R^3 y R^4 son independientemente un átomo de hidrógeno, un grupo hidrocarburo opcionalmente substituido, un grupo heterocíclico opcionalmente substituido, un grupo hidroxilo opcionalmente substituido, un grupo mercapto opcionalmente substituido o un grupo amino opcionalmente substituido, o R^2 y R^3 pueden tomarse juntos para formar un enlace, o R^1 y R^2 pueden tomarse con el átomo de carbono adyacente para formar un anillo opcionalmente substituido,

R^5 es un átomo de hidrógeno o un grupo hidrocarburo opcionalmente substituido, R^6 es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente substituido, un grupo hidroxilo opcionalmente substituido o un grupo amino opcionalmente substituido, o R^5 y R^6 pueden tomarse junto con el átomo de carbono adyacente o átomo de azufre y átomo de nitrógeno para formar un anillo opcionalmente substituido, y

el anillo A es un anillo de benceno el cual tiene además un substituyente además de un grupo representado por la fórmula $-NHR_5$ (en donde, cada uno de los símbolos tiene el mismo significado como se describe arriba), o una sal del mismo con,

R^6YL, $(R^6Y)_2O$ ó $R^6N{=}Y$, en donde, L es un grupo de partida, e Y es -CO-, -SO-, ó $-SO_2-$.

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

1971
2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 05-129098- -00004-0000

Fecha: 2008-07-04 16:56:02 Dep: 2920 NUECREACION
Tra: 11 PATENTEIY Eve: 379 FASENACIONAL
Act: 329 CTOINFORMACION Folios: 13

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

OFICIAL DE CAJA : OB - 48,140
FECHA : JUNIO 17 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	VR. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2677868	16/06/2008	[illegible]

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES	103,000.00
		TOTAL :	$ 103,000.0

SON: CIENTO TRES MIL PESOS

8

RESPONSABLE : _____

010 14656-891-005-3

Industria y Comercio
SUPERINTENDENCIA

1972
2009

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 05-129098

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **565** DE

FECHA **30 DE JUNIO DE 2006** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **28 DE SEPTIEMBRE DE 2006**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Articulo 44 de la Decisiòn 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ___X___

1993
2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

Bogotá, D.C., 23-sept-2009

Apoderado: Emilio Ferrero.

ASUNTO	Radicación	05-129098
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	№ 11343
	Folios	

Patente de Invención ⊗

Vía PCT (fase nacional) ⊗ Cap.I ⊗ *Cap. II* ☐

No. Sol. Internacional PCT/JP2004/009355
Fecha de Presentación Internal. 06/ene/2005

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. *Documentos estudiados*

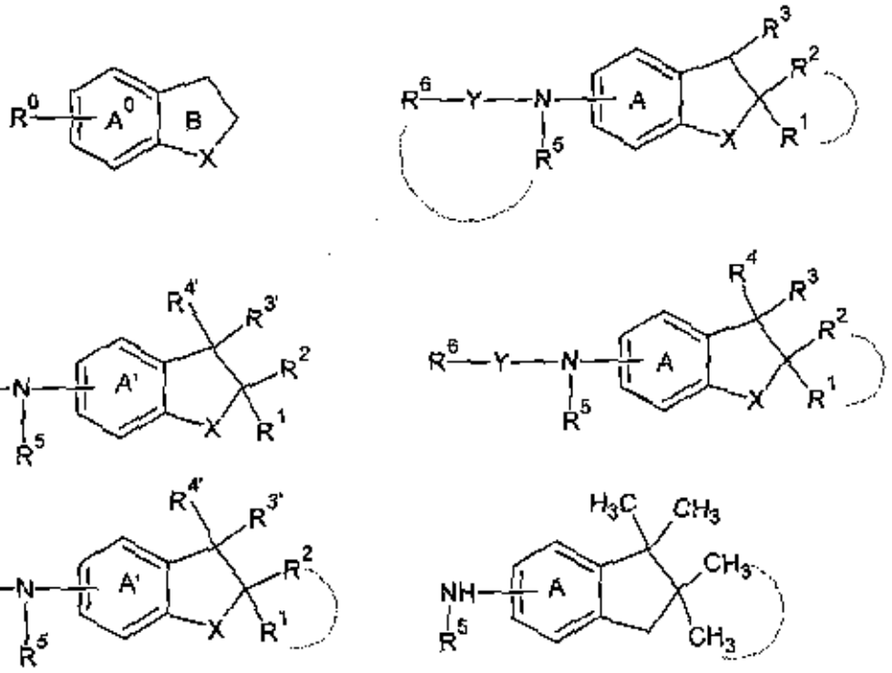
1.1.	Descripción:	Folios: 664 a 1331	Como se radicó inicialmente.
		Folios 1389 a 1943	Modificaciones realizadas.
1.2.	Reivindicaciones:	Folios 1332 a 1347	Como se radicó inicialmente.
		Folios 1366 a 1380	Modificaciones realizadas.
		Folios 1944 a 1959	Nuevas modificaciones.
		Folios 1960 a 1970	Nuevas Modificaciones,
1.3.	Prioridad:	Folio: 1, JP 2003-182039, 26-jun-2003.	

2. *Objeto de la invención*

Título de la solicitud: MODULADOR DEL RECEPTOR CANABINOIDE

El objeto de la presente solicitud de patente de invención consiste en compuestos derivados 2,3-dihidro-benzofuranaminas, derivados de 2,3-dihydro-5-benzotiofenaminas y derivados 3,4-dihidroquinolinamina de las fórmulas:

1974
2011



-Reivindicación 1: Compuestos de la fórmula (I_0);
-Reivindicaciones 2-12: Compuestos de la fórmula (I_0);
-Reivindicaciones 13-49: Compuestos de fórmula (I');
-Reivindicación 50: Un profármaco;
-Reivindicación 51: fármaco o profármaco de la reivindicación 13;
-Reivindicaciones 52-54: Uso de compuestos;
-Reivindicación 55: Método de tratamiento.

El problema planteado en esta solicitud es la necesidad de compuestos útiles para tratar inflamación, osteoartritis, artritis reumatoide, cáncer, repercusión ó isquemia en apoplejía ó ataque cardíaco, enfermedades inmunes.

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.):A61K31/343, A61K31/357, A61K31/381.

3. De la solicitud de Patente (Art. 28 de la Decisión 486 o art. 22 del Tratado PCT)

3.1. Reivindicaciones (artículo 30 D 486 de la C.A.N.)

-La reivindicación 1 es indefinida, porque aparece un sustituyente R^0 bajo la denominación genérica de "*grupo acilamino opcionalmente sustituido*" esos términos no delimitan perfectamente el alcance de la invención ya, que no son equivalentes técnicos de ninguna estructura química de manera inequívoca.
-Las reivindicaciones que reclaman materia con el término "*profarmaco*", estos compuestos están reclamados por referencias o propiedades deseadas, a saber, su capacidad del que es metabolizado in vivo para obtener un compuesto definido mediante modelismo molecular en las reivindicaciones, sin proporcionar la información técnica de cuál es su estructura y cómo alcanzar esa meta.
-Las reivindicaciones 5-12, no son claras, se encabezan como "el modulador", es un sustantivo que reemplaza a compuesto y el resto del texto de la reivindicación se refiere a su actividad farmacológica y a las enfermedades a tratar, lo cual no son características técnicas de compuesto.

~~1975~~
2012

- Las reivindicaciones 1-29 *no son claras y concisas*, ya que reclaman un número extremadamente *grande de compuestos*, mediante modelismo moleculares, muy amplios y *especulativos obtenidos por extrapolación* mediante computadoras, ya que el *sustento técnico real, aparece* sólo para una pequeña parte del total de los *compuestos reclamados*.
-*Las reivindicaciones* 50 y 51 reclaman "profarmaco", estos compuestos están *reclamados por referencias* o propiedades deseadas, a saber, su capacidad del que *es metabolizado* in vivo para obtener un compuesto definido mediante modelismo *molecular en* las reivindicaciones, sin proporcionar la información técnica de cuál es *su estructura* y cómo alcanzar esa meta.

El capitulo reivindicatorio estudiado [folios 1960-1970] no cumplen con el requisito de definición, claridad, concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

-Excepción a la patentabilidad *(artículo 20 D486 literal d) de la C.A.N.)*

-Las reivindicación 55 reclama un método de tratamiento terapéutico; el objeto de esta reivindicación no puede ser patentable según el artículo 20 D486 *literal d) de la* C.A.N.

4. Reivindicaciones relativas a un uso o a un segundo uso *(artículos 14 y 21 D 486 de la C.A.N.)*

Las reivindicaciones 52-54 *reclaman* el *uso de* compuestos y el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina *"... Los Países Miembros otorgarán patentes para las invenciones sean de productos o procedimientos en todos los campos de la tecnología..."*; aquí no se hace alusión al uso para otorgarle patente. Los usos o segundos *usos no son patentables*, de conformidad con la sentencia del TJAC 89-AI-2000, los usos en general no son patentables

5. Determinación del Estado de la Técnica

La fecha que *se ha tenido en* cuenta para determinar el Estado de la Técnica es la *fecha de presentación* de la solicitud prioritaria 26-jun-2003.

Teniendo en cuenta la fecha indicada se realizó la búsqueda *en el estado de la* técnica de documentos relacionados con *la materia reclamada* como nueva e inventiva en la solicitud, *encontrándose los siguientes* documentos más relevantes:

- *Relacionar los documentos encontrados dentro del cuadro*

Nº	Documento	Título	Fecha de publicación*
D1	EP0483772	Aminocumaran derivatives, their production and use	06-may-1992

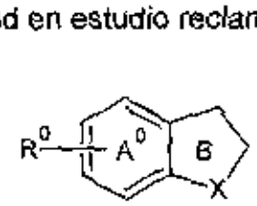
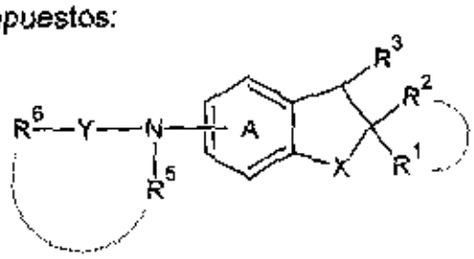
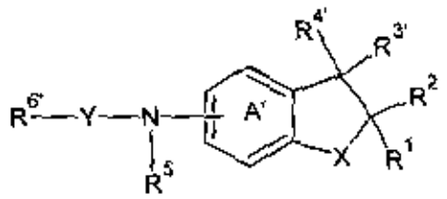
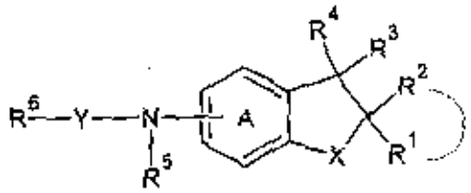
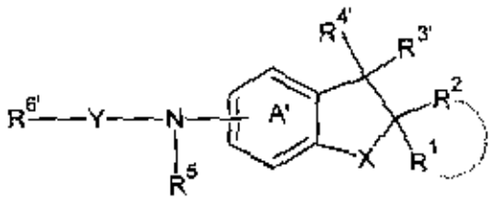
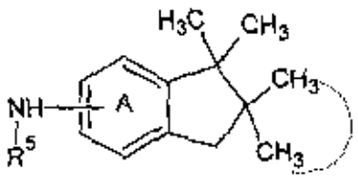
~~1976~~
2013

D2	WO9529907	Benzofuran derivatives useful as inhibitors of bone resorption	09-nov-1995
D3	US5.496.853	Benzoxa condensed ring compounds, process for producing same and pharmaceutical composition comprising the sams	05-mar-1996
D4	WO9607651	Dihydrobenzofuran and related compounds useful as anti-inflamatory agents	14-mar-1996
D5	WO9808842	Cyclic ether compounds as sodium channel modulators	5-mar-1998
D6	EP1138477	Benzofuran derivatives, process for the preparation of the same and uses threof	15-jun-2000
D7	US 6.172.085	Cyclicether compounds as sodium chennel modulators	09-ene-2001
D8	EP 1323716	Promoters for the proliferation and differentiation of stem cells and/or neuron precursor cell	11-abr-2002

12. Análisis de patentabilidad (artículo 14 D486 de la C.A.N.)

12.1 Novedad (artículo 16 D486 de la C.A.N.)

La solicitud en estudio reclama los compuestos:

-D1 enseña derivados aminocumaran que son reclamados como nuevos e inventivos en la presente solicitud, véase toda la anterioridad, especialmente pg.2-15,18,19.
--D2 enseña derivados amino-benzofurano que son reclamados como nuevos e inventivos en la presente solicitud, véase toda la anterioridad, especialmente pg. 2-9 y ejemplos.
-D3 enseña derivados Benzofurano que son reclamados como nuevos e inventivos en la presente solicitud, véase toda la anterioridad, especialmente columnas 9,10, 13-16, 27-30.

1977
2019

-D4 enseña derivados dihydrobenzofuran que son reclamados como nuevos e inventivos en la presente solicitud, véase toda la anterioridad, especialmente pgs. 1-6, 9,12,15,16.

-D5 enseña derivados aminobenzofurano que son reclamados como nuevos e inventivos en la presente solicitud, véase toda la anterioridad, especialmente pg.2-15,52,73,89,90, tablas 1-5, pg.167.

-D6 enseña derivados aminobenzofuran que son reclamados como nuevos e inventivos en la presente solicitud, véase toda la anterioridad, especialmente pg.7-17, tablas 1-2

-D7 enseña derivados aminbenzofurano que son reclamados como nuevos e inventivos en la presente solicitud, véase toda la anterioridad, especialmente columnas 21, 22,37,38, 63,64.

-D8 enseña derivados aminobenzofurano que son reclamados como nuevos e inventivos en la presente solicitud, véase toda la anterioridad, especialmente pg. 4-15,18,19.

Tal como puede verse el capitulo reivindicatorio no cumple con el requisito del artículo 16 D486 de la C.A.N.

13. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

*La solicitud que no cumple con el requisito de novedad, obviamente tampoco cumple con el requisito de nivel inventivo.

Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	1-55	Novedad y nivel inventivo
D2	1-55	Novedad y nivel inventivo
D3	1-55	Novedad y nivel inventivo
D4	1-55	Novedad y nivel inventivo
D5	1-55	Novedad y nivel inventivo
D6	1-55	Novedad y nivel inventivo
D7	1-55	Novedad y nivel inventivo
D8	1-55	Novedad y nivel inventivo

1978
206

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 09 OCT. 2009

CONCEPTO TÉCNICO No.	**EXAMINADOR TÉCNICO** Código No.202012

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 483 772 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 91118448.9

(22) Date of filing: 29.10.91

(51) Int. Cl.5: C07D 307/79, C07D 307/80, C07D 307/81, C07D 405/04, C07D 405/12, C07D 417/12, A61K 31/34

(30) Priority: 01.11.90 JP 296650/90
25.09.91 JP 245857/91

(43) Date of publication of application:
06.05.92 Bulletin 92/19

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

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Lederer, Keller & Riederer, Patentanwälte,
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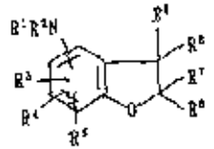
W-8000 München 80(DE)

(54) Aminocoumaran derivatives, their production and use.

(57) A novel aminocoumaran derivatives of the general formula (I).



wherein R^1 and R^2 are a hydrogen atom, an acyl group, an alkoxycarbonyl group, an aliphatic group or aromatic group; R^3, R^4 and R^5 are an optionally acylated hydroxyl, optionally substituted amino group, alkoxy group or aliphatic group, or two of R^3, R^4 and R^5 may be linked together to form a carbocyclic group; R^6 and R^7 are an aliphatic group and at least one of them has a methylene group at the ω-position; R^8 and R^9 are a hydrogen atom or an aliphatic group or aromatic group, or a salt thereof is useful for medicines for preventing and treating various diseases such as arterial sclerosis, hepatopathy, cerebrovascular diseases and the like.

EP 0 483 772 A1

FIELD OF THE INVENTION

The present invention relates to novel aminocoumaran derivatives or salts thereof and pharmaceutical compositions containing them as an active component. More specifically, the present invention relates to novel aminocoumaran derivatives or salts thereof and lipoperoxide formation inhibitory preparations containing them as an active component, which are useful as medicines for preventing and treating various diseases such as arterial sclerosis, hepatopathy, cerebrovascular diseases and the like.

BACKGROUND OF THE INVENTION

As it has become evident that the formation of a lipoperoxide in the body and a concomitant radical reaction have various harmful effects on the living body through membrane disorders, enzymatic disorders and the like, various attempts to use antioxidants and lipoperoxide formation inhibitors as medicines have been made. At present, the main lipoperoxide formation inhibitors used in the art are derivatives of natural antioxidants such as vitamin C, vitamin E and the like, and phenol derivatives (Kenji Fukuzawa, The Japanese Journal of Clinical Medicine, 46, 2269-2276, 1988). However, their fundamental structural skeletons are limited and they are not always satisfactory in practical use. Thus, it is desired to develop a lipoperoxide formation inhibitor having a novel structure that can be effectively and widely utilized in the medical field.

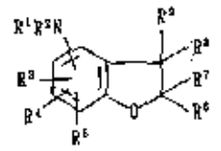
OBJECTS OF THE INVENTION

The main objects of the present invention is to provide novel compounds having a lipoperoxide formation inhibitory activity and lipoperoxide formation inhibitory preparations containing them as an active component.

SUMMARY OF THE INVENTION

Under these circumstances, the present inventors synthesized a number of novel compounds and tested their antioxidation activity and lipoperoxide formation inhibitory activity, respectively, in order to attain the above object.

As a result, the inventors have succeeded in creating aminocoumaran derivatives having a novel structure of the general formula (I):



(I)

wherein R^1 and R^2 are the same or different and are a hydrogen atom, an acyl group, an alkoxycarbonyl group, an optionally substituted aliphatic or an optionally substituted aromatic group; R^3, R^4 and R^5 are the same or different and are an optionally acylated hydroxyl group, an optionally substituted amino group, an optionally substituted alkoxy group or an optionally substituted aliphatic group, or two of R^3, R^4 and R^5 may linked together to form an optionally substituted carbocyclic group; R^6 and R^7 are the same or different and are an optionally substituted aliphatic group, provided that at least one of R^6 and R^7 has methylene at the ω-position; and R^8 and R^9 are the same or different and are a hydrogen atom or an optionally substituted aliphatic group or an optionally substituted aromatic group, or a salt thereof. Further, it has been found that the novel compounds have activities useful for medicines, for example, strong lipoperoxide formation inhibitory activity and the like. Thus, the present invention has been completed.

That is, the present invention provides the novel aminocoumaran derivatives of the general formula (I) or salts thereof and a pharmaceutical composition comprising them as an active component.

DETAILED DESCRIPTION OF THE INVENTION

In the general formula (I), the acyl group represented by R^1 and R^2 includes an acyl group derived from a carboxylic acid and an acyl group derived from a sulfonic acid and the like. As the acyl group derived from a carboxylic acid, there is a C_{1-6} acyl group (e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, etc.). As the acyl group derived from a sulfonic acid, there is a C_{1-3} alkylsulfonyl group such as methanesulfonyl, ethanesulfonyl, propanesulfonyl and the like and phenylsulfonyl group. As the alkoxycarbonyl group represented by R^1 and R^2, there are a lower alkoxycarbonyl group the alkoxy of which has 1 to 5 carbon atoms such as methoxycarbonyl group, ethoxycarbonyl group and the like. The aliphatic group represented by R^1 and R^2 may be a saturated or unsaturated group and examplet thereof include an alkyl group, an alkenyl group and an alkynyl group. The alkyl group may be straight, branched or cyclic. Among the alkyl groups, a lower alkyl group having 1 to 6 carbon atoms is preferred and the examples thereof include methyl, ethyl, n-propyl, butyl, n-butyl, t-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl and the like. As the alkenyl group represented by R^1 and R^2, in general, that having 2 to 6 carbon atoms is preferred and examples thereof include allyl, propenyl, i-propenyl, 2-butenyl, 2,4-butadienyl, 2-pentenyl and the like. As the alkynyl group represented by R^1 and R^2, in general, that having 2 to 6 carbon atoms is preferred and examples thereof include ethynyl, 2-propynyl and the like. The substituents which these aliphatic groups may have are not especially limited. As the substituents, any groups which can normally be used for medicines may be used and examples thereof include hydroxyl, C_{1-3} alkoxy (e.g., methoxy, ethoxy, n-propoxy or iso-propoxy, etc.), aralkyloxy (phenyl-C_{1-3} alkyloxy or naphthyl-C_{1-3} alkyloxy, e.g., benzyloxy, phenethyloxy, etc.), aryloxy (e.g., phenyloxy, naphthyloxy, pyridyloxy, imidazolyloxy, etc.), mercapto, C_{1-3} alkylthio (e.g., methylthio or ethylthio, etc.), C_{1-3} alkylsulfonyl (e.g., methylsulfonyl or ethylsulfonyl, etc.), C_{1-3} alkylsulfinyl (e.g., methylsulfinyl or ethylsulfinyl, etc.), aralkylthio (phenyl-C_{1-3} alkylthio or naphthyl-C_{1-3} alkylthio, e.g., benzylthio, phenethylthio, etc.), aralkylsulfonyl (phenyl-C_{1-3} alkylsulfonyl or naphthyl-C_{1-3} alkylsulfonyl, e.g., benzylsulfonyl, phenethylsulfonyl, etc.), aralkylsulfinyl (phenyl-C_{1-3} alkylsulfinyl or naphthyl-C_{1-3} alkylsulfinyl, e.g., benzylsulfinyl, phenethylsulfinyl, etc.), arylthio (e.g., phenylthio, naphthylthio, pyridylthio, imidazolylthio, etc.), arylsulfonyl (e.g., phenylsulfonyl, naphthylsulfonyl, pyridylsulfonyl or imidazolylsulfonyl, etc.), arylsulfinyl (e.g., phenylsulfinyl, naphthylsulfinyl, pyridylsulfinyl or imidazolylsulfinyl, etc.), amino, mono- or di-substituted amino which is substituted with 1 or 2 groups of C_{1-3} alkyl, aralkyl (phenyl-C_{1-3} alkyl or naphthyl-C_{1-3} alkyl, etc.) and aryl (phenyl, naphthyl, pyridyl or imidazolyl, etc.) (e.g., methylamino, ethylamino, dimethylamino, benzylamino, phenylamino, pyridylamino, etc.), halogen (e.g., chloro or fluoro), esterified carboxyl (e.g., C_{2-5} alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, etc.)], C_{2-5} acyl (e.g., acetyl, propionyl, etc.), C_{2-5} acyloxy (e.g., acetoxy, propionyloxy, etc.), C_{2-3} acylamide (e.g., acetamide, etc.), C_{2-5} alkoxycarbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, etc.), a cyclic amino group (e.g., pyrrolidino, morpholino, piperazino, etc.), a carboxyl group, a carbamoyl group and the like. The number of these substituents is preferably 1 to 2.

As the aromatic group represented by R_1 and R_2, there is a phenyl group. Examples of the substituent on the phenyl group include an amino group, a mono- or di-alkylamino group substituted with a C_{1-3} lower alkyl group, halogen, nitro, sulfo, cyano, hydroxyl, carboxyl, C_{1-3} lower alkyl, C_{1-3} lower alkoxy, C_{2-5} acyl, C_{1-3} lower alkylmercapto and the like. The number of the substituents is not limited but is preferably 1 to 3.

The group represented by $-NR^1R^2$ may substitute the benzene ring of the coumaran at any position of the ring, preferably at the 5-position of the coumaran.

It is preferable that one of R^1 and R^2 is a hydrogen atom and the other is a hydrogen atom, a phenyl group or a straight, branched or cyclic C_{1-6} alkyl group.

When the hydroxyl group represented by R^3, R^4 and R^5 is acylated, the acyl group includes a C_{2-5} straight or branched carboxylic acid acyl group (e.g., acetyl, propionyl, butyryl, isobutyryl, etc.). When the amino group represented by R^3, R^4 and R^5 has substituents, examples of the substituents include those of the optionally substituted aliphatic or aromatic groups represented by R^1 and R^2. As the alkoxy group represented by R^3, R^4 and R^5, there is a C_{1-6} straight or branched alkyl group or an alkoxy group composed of a cyclic alkyl group. As the substituent of the alkoxy group, there are, for example, an amino group, a mono- or di-alkylamino group substituted with a C_{1-3} lower alkyl group, halogen, hydroxyl, lower alkoxy, lower alkylmercapto and the like. Examples of the aliphatic group represented by R^3, R^4 and R^5 and the substituents thereof include the groups described with respect to the aliphatic group represented by R^1 and R^2. Two of R^3, R^4 and R^5 may linked together to form an optionally substituted carbocyclic group and, in this case, a 5- or 6-membered carbocyclic group is preferred. Examples of the substituents thereof include a C_{1-3} alkyl group, a C_{1-6} alkoxy group, hydroxyl group and the like.

R^3, R^4 and R^5 are preferably straight, branched or cyclic C_{1-6} alkyl groups.

Examples of the aliphatic group represented by R^6 and R^7 include the groups described with respect to R^1 and R^2. The substituent of the aliphatic group represented by R^6 and R^7 includes an optionally substituted aromatic group in addition to the substituents described with respect to the aliphatic group represented by R^1 and R^2. The optionally substituted aromatic groups and the substituent thereof include those described with respect to R^1 and R^2. Further, at least one of R^6 and R^7 has methylene group in the α-position. In other words, R^6 and R^7 are optionally substituted aliphatic groups and at least one of them are a group of the formula $-CH_2R^1$ wherein R^1 is hydrogen or R^1 together with $-CH_2$ form an optionally substituted aliphatic group. Examples of such an aliphatic group and its substituent include those exemplified with respect to the groups R^1 and R^2.

It is preferable that one of R^6 and R^7 is a straight, branched or cyclic C_{1-6} alkyl group, and the other is a straight, branched or cyclic C_{1-6} alkyl group or aralkyl group (preferably phenyl-C_{1-4} alkyl or naphthyl-C_{1-4} alkyl such as benzyl, phenethyl, phenylpropyl or the like) which may be substituted with a group having 1 to 5 hetero atoms (N, S, O). Examples of the group having 1 to 5 hetero atoms are C_{1-3} alkoxy, aralkyloxy, aryloxy, C_{1-3} alkylthio, C_{1-3} alkylsulfonyl, C_{1-3} alkylsulfinyl, aralkylthio, aralkylsulfonyl, aralkylsulfinyl, arylthio, arylsulfonyl, arylsulfinyl, mono- or di-substituted amino which is substituted with 1 or 2 groups of C_{1-3} alkyl, aralkyl and aryl, and cyclic amino group.

The aliphatic group represented by R^6 and R^7 includes that described with respect to R^6 and R^7. The aromatic group represented by R^6 and R^7 includes that described with respect to R^1 and R^2.

It is preferable that one of R^6 and R^7 is a hydrogen atom and the other is a phenyl group optionally substituted with a hydrogen atom, halogen or a straight, branched or cyclic C_{1-6} alkyl group, or a straight, branched or cyclic C_{1-6} alkyl group.

The compound represented by the general formula (I) may have its stereoisomer depending upon a particular kind of the substituent. The present invention includes not only one isomer but also the mixture thereof.

Salts of the compounds represented by the general formula (I) are preferably pharmaceutically acceptable salts, and examples of the pharmaceutically acceptable salt include those formed with inorganic acids such as hydrohalogenic acid (e.g., hydrochloric acid, hydrobromic acid, etc.), phosphoric acid, sulfuric acid and the like, and organic acids such as organic carboxylic acids (e.g., oxalic acid, phthalic acid, fumaric acid, maleic acid, etc.), sulfonic acids (e.g., methanesulfonic acid, benzenesulfonic acid) and the like. Further, when the compounds (I) contain acidic groups such as carboxyl group and the like as the substituents, the salts include inorganic base salts formed with alkaline metals (e.g., sodium, potassium, etc.) or alkaline earth metals (e.g., magnesium) and the like and salts formed with organic bases (e.g., amines such as dicyclohexylamine, triethylamine, 2,6-lutidine, etc.).

Hereinafter, the compounds of the formula (I) and the salts thereof are simply referred to as "the compound (I)".

The compound (I) of the present invention can be produced, for example, according to the process of the Scheme-I:

Example 2

5-Amino-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran hydrochloride

4-Amino-2,3,5-trimethylphenol (2.0 g, 13.2 mmol) and 2-methyl-2-propenol (1.15 g, 15.8 g) were heated under reflux in dichloromethane (20 ml) together with sulfuric acid (2 ml) for 18 hours. The reaction mixture was washed with aqueous saturated sodium bicarbonate solution, dried and then concentrated. The residue was purified by silica gel column chromatography (isopropyl ether). The purified product was converted into its hydrochloride and it was crystallized from ethanol-isopropyl ether to obtain the desired compound (480 mg, yield: 14.4%), m.p. 248-250°C.

NMR (DMSO-d_6) δ 1.47 (6H, s), 2.06 (3H, s), 2.18 (6H, s), 3.03 (2H, s), 9.80 (2H, broad s).

Example 3

5-Amino-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran hydrochloride

4-Formylamino2,3,5-trimethyl-1-(2-methyl-2-propenyloxy)benzene (7.33 g, 35.7mmol) was dissolved in methanol (100 ml) and to the solution was added conc. hydrochloric acid (30 ml) with ice-cooling. After the atmosphere in the flask was displaced with argon, the mixture was heated under reflux for 2 hours. The reaction mixture was cooled, then neutralized with aqueous sodium bicarbonate solution and extracted with chloroform. The extract was washed with water and then dried over anhydrous magnesium sulfate. The residue was crystallized from isopropyl ether to obtain the desired compound (6.40 g, yield: 98.2%). A part of the compound was converted into its hydrochloride and then crystallized from methanol, m.p. 248-250°C (dec.).

NMR (DMSO-d_6) δ 1.41 (6H, s), 2.05 (3H, s), 2.20 (6H, s), 9.65 (2H, broad s).

Example 4

5-Amino-2,2,4,6-tetramethyl-7-(2-methyl-1-propenyl)-2,3-dihydrobenzofuran hydrochloride

According to the same manner as that described above, the title compound was synthesized (yield: 90.1%), m.p. 207-208°C (dec.).

NMR (DMSO-d_6) δ 1.38 (6H, s), 1.46 (3H, s), 1.86 (3H, s), 2.18 (3H, s), 2.21 (3H, s), 2.97 (2H, s), 5.90 (1H, s), 9.36 (2H, broad s)

Example 5

5-Acetylamino-2,2,6,7-tetramethyl-4-nitro-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described in Reference Example 48 hereinafter (yield: 88.4%), m.p. 203°C (dichloromethane-isopropyl ether).

NMR (CDCl$_3$) δ 1.48 (6H, s), 2.15 (3H, s), 2.18 (3H, s), 2.19 (3H, s), 3.28 (2H, S), 7.79 (1H, broad s).

Example 6

5-Acetylamino-2,2,4,7-tetramethyl-6-nitro-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 77.6%), m.p. 203-204°C (dichloromethane-isopropyl ether).

NMR (CDCl$_3$) δ 1.50 (6H, s), 2.09 (3H, s), 2.12 (3H, s), 2.14 (3H, s), 3.00 (2H, s), 7.09 (1H, s).

Example 7

7-Amino-2,2,4,6,6-pentamethyl-2,3-dihydrobenzofuran hydrochloride

2,2,4,6,6-Pentamethyl-7-nitro-2,3-dihydrobenzofuran (310 mg, 1.3 mmol) was dissolved in ethanol (10 ml) and the solution was subjected to catalytic reduction using 5% palladium carbon (0.6 g) as a catalyst. After the catalyst was filtered off, the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane-isopropyl ether, 7:3), converted into its hydrochloride and then crystallized from ethanol-isopropyl ether to obtain the desired compound (170 mg, yield: 53.3%), m.p. 207-212°C.

NMR (DMSO-d_6) δ 1.47 (6H, s), 2.08 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 3.03 (2H, s), 9.80 (2H, broad s).

Example 8

5-Amino-2,2,4,6,7-pentamethyl-3-phenyl-2,3-dihydrobenzofuran

2,2,4,6,7-Pentamethyl-5-nitro-3-phenyl-2,3-dihydrobenzofuran (2.0 g, 6.4 mmol) was dissolved in ethanol (15 ml) and the solution was subjected to catalytic reduction using 5% palladium carbon (2.0 g) as a catalyst. After the catalyst was filtered off, the filtrate was concentrated. The residue was purified by column chromatography on silica gel (isopropyl ether) and then crystallized from hexane to obtain the desired compound (1.33 g, yield: 73.6%), m.p. 131-132°C.

NMR (CDCl$_3$) δ 1.50 (3H, s), 1.45 (6H, s), 1.77 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 3.10 (2H, broad s), 4.11 (1H, s), 6.95 (2H, m), 7.20 (3H, m).

Example 9

5-Amino-3-(4-fluorophenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 70.2%), m.p. 126-127°C (hexane).

NMR (CDCl$_3$) δ 0.99 (3H, s), 1.47 (3H, s), 1.77 (3H, s), 2.12 (3H, s), 2.18 (3H, s), 3.10 (2H, broad s), 4.09 (1H, s), 6.92 (4H, m).

Example 10

5-Amino-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 68.0%), m.p. 134-135°C (hexane).

NMR (CDCl$_3$) δ 1.00 (3H, s), 1.22 (6H, d, J = 6.6Hz), 1.47 (3H, s), 1.78 (3H, s), 2.13 (3H, s), 2.19 (3H, s), 2.85 (1H, septet, J = 6.6Hz), 3.10 (2H, broad s), 4.08 (1H, s), 6.85 (2H, m), 7.07 (2H, d, J = 8.0Hz).

Example 11

5-Amino-2,2,4,6,7-pentamethyl-3-(3-pyridyl)-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 53.8%), m.p. 130-131°C (hexane).

NMR (CDCl$_3$) δ 1.02 (3H, s), 1.50 (3H, s), 1.77 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 3.04 (2H, broad s), 4.12 (1H, s), 7.48 (2H, m), 8.38 (1H, m), 8.48 (1H, t, J = 3.2Hz).

Example 12

5-Amino-3-(3-amino-4-dimethylaminophenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran dihydrochloride

The title compound was synthesized as an amorphous product according to the same manner as that described above (yield: 42.4%).

NMR (DMSO-d_6) δ 1.04 (3H, s), 1.44 (3H, s), 1.88 (3H, s), 2.13 (3H, s), 2.29 (3H, s), 3.02 (6H, s), 4.24 (1H, s), 6.90-7.50 (5H, m), 9.85 (2H, broad s).

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Example 13

5-Amino-3-isopropyl-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran hydrochloride

The title compound was synthesized according to the same manner as that described above (yield: 76.8%), m.p. 225-230°C (ethanol)

NMR (DMSO-d_6) δ 0.70 (3H, d, J=6.6Hz), 0.96 (3H, d, J=6.6Hz), 1.21 (3H, s), 1.57 (3H, s), 1.82 (1H, m), 2.09 (3H, s), 2.53 (3H, s), 2.57 (3H, s), 2.78 (1H, d, J=2.8Hz), 10.07 (2H, broad s).

Example 14

4,5-Diamino-2,2,6,7-tetramethyl-2,3-dihydrobenzofuran hydrochloride

The title compound was synthesized according to the same manner as that described above (yield: 96.9%), m.p. 248-251°C (ethanol).

NMR (DMSO-d_6) δ 1.39 (6H, s), 1.93 (3H, s), 2.09 (3H, s), 2.82 (2H, s), 3.38 (4H, broad s).

Example 15

5-Acetylamino-6-amino-2,2,4,7-tetramethyl-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 98.7%), m.p. 155-157°C (isopropyl ether).

NMR ($CDCl_3$) δ 1.44 (6H, s), 1.82 and 2.23 (3H, s), 2.00-2.05 (6H, m), 2.67 (2H, s), 3.75 (2H, broad s), 6.40 and 6.82 (1H, broad s).

Example 16

5-Acetylamino-4-amino-2,2,6,7-tetramethyl-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 91.4%), m.p. 172-173 (ethanol-ether).

NMR ($CDCl_3$) δ 1.46 (6H, s), 1.83 and 2.20 (3H, s), 2.05-2.09 (6H, m), 2.83 (2H, s).

Example 17

5-Amino-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran

2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-5-nitro-2,3-dihydrobenzofuran (1.26 g, 3.9 mmol) was dissolved in methanol (30 ml). Zinc powder (1.3 g) and 1N sodium hydroxide (15 ml) were added to the solution and the mixture was heated under reflux for 3 hours. Insoluble materials were filtered off and water was added. The mixture was extracted with ethyl acetate. The extract was washed with water, dried and then the solvent was distilled off. The residue was purified by column chromatography on silica gel (hexane-isopropyl ether, 95:5) and crystallized from hexane to obtain the desired compound (710 mg, yield: 63.7%), m.p. 119-120°C.

NMR ($CDCl_3$) δ 1.00 (3H, s), 1.47 (3H, s), 1.78 (3H, s), 2.13 (3H, s), 2.20 (3H, s), 2.31 (3H, s), 3.20 (2H, broad s), 4.09 (1H, s), 6.82 (2H, m), 7.10 (2H, m).

Example 18

5-Amino-2,2,4,6,7-pentamethyl-3-(4-propylphenyl)-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 65.6%), m.p. 68-69°C (methanol).

NMR ($CDCl_3$) δ 0.90 (3H, t, J=7.2Hz), 0.99 (3H, s), 1.47 (3H, s), 1.60 (2H, sextet, J=7.2Hz), 1.77 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 2.54 (2H, t, J=7.2Hz), 3.10 (2H, broad s), 4.09 (1H, s), 6.82 (2H, m), 7.03 (2H, d, J=8.0Hz).

Example 19

5-Amino-2,2,4,6,7-pentamethyl-3-(4-pentylphenyl)-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 55.6%), m.p. 67-68°C (methanol).

NMR ($CDCl_3$) δ 0.87 (3H, t, J=6.6Hz), 1.00 (3H, s), 1.31 (4H, m), 1.47 (3H, s), 1.58 (2H, m), 1.78 (3H, s), 2.12 (3H, s), 2.18 (3H, s), 2.55 (2H, t, J=7.2Hz), 3.20 (2H, broad s), 4.09 (1H, s), 6.82 (2H, m), 7.03 (2H, d, J=8.0Hz).

Example 20

5-Amino-2,4,6,7-tetramethyl-2-piperidinomethyl-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 82.1%), m.p. 60-61°C (isopropyl ether).

NMR ($CDCl_3$) δ 1.30-1.60 (6H, m), 1.42 (3H, s), 2.07 (6H, s), 2.10 (3H, s), 2.35-2.65 (6H, m), 2.80 (1H, d, J=15.0Hz), 3.10 (2H, broad s), 3.11 (1H, d, J=15.0Hz).

Example 21

5-Amino-2,4,6,7-tetramethyl-2-morpholinomethyl-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 38.0%), m.p. 114-115°C (isopropyl ether).

NMR ($CDCl_3$) δ 1.42 (3H, s), 2.07 (9H, s), 2.40-2.70 (6H, m), 2.81 (1H, d, J=15.0Hz), 3.13 (1H, d, J=15.0Hz), 3.20 (2H, broad s), 3.67 (4H, t, J=4.8Hz).

Example 22

5-Amino-2,4,6,7-tetramethyl-2-[2-(dimethylamino)-ethyl]-2,3-dihydrobenzofuran dihydrochloride

The title compound was synthesized according to the same manner as that described above (yield: 46.5%), m.p. 200-203°C (dec.) (ethanol-isopropyl ether).

NMR (DMSO-d_6) δ 1.41 (3H, s), 2.08 (3H, s), 2.17 (2H, m), 2.22 (3H, s), 2.24 (3H, s), 2.74 (6H, s), 2.96 (1H, d, J=16.0Hz), 3.11 (2H, m), 3.16 (1H, d, J=16.0Hz), 9.78 (2H, broad s).

Example 23

5-Amino-2,4,6,7-tetramethyl-2-[2-piperidinoethyl]-2,3-dihydrobenzofuran dihydrochloride

The title compound was synthesized according to the same manner as that described above (yield: 41.8%), m.p. 260-270°C (dec.) (ethanol-isopropyl ether).

NMR (DMSO-d_6) δ 1.41 (3H, s), 1.78 (6H, m), 2.06 (3H, s), 2.22 (3H, s), 2.23 (3H, s), 2.23 (2H, m), 2.84 (4H, m), 2.95 (1H, d, J=15.8Hz), 3.05 (2H, m), 3.15 (1H, d, J=15.8Hz), 9.65 (2H, broad s).

Example 24

5-Amino-2,2,4,6-tetramethyl-7-(dimethylamino)-methyl-2,3-dihydrobenzofuran oxalate

Aqueous 50% dimethylamine solution (8.46 ml, 64.2 mmol) was added dropwise to a suspension of paraformaldehyde (1.61 g, 42.8 mmol) in ethanol (10 ml). The mixture was stirred at room temperature until the mixture became homogeneous (for 30 minutes). This solution was added dropwise to a solution of 4-acetylamino-3,5-dimethyl-2-(2-methyl-2-propenyl)phenol (4.88 g, 21.4 mmol) in ethanol (30 ml). The resulting mixture was heated under reflux for 3.5 hours under an argon atmosphere. The reaction mixture was cooled and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform-methanol, 95:5) to obtain the desired compound (5.46 g, yield: 87.7%) as brown oil.

This was dissolved in methanol (60 ml) and conc. hydrochloric acid (20 ml) was added. The mixture was heated under reflux for 1.5 hours under an argon atmosphere. After the reaction mixture was cooled, excess aqueous sodium bicarbonate solution was added and the mixture was extracted with chloroform. The extract was washed with water, dried and concentrated. The residue was purified by column chromatography on silica gel (chloroform-methanol, 88:12) to obtain the desired compound (4.86 g, yield: 90.5%) as brown oil.

This was dissolved in ethanol (3 ml) and 5N sodium hydroxide was added to the solution. The mixture was stirred for 13 hours at 200°C in a sealed tube under an argon atmosphere. After the reaction mixture was cooled, water was added and the mixture was extracted with chloroform. The extract was washed with water, dried and then concentrated. The residue was purified by column chromatography on silica gel (chloroform-methanol, 88:12) to obtain the product (1.70 g, yield: 41.5%). A part of the product was converted into its oxalate salt and then recrystallized from ethanol to obtain the desired compound, m.p. 178-180°C (ethanol).

NMR (DMSO-d_6) δ 1.39 (6H, s), 2.02 (3H, s), 2.07 (3H, s), 2.74 (6H, s), 2.93 (2H, s), 4.13 (2H, s), 4.52 (4H, broad s).

Example 25

5-Amino-2,2,4,6-tetramethyl-7-piperidinomethyl-2,3-dihydrobenzofuran oxalate

The title compound was synthesized according to the same manner as that described above (yield: 47.8%-41.0%-55.7%), m.p. 110-112°C (ethanol).

NMR (DMSO-d_6) δ 1.44 (6H, s), 1.82-1.80 (6H, m), 2.01 (3H, s), 2.03 (3H, s), 2.89 (2H, s), 3.11 (4H, broad s), 4.09 (2H, s), 4.48 (4H, broad s).

Example 26

5-Amino-2,2,4,6-tetramethyl-7-morpholinomethyl-2,3-dihydrobenzofuran oxalate

The title compound was synthesized according to the same manner as that described above (yield: 55.1%-77.3%-55.2%), m.p. 118-120°C (ethanol).

NMR (DMSO-d_6) δ 1.38 (6H, s), 2.01 (3H, s), 2.08 (3H, s), 2.85 (4H, broad s), 2.90 (2H, s), 3.58 (4H, broad s), 3.83 (2H, s), 5.03 (4H, *broad s*)

Example 27

5-Acetylamino-2-hydroxymethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran

4-Acetylamino-2,3,5-trimethyl-6-(2-methyl-2-propenyl) phenol (2.0 g, 8.1 mmol) was dissolved in dichloromethane (20 ml). m-Chloroperbenzoic acid (70% purity, 2.2 g, 8.9 mmol) was added slowly to the solution with stirring under ice cooling. *After the addition was completed, the reaction mixture was stirred at* room temperature for 1 hour and triethylamine (2 ml) was added. The reaction mixture was washed with water, dried and then concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate) to obtain the desired compound (1.1 g, yield: 51.7% yield) as oil.

NMR ($CDCl_3$) δ 1.43 (3H, s), 1.96 (1H, m), 2.07 (3H, s), 2.09 (6H, s), *2.20 (3H, s), 2.81 (1H, d,* J = 15.4Hz), 3.16 (1H, d, J = 15.4Hz), 3.63 (2H, m), 6.66 (1H, broad s).

Example 28

5-Formylamino-2-hydroxymethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 59.9%), m.p. 149-150°C (ethyl acetate-hexane).

NMR (DMSO-d_6) δ 1.33 (3H, s), 1.97 (3H, s), 1.98 (3H, s), 2.00 (3H, s), 2.73 (1H, d, J = 15.4Hz), 3.13 (1H, d, J = 15.4Hz), 3.42 (2H, d, J = 5.8Hz), 5.01 (1H, t, J = 5.8Hz), 7.83 (0.2H, d, J = 11.6Hz), 8.21 (0.8H, d, J = 1.2H), 9.06 (0.2H, d, J = 11.6Hz), 9.20 (0.8H, broad s).

Example 29

2-Bromomethyl-5-formylamino-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran

4-Formylamino-2,3,5-trimethyl-6-(2-methyl-2-propenyl)phenol (30 g, 0.21 mol) and sodium acetate (30.5 g, 0.37 mol) were added to acetic acid (500 ml). Bromine (16.5 ml, 0.21 mol) was added dropwise to the mixture with stirring. After the reaction mixture was stirred for 30 minutes, the mixture was poured into ice water and the product was extracted with ethyl acetate. The extract was washed with aqueous saturated sodium bicarbonate solution, dried and then concentrated. The residue was dissolved in ethyl acetate again and insoluble materials were filtered off. The filtrate was concentrated and isopropyl ether was added to the residue. The crystals precipitated were filtered off to obtain the desired compound (44.0 g, yield: 65.7%), m.p. 157-158°C.

NMR ($CDCl_3$) δ 1.61 (1.5H, s), 1.63 (1.5H, s), 2.09 (3H, s), 2.11 (3H, s), 2.13 (1.5H, s), 2.16 (1.5H, s), *2.93 (1H, d, J = 15.6Hz), 3.29 (0.5H, d, J = 15.6Hz), 3.29 (0.5H, d, J = 15.8Hz), 3.50 (1H, s), 3.53 (1H, s),* 6.77 (0.5H, broad s), 6.85 (0.5H, d, J = 12.0Hz), 7.96 (0.5H, d, J = 12.0Hz), 8.40 (0.5H, d, J = 1.4Hz).

Example 30

5-Acetylamino-2-formyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran

A solution of oxalyl chloride (0.45 ml, 4.7 mmol) in dichloromethane (10 ml) was cooled to -78°C and dimethyl sulfoxide (1 ml) was added dropwise with stirring. *After stirred at the same temperature for 2* hours, a solution of 5-acetylamino-2-hydroxymethyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran(1.1 g, 4.2 mmol) in dichloromethane (5 ml) was added dropwise and the mixture was stirred for additional 30 minutes. Triethylamine (3.5 ml) was added and the mixture was stirred for 10 minutes. The reaction mixture was washed with 1N hydrochloric acid and aqueous saturated sodium bicarbonate solution. *The reaction mixture* was dried and then concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate) to obtain the desired compound (0.47 g, yield: 43.1%) as oil.

NMR ($CDCl_3$) δ 1.55 (3H, s), 2.06 (3H, s), 2.11 (3H, s), 2.13 (3H, s), 2.21 (3H, s), 2.94 (1H, d, J = 15.8Hz), 3.41 (1H, d, J = 15.8Hz), 6.72 (1H, broad s).

Example 31

2-Formyl-5-formylamino-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran

The title compound was synthesized as oil according to the same manner as that described above (yield: 25.5%).

NMR ($CDCl_3$) δ 1.55 (1.5H, s), 1.57 (1.5H, s), 2.08 (3H, s), 2.12 (3H, s), 2.15 (3H, s), *2.94* (1H, d, J = 15.4Hz), 3.41 (0.5H, d, J = 15.4Hz), 3.44 (0.5H, d, J = 15.4Hz), 7.00 (1H, m), 7.85 (0.5H, d, J = 12.0Hz), 8.34 (0.5H, d, J = 1.8Hz), 8.73 (0.5H, s), 9.74 (0.5Hz, s).

Example 32

(Z)-5-Acetylamino-2,4,6,7-tetramethyl-2-styryl-2,3-dihydrobenzofuran

A suspension of benzyltriphenylphosphonium chloride (0.7 g, 1.8 mmol) in tetrahydrofuran (10 ml) was cooled to -20°C and n-butyllithium hexane solution (1.5 M, 1.12 ml, 1.8 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes and then a solution of 5-acetylamino-2-formyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (0.45 g, 1.7 mmol) in tetrahydrofuran (5 ml) was added. The reaction mixture was stirred at room temperature for additional 30 minutes. Water was added to the reaction mixture and the product was extracted with ethyl acetate. The extract was washed with water, dried and then concentrated. The residue was purified by column chromatography on silica gel (isopropyl ether-ethyl acetate, 1:1) to obtain the desired compound (0.44 g, yield: 76.2%) as oil.

NMR ($CDCl_3$) δ 1.95 (3H, s), 1.97 (3H, s), 1.98 (3H, s), 2.05 (3H, s), 2.19 (3H, s), 2.94 (1H, d, J = 15.4Hz), 3.19 (1H, d, J = 15.4Hz), 5.82 (1H, d, J = 12.8Hz), 6.50 (1H, d, J = 12.8Hz), 6.62 (1H, broad s), 7.25 (5H, m).

Example 33

(Z)-5-Acetylamino-2,4,6,7-tetramethyl-2-(2-(4-bromophenyl) ethenyl)-2,3-dihydrobenzofuran

The title compound was synthesized as in according to the same manner as that described above (yield: 81.3%).

NMR ($CDCl_3$) δ 1.56 (3H, s), 1.64 (6H, s), 2.00 (3H, s), 2.05 (3H, s), 2.19 (3H, s), 2.95 (1H, d, J=14.0Hz), 3.19 (1H, d, J=14.0Hz), 5.86 (1H, d, J=12.8Hz), 6.45 (1H, d, J=12.8Hz), 6.93 (1H, broad s), 7.00 (2H, m), 7.25 (2H, m).

Example 34

Ethyl 3-[5-formylamino-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran-2-yl]acrylate

2-Formyl-5-formylamino-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (1.0 g, 4.1 mmol), triethyl-phosphonoacetate (0.81 g, 4.1 mmol) and sodium hydride (60% purity, 162 mg, 4.1 mmol) were added to dimethylformamide and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with water and the product was extracted with ethyl acetate. The extract was washed with water and dried and then the solvent was distilled off. The residue was purified by column chromatography on silica gel (ethyl acetate-isopropyl ether, 1:1) to obtain the desired compound (0.5 g, yield: 39.9%) as oil.

NMR ($CDCl_3$) δ 1.29 (3H, t, J=7.2Hz), 1.60 (3H, s), 2.08 (1.5H, s), 2.11 (1.5H, s), 2.12 (1.5H, s), 2.15 (1.5H, s), 2.17 (3H, s), 3.05 (1H, d, J=15.4Hz), 3.15 (1H, d, J=15.4Hz), 4.18 (2H, q, J=7.2Hz), 5.82 (1H, d, J=15.8Hz), 6.92 (0.5H, broad s), 6.95 (0.5H, d, J=12.0Hz), 7.02 (1H, d, J=15.6Hz), 7.95 (0.5H, d, J=12.0Hz), 8.38 (0.5H, d, J=1.6Hz).

Example 35

5-Acetylamino-2,4,6,7-tetramethyl-2-(2-phenylethenyl)-2,3-dihydrobenzofuran

5% Palladium carbon (0.3 g) was added to a solution of (Z)-5-acetylamino-2,4,6,7-tetramethyl-2-styryl-2,3-dihydrobenzofuran (1.0 g, 3.0 mmol) in ethanol and the mixture was stirred for 1 hour under a hydrogen atmosphere. The catalyst was filtered off and then the filtrate was concentrated. The residue was purified by column chromatography on silica gel (isopropyl ether-ethyl acetate, 1:1) to obtain the desired compound (0.85 g, yield: 84.4%) as oil.

NMR ($CDCl_3$) δ 1.48 (3H, s), 2.02 (2H, m), 2.05 (3H, s), 2.08 (3H, s), 2.14 (3H, s), 2.22 (3H, s), 2.72 (2H, m), 2.99 (1H, d, J=15.4Hz), 3.05 (1H, d, J=15.4Hz), 7.10-7.30 (5H, m), 7.75 (1H, broad s).

Example 36

5-Acetylamino-2-[2-(4-fluorophenyl) ethyl]-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran

The title compound was synthesized as in according to the same manner as that described above (yield: 90.3%).

NMR ($CDCl_3$) δ 1.47 (3H, s), 1.48 (2H, m), 2.05 (3H, s), 2.10 (6H, s), 2.20 (3H, s), 2.69 (2H, m), 2.90 (1H, d, J=15.4Hz), 3.05 (1H, d, J=15.4Hz), 6.75 (1H, broad s), 6.95 (2H, m), 7.13 (2H, m).

Example 37

5-Amino-7-[2-methylpropyl)-2,2,4,6-tetramethyl-2,3-dihydrobenzofuran hydrochloride

10% Palladium carbon (1.0 g) was added to a solution of 5-amino-7-(2-methyl-1-propenyl)-2,2,4,6-tetramethyl-2,3-dihydrobenzofuran (1.97 g, 6.11 mmol) in ethanol (100 ml) and the mixture was heated under reflux for 3 hour under a hydrogen atmosphere. The reaction mixture was cooled and filtered and then the filtrate was concentrated. The residue was crystallized from isopropyl ether to obtain a product (1.45 g, yield: 95.9% yield). This compound was converted into its hydrochloride salt and then recrystallized from ethanol to obtain the desired compound (0.99 g, yield: 51.9% yield), m.p. 223-225 °C (ethanol).

NMR (DMSO-d_6) δ 0.85 (6H, d, J=6.6Hz), 1.39 (6H, s), 1.83-1.84 (1H, m), 2.21 (3H, s), 2.22 (3H, s), 2.38 (2H, d, J=7.2Hz), 2.86 (2H, s), 8.54 (2H, broad s).

Example 38

5-Formylamino-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

5-Amino-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran (1.00 g, 4.87 mmol) was dissolved in formic acid (20 ml) and the solution was heated under reflux for 48 hours. The reaction mixture was concentrated under reduced pressure. Saturated sodium bicarbonate solution was added to the residue and the mixture was extracted with chloroform. The extract was washed with saturated saline, dried and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform-methanol, 97:3) to obtain the desired compound (1.08 g, yield: 93.3%). A part of it was recrystallized from dichloromethan-isopropyl ether to obtain white prisms, m.p. 177-178 °C.

NMR ($CDCl_3$) δ 1.46 (3H, s), 1.48 (3H, s), 2.09-2.16 (9H, m), 2.94 (2H, s), 8.68 (1H, broad s), 7.97 (0.5H, d, J=12.0Hz), 8.40 (0.5H, s, J=1.4Hz).

Example 39

5-Acetylamino-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

Acetyl chloride (460 mg, 5.84 mmol) was added dropwise with ice cooling to a solution of 5-amino-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran (1000g, 4.87 mmol) and triethylamine (640 mg, 6.33 mmol) in tetrahydrofuran (20 ml). After the addition was completed, the mixture was stirred for 4 hours. Water was added to the reaction mixture and the mixture was extracted with chloroform. The extract was washed with saturated sodium bicarbonate solution and saturated saline, dried and concentrated. The residue was purified by column chromatography on silica gel (chloroform-methanol, 97:3) to obtain the desired compound (920 mg, yield: 78.4%). A part of it was recrystallized from dichloromethane-isopropyl ether, m.p. 150 °C (dichloromethane-isopropyl ether).

NMR ($CDCl_3$) δ 1.46 (6H, s), 1.73 and 2.21 (3H, s), 2.06 (2H, s), 2.09 (3H, s), 2.14 (3H, s), 2.93 (2H, s), 8.53 (1H, broad s).

Example 40

2,2,4,6,7-Pentamethyl-5-propionylamino-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 93.8%), m.p. 146 °C (dichloromethane-isopropyl ether).

NMR ($CDCl_3$) δ 1.06 and 1.31 (3H, t, J=7.4Hz), 1.46 and 1.50 (6H, s), 1.92 and 2.44 (2H, q, J=7.4Hz), 2.04-2.13 (9H, m), 2.93 (2H, s), 6.53 and 6.58 (1H, broad s).

Example 41

5-Butyrylamino-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 70.8%), m.p. 136-136 °C (dichloromethane-isopropyl ether).

NMR ($CDCl_3$) δ 0.97 and 1.05 (3H, t, J=7.4Hz), 1.48 and 1.51 (6H, s), 1.74-1.92 (2H, m), 2.05-2.09 (9H, m), 2.10-2.12 (2H, m), 2.39 (2H, t, J=7.4Hz), 2.93 (2H, s), 5.52-6.62 (1H, m), 6.53 and 6.60 (1H, broad s).

Example 42

5-Benzoylamino-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 94.5%), m.p. 253-255 °C (dichloromethane-isopropyl ether).

NMR ($CDCl_3$) δ 1.49 (6H, s), 2.12 (6H,s), 2.15 (3H, s), 2.96 (2H, s), 7.45-7.57 (3H, m), 7.90-7.98 (2H, m).

Example 43

5-Isobutyrylamino-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 92.3%), m.p. 170-172° C (dichloromethane-isopropyl ether).

NMR ($CDCl_3$) δ 1.30 (6H, d, J = 7.0Hz), 1.48 (6H, s), 2.03 (3H, s), 2.08 (6H, s), 2.61 (1H, septet, J = 7.0Hz), 2.92 (2H, s), 6.57 (1H, broad s).

Example 44

5-Ethoxycarbonylamino-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 74.6%), m.p. 102-104° C (isopropyl ether-pentane).

NMR ($CDCl_3$) δ 1.31 (3H, t, J = 7.4Hz), 1.45 and 1.46 (6H, s), 2.09 (3H, s), 2.13 (3H, s), 2.93 (2H, s), 4.20 (2H, q, J = 7.4Hz), 5.87 (1H, broad s).

Example 45

5-Methanesulfonylamino-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

The title compound was synthesized according to the same manner as that described above (yield: 65.7%), m.p. 159-160° C (dichloromethane-isopropyl ether).

NMR ($CDCl_3$) δ 1.47 (6H, s), 2.10 (3H, s), 2.25 (3H, s), 2.29 (3H, s), 2.93 (2h, s), 3.03 (3H, s), 5.70 (1H, s).

Example 46

2,2,4,6,7-Pentamethyl-5-(p-toluenesulfonylamino)-2,3-dihydrobenzofuran

5-Amino-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran (2.00 g, 9.74 mmol) and p-toluenesulfonyl chloride (2.04 g, 10.7 mmol) were dissolved in pyridine (30 ml) and stirred at 50° C for 1 hour. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in chloroform. The mixture was washed with 1N hydrochloric acid and saturated saline and dried and then the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate, 97:3). The crude crystals were recrystallized from dichloromethane-isopropyl ether to obtain the desired compound (2.41 g, yield: 68.8%, yield), m.p. 219-220° C (dichloromethane-isopropyl ether).

NMR ($CDCl_3$) δ 1.45 (6H, s), 1.80 (3H, s), 1.93 (3H, s), 2.01 (3H, s), 2.43 (3H, s), 2.87 (2H, s), 5.81 (1H, s), 7.24 (2H, d, J = 8.4Hz), 7.60 (2H, d, J = 8.4Hz).

Example 47

5-Ethylamino-2-[2-(4-fluorophenyl) ethyl]-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran

To tetrahydrofuran (20 ml) were added 5-acetylamino-2,4,6,7-tetramethyl-2-[2-(4-fluorophenyl) ethyl]-2,3-dihydrobenzofuran (1.2 g, 3.4 mmol) and lithium aluminum hydride. The mixture was heated under reflux for 3 hours. The reaction mixture was poured into ice water and the product was extracted with ethyl acetate. The extract was washed with water and dried and then the solvent was distilled off. The residue was purified by column chromatography on silica gel (isopropyl ether-ethyl acetate, 2:1) to obtain the desired compound (0.82 g, yield: 71.2%) as oil.

NMR ($CDCl_3$) δ 1.21 (3H, t, J = 7.2Hz), 1.47 (3H, s), 1.98 (2H, m), 2.11 (3H, s), 2.14 (3H, s), 2.18 (3H, s), 2.70 (2H, m), 2.84 (2H, q, J = 7.2Hz), 2.85 (1H, broad s), 2.90 (1H, d, J = 14.0Hz), 3.02 (1H, d, J = 14.0Hz), 6.94 (2H, m), 7.12 (2H, m).

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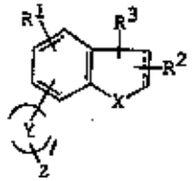
(54) Title: BENZOFURAN DERIVATIVES USEFUL AS INHIBITORS OF BONE RESORPTION

(57) Abstract

This invention relates to a novel heterocyclic compound represented by formula (I), wherein X is O or S, Y is vinylene, or a group of formula: -NHCO-, -NHSO$_2$-, -OCO-, -OCH$_2$-, -NHCOCO-, -NHCOCH=CH-, -NHCOCH$_2$-, -NHCONH- or (a) (wherein R^6 is lower alkyl), Z is heterocyclic group which may have one or more suitable substituent(s), or aryl which may have one or more suitable substituent(s), l = 0, 1 and the other symbols are as defined in the specification and a pharmaceutically acceptable salt thereof which are the inhibitors of bone resorption and bone metabolism, to processes for preparation thereof, to a pharmaceutical composition comprising the same and to a method for the treatment of diseases caused by abnormal bone metabolism in human being or an animal.

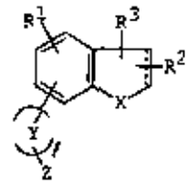


(I)

(a)

therapeutic treatment of above-mentioned diseases in human being or an animal.

The heterocyclic derivatives of this invention are new and can be represented by the following general formula (I) :



(I)

wherein

R^1 is hydrogen, lower alkyl, an acyl group, amino, acylamino, nitro, halogen or hydroxy(lower)alkyl which may have one or more suitable substituent(s),

R^2 is hydrogen, lower alkyl, an acyl group, lower alkoxy, acyl(lower)alkyl, aryl, cyano, mono-(or di- or tri-)-halo(lower)alkyl, lower alkylthio or hydroxy(lower)alkyl which may have one or more suitable substituent(s),

R^3 is hydrogen, lower alkyl, lower alkenyl, cyclo(lower)alkyl(lower)alkyl, halogen, an acyl group, acyl(lower)alkyl, acylamino, acylamino(lower)alkyl, acyl(lower)alkenyl, acyloxy(lower)alkyl, acyl(lower)alkylthio(lower)alkyl, amino(lower)alkyl, mono-(or di-)lower alkylamino, lower alkylthio(lower)alkyl, hydroxyimino(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkylthio(lower)alkyl, cyano(lower)alkyl, mono-(or di-)lower alkoxy(lower)alkyl which may have one or more suitable substituent(s), lower alkyl substituted with aryl which may have one or more suitable substituent(s), mono-(or di-)lower

alkylamino(lower)alkyl, lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), heterocyclic group which may have one or more suitable substituent(s), heterocyclicthio, heterocyclicthio(lower)alkyl, heterocyclicoxy, heterocyclicoxy(lower)alkyl, heterocyclicaminoimino-(lower)alkyl, aryl, amino or nitro,

in which R^2 and R^3 may be linked together to form

(1) lower alkylene which may have one or more suitable substituent(s),

(2) lower alkenylene which may have one or more suitable substituent(s), or

(3) a group of the formula :

$$-(A^1)_m-W-(A^2)_n-$$

[wherein A^1 and A^2 are each lower alkylene which may have one or more suitable substituent(s) or lower alkenylene which may have one or more suitable substituent(s),

W is $-S-$, $-\overset{O}{\overset{\|}{S}}-$, or $-\overset{R^5}{\overset{|}{N}}-$ (wherein R^5 is hydrogen, lower alkyl or an acyl group)

and

m and n are each integer of 0 or 1.],

X is O or S,

Y is vinylene, or a group of the formula :

$-NHCO-$, $-NHSO_2-$, $-OCO-$, $-OCH_2-$, $-NHCOCO-$, $-NHCOCH=CH-$, $-NHCOCH_2-$, $-NHCONH-$ or $-\overset{R^6}{\overset{|}{N}}-CO-$

(wherein R^6 is lower alkyl),

Z is heterocyclic group which may have one or more suitable substituent(s), or aryl which may have one or more suitable substituent(s),

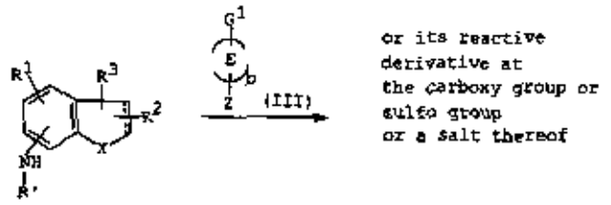
t is an integer of 0 or 1, and

$\overset{\frown}{---}$ is a single bond or a double bond,

and a pharmaceutically acceptable salt thereof.

The object compound (I) or a salt thereof can be prepared by the processes as illustrated in the following reaction schemes.

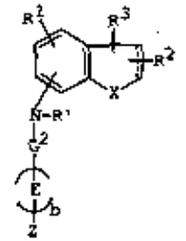
Process 1



(II)

or its reactive derivative at the amino group or a salt thereof

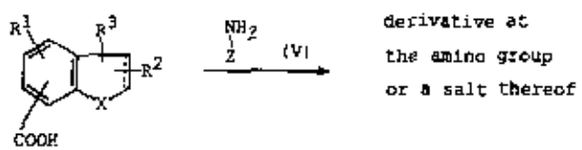
or its reactive derivative at the carboxy group or sulfo group or a salt thereof



(Ia)

or a salt thereof

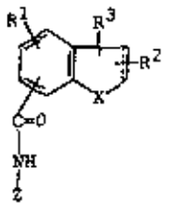
Process 2



(IV)
or its reactive derivative at the carboxy group or a salt thereof

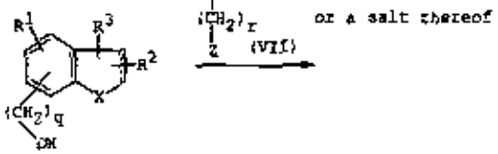
(V)

or its reactive derivative at the amino group or a salt thereof



(Ib)
or a salt thereof

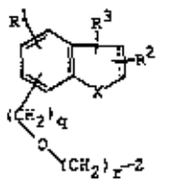
Process 3



(VI)
or its reactive derivative at the hydroxy group or a salt thereof

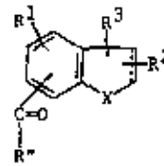
(VII)

or a salt thereof



(Ic)
or a salt thereof

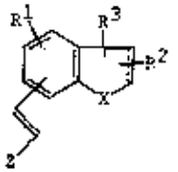
Process 4



(VIII)
or a salt thereof

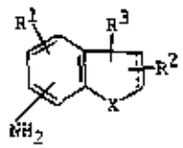
(IX)

or salt thereof



(Id)
or a salt thereof

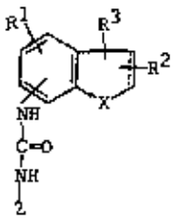
Process 5



(X)
or its reactive derivative at the amino group or a salt thereof

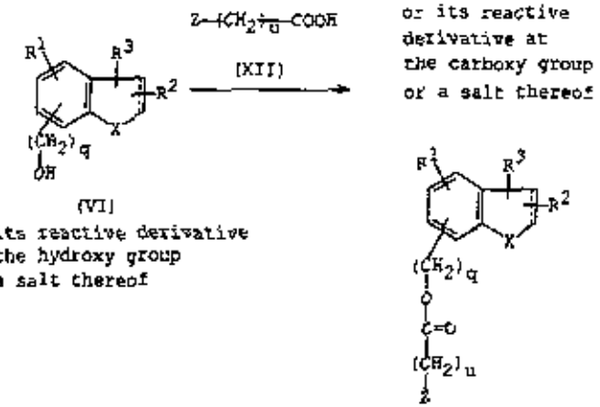
Z-N=C=O
(XI)

or a salt thereof



(Ie)
or a salt thereof

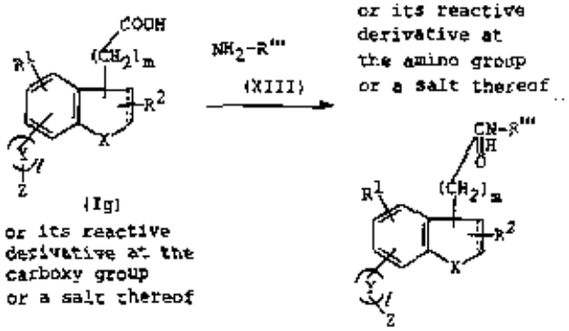
Process 6



(VI)
or its reactive derivative at the hydroxy group or a salt thereof

(If)
or a salt thereof

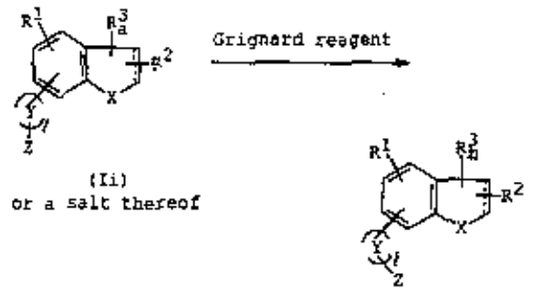
Process 7



(Ig)
or its reactive derivative at the carboxy group or a salt thereof

(Ih)
or a salt thereof

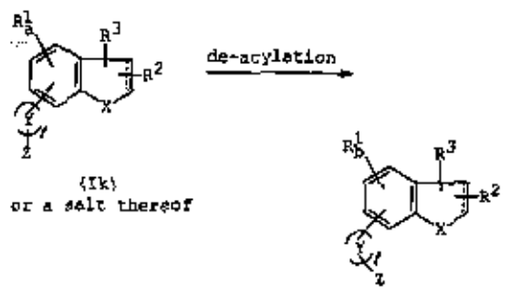
Process 8



(Ii)
or a salt thereof

(Ij)
or a salt thereof

Process 9



(Ik)
or a salt thereof

(Il)
or a salt thereof

US005496853A

United States Patent [19]

Shiota et al.

[11] Patent Number: 5,496,853

[45] Date of Patent: Mar. 5, 1996

[54] **BENZOXA CONDENSED RING COMPOUNDS, PROCESS FOR PRODUCING THE SAME AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME**

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[73] Assignee: Taiho Limited, Osaka, Japan

[21] Appl. No.: 429,023

[22] Filed: Apr. 26, 1995

Related U.S. Application Data

[63] Continuation of Ser. No. 78,374, filed as PCT/JP91/01793, Dec. 27, 1991, abandoned.

[30] Foreign Application Priority Data

Dec. 28, 1990 [JP] Japan 2-415443
Jan. 31, 1991 [JP] Japan 3-029143

[51] Int. Cl.[6] C07D 301/79; C07D 263/56; A61K 31/34; A61K 31/42

[52] U.S. Cl. 514/469; 514/253; 514/320; 514/337; 514/340; 514/375; 544/368; 546/276; 546/197; 546/264; 546/270; 548/217; 548/224; 549/407; 549/467

[58] Field of Search 549/467; 514/469

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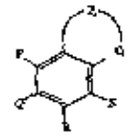
Primary Examiner—Donald G. Daus
Attorney, Agent, or Firm—Seghrue, Mion, Zinn, Macpeak & Seas

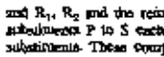
[57] **ABSTRACT**

Pharmaceutical compositions containing a benzoxazole compound and a 2,3-dihydrobenzofuran compound represented by the following formula (I) *and for pharmaceutically acceptable salts.*

(I)



In the formula, any one of P, Q, R and S is a group represented by the formula:

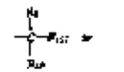


and R_1, R_2 and the remaining three substituents out of the substituents P to S each independently stand for various substituents. These compositions are used as ACAT inhibitor or *for treating hyperlipidemia and atherosclerosis.*

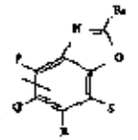
8 Claims, No Drawings

represented by the formulae (I-1) and (I-2). However, compounds wherein the group represented by the above-mentioned formula is bonded to the 7-position (S) is particularly preferred from the viewpoint of the intended drug efficacy and are important also because most of them are novel compounds.

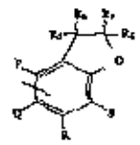
In the formulae (I-1) and (I-2), the R_1 stands for (i) an unsubstituted cycloalkyl or cycloalkenyl group, or a cycloalkyl or cycloalkenyl group substituted at its position other than the 1-position; a group represented by the formula:



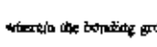
a substituted or unsubstituted aryl group or a group represented by the formula:



or



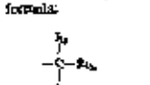
wherein the bonding group substituted for the group:



with the remaining groups being as defined above.

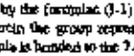
In the R_1, favorable specific examples of the unsubstituted cycloalkyl or cycloalkenyl group or cycloalkyl or cycloalkenyl group substituted at its position other than the 1-position include cyclopentyl, cyclohexyl, cycloheptyl, 1-cyclohexen-1-yl, 4-hexylcyclohexyl and 4-decyloxycyclohexyl.

When the R_1 stands for a group represented by the formula:



the R_9 and R_{10} each independently stand for a hydrogen atom or a lower alkyl group, or combine with each other to form a C_3–C_7 carbon ring.

Examples of the lower alkyl group include those described above, and when the R_9 and R_{10} combine with each other to form a C_3–C_7 carbon ring, examples of the R_1 include a group represented by the following formula:



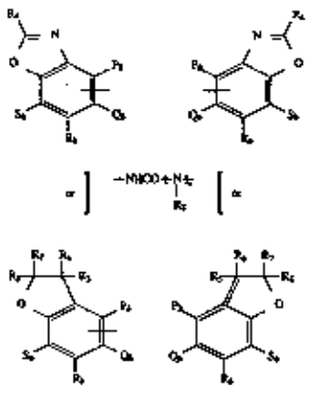
In the R_{11}, favorable examples of the substituted or unsubstituted C_1–C_{19} alkyl include, besides the above-described lower alkyls, isohexyl, octyl, decyl, undecyl, dodecyl, tridecyl, pentadecyl, hexadecyl, heptadecyl, nonadecyl, icosyl, 1,1-dimethylheptyl, 1,1-dimethylundecyl, 1,1,12,12-tetramethyltridecyl, 1-methyltridecyl, 1-decylcyclohexyl, 1-dodecylcyclopentyl, 1-dodecylcyclopentyl, 1-cyclohexyl-1-methylethyl, 1-ethyloctyl and 10,10-dimethyloctadecyl.

In the R_{11}, examples of the C_2–C_{19} alkenyl include vinyl, allyl, butenyl, hexenyl, 8-tridecenyl, 8-heptadecenyl, 9-octadecenyl, 8,11-heptadecadienyl, 1,1-dimethyl- 8-nonenyl, cyclohexylmethyl, 2-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 3-cyclohexen-1-yl and 2,5-cyclohexadien-1-yl.

Specific examples of the R_{11} when the R_{11} stands for a C_6–C_{10} aryl group include phenyl, naphthyl, pyridyl and thienyl. Accordingly, in this case, specific examples of the R_1 include benzyl, 1-phenylcyclopentyl, 1-phenylethyl and 1-methyl-1-(2-pyridyl)ethyl. Favorable specific examples of the R_1 when the R_{11} stands for a C_7–C_{19} aryl alkyl include 2-phenylethyl, 8-phenyloctyl, 1,1-dimethyl- 11-phenylundecyl, 1-benzylcyclopentyl, (1-phenylcyclopentyl)methyl, 1,1-dimethyl-4-(1-naphthyl- 1,2,3,4-tetrahydroquinolin-6-yl)butyl, 1,1-dimethyl-7-pyridylheptyl, 2,2-diphenylethyl, 1,1-dimethyl-6-phenylhexyl, 1,1-dimethyl-7-phenylheptyl, 1,1-dimethyl-5-phenylpentyl and 1,1-dimethyl-4-phenylbutyl.

Favorable examples of the R_{11} when the R_{11} stands for a C_1–C_{19} chain acyl group, C_6–C_{19} cyclic hydrocarbon acyl group or a heyl group having a aromatic ring include groups wherein a carbonyl group is bonded to a favorable group of the above-described alkyl, cyclic alkyl, chain alkenyl, cyclic alkenyl, aryl and arylalkyl groups.

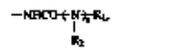
The R_{11} embraces also groups wherein one or more hydrogen atoms, preferably 1 to 3 hydrogen atoms, on carbon(s) in the chain or on carbons constituting the ring are substituted with halogen atoms (for example, fluorine, chlorine, bromine and iodine, preferably fluorine and chlorine), amino, nitro, cyano, carboxyl and hydroxyl groups and further C_1–C_{16} alkyl (as described above), alkoxy (for example, lower alkoxy, such as methoxy, ethoxy and propoxy, pentadecanoxy, decyloxy and octyloxy), acylamino (for example, lower acylamino, such as acetamido, propionylamido, butyrylamino and heptanoylamino, and hexadecanoylamino and heptadecanoylamino), mono-or dialkylamino (for example, methylamino, ethylamino, dimethylamino, diethylamino and decanylamino), alkyloxycarbonyl (for example, groups wherein a carbonyl group is bonded to the above-described alkoxy), such as methoxycarbonyl and ethoxycarbonyl), acyl (formyl, acetyl, propionyl, isovaleryl, pivaloyl, myristoyl, palmitoyl, etc.), and oxiranyl (hexadecyloxy, pivaloyloxy, myristoyloxy, etc.). Specific examples of the R_{11} having R_{11} substituted with the above-described groups include 3,7-dimethyl-11-chloroundecyl, 1,1-dimethyl- 7-bromoheptyl, 9-ethoxycarbonylnonyl, 1,1-dimethyl- 11-hydroxyundecyl, 1,1-dimethyl-10-carboxydecyl, 1-[4-dimethylaminophenyl]cyclopentyl, 1-methyl- 1-(4-chlorophenyl)ethyl, 1-methyl-1-(4-acetyloxyphenyl)ethyl, 1-(4-chlorophenyloxy)-cyclopentyl methyl, 1,1-(4-dimethylaminophenyl)cyclopentyl methyl, 1,1-dimethyl-4-(4-isobutylphenyl)butyl, 1,1-dimethyl-4-(4-hexyloxyphenyl)butyl, 1,1-dimethyl-2-(4-decyloxyphenyl)ethyl, 1,1-dimethyl-2-(4-decylaminophenyl)ethyl and 1,1-dimethyl-7-(4-chlorophenyl)heptyl groups.



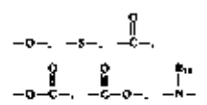
Therefore, the compound represented by the formula (I) include also a compound having such a structure that the above-described individual moieties are linked together through the divalent linking group of the ureylene group or amide group indicated at the center of the above-described structural formulae and the linking group of the left and right condensed ring molecule.

The R_3 stands for a hydrogen atom or a C_1–C_4 alkyl group. Favorable examples of the alkyl group include, besides the above-described specific examples of the lower alkyl group, heptane, octane, cyclohexylmethyl and cyclohexylethyl.

When P, Q, R and S in the formulae (I-1) and (I-2) stand for a group other than the group represented by the formula:



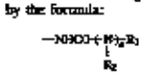
the remaining three groups each independently stand for a hydrogen atom, a halogen atom, an amino, nitro, cyano, carboxyl or hydroxyl group, a C_1–C_{20} alkyl, alkoxy, acylamino, monoalkylamino, alkyloxycarbonyl, acyl or acyloxy group, or a C_2–C_{20} dialkylamino group; and the alkyl portion of these groups may be interrupted by:



wherein R_{13} stands for a hydrogen atom or a lower alkyl, acyl or arylalkyl group.

arylene or aryleneoxy, or 1 to 3 hydrogen atoms on the carbon atom may be substituted with an acyl or aryloxy group, a halogen atom or a cyano group, or the aryl portion as the substituent may be substituted with a halogen atom, an amino, nitro, cyano, carboxyl or hydroxyl group, a C_1–C_{20} alkyl, alkoxy, monoalkylamino, acylamino, alkyloxycarbonyl, acyl or acyloxy group, or a C_2–C_{20} dialkylamino group.

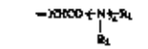
The meaning and specific examples of these groups are the same as the meaning and specific examples of the corresponding groups described above in connection with the R_1. More preferably, when any three of the groups P, Q, R and S stand for a group other than the group represented by the formula:



although these three groups may be the same or different, if the R_1 stands for a group having a large number of constituent atoms (number of carbon atoms: 10 to 20), these groups preferably comprise a group having a small number of constituent atoms, for example, a hydrogen atom, a halogen atom (particularly, fluorine, chlorine or bromine), an amino, nitro, cyano, carboxy or hydroxyl group, a lower alkyl group (particularly, methyl, ethyl, propyl or isopropyl), a lower alkyloxy group (particularly, methoxy, ethoxy or propoxy), a lower acylamino group (particularly, acetamide or propionylamide), a mono- or di-lower alkylamino group (particularly, methylamino, ethylamino or dimethylamino), a lower alkyloxycarbonyl group (particularly, methoxycarbonyl or ethoxycarbonyl), a lower acyl group (particularly, acetyl, propionyl or butyryl), or a lower acyloxy group (particularly, acetyloxy or propionyloxy). On the other hand, when the R_1 is a group having a small number of constituent atoms (number of carbon atoms: 6 or less), it is preferred that at least one group among the P, Q, R and S except for the group represented by the formula:

be a group having a large number of constituent atoms. Specific examples of the group having a large number of constituent atoms include decyloxy, decanoylamide, dodecyloxy, 4-decyloxybenzoylamide, decyl, decylamino, 2,2-dimethyldodecanoamido, 6-(4-chlorophenyl)hexyloxy, 4-(6-phenyloxy)hexyloxybenzoyl and 6-(N-methyl-N-4-chlorobenzyl)aminohexyloxy.

As described above, the compound represented by the formula (I) wherein a group represented by the formula:



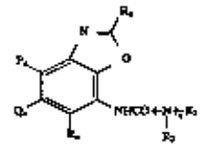
is bonded to the 7-position (S) is particularly preferred from the viewpoint of drug efficacy. In this case, it is still preferred for the 6-position (R) to be a group other than a hydrogen atom from the viewpoint of the drug efficacy. In particular, when the R_1 contained in the group bonded to the 7-position stands for a group having a large number of constituent atoms, it is preferred for the substituent at the 6-position to be a lower alkyl, a lower alkoxy or a halogen.

when the R_4 in the formula (I-1) stands for a C_1–C_{20} alkyl group, specific examples of such an alkyl group are the same as those of the alkyl group described above in connection with the definition of P, Q, R and S. When the R_4 stands for an alkenyl group, the alkenyl group is preferably a lower alkenyl group and examples thereof include vinyl, propenyl and cyclohexenyl. When the R_4 stands for an alkynyl group, the alkynyl group is preferably a lower alkynyl group and examples thereof include ethynyl and propynyl. When the R_4 stands for a substituted or unsubstituted aryl group, examples of the substituent are the same as those of the substituent at the site of the aryl in the definition of the R_{11} and preferred examples thereof include a halogen atom, a lower alkyl, a lower alkoxy, a lower acyl, a lower alkylamino or a lower alkyloxycarbonyl. When the R_4 stands for the above-described aryl group, favorable specific examples of the aryl group include phenyl, pyridyl, thienyl, 4-methylphenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-decanoxyphenyl and 3-nitrophenyl.

When the R_5, R_6, R_7 and R_8 in the formula (I-2) stand for a C_1–C_{20} alkyl group, specific examples of such an alkyl group are the same as those of the alkyl group described in connection with the R_4. Among them, a lower alkyl, such as methyl, ethyl, propyl and isopropyl, are particularly preferred. These four groups may be the same or different. It is preferred that the R_5 and R_6 stand for a hydrogen atom with the R_7 and R_8 standing for a lower alkyl group. When R_5 and R_6 or R_7 and R_8 combine with a carbon atom bonded thereto to form a C_3–C_7 carbon ring, favorable specific examples of such a carbon ring include C_3–C_7 carbon rings described above in connection with the R_{11}.

Compounds represented by the formula (Ia), more specifically, benzotriazole compounds represented by the following formula (Ia-1):

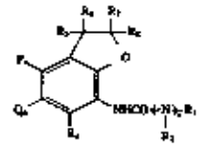
(I-1)



wherein P_a, Q_a, R_a, R_1, R_2, R_3 and n are as defined above.

provided that R_a stands for a group other than a hydrogen atom, and 2,3-dihydrobenzofuran compounds represented by the following formula (Ia-2):

(I-2)

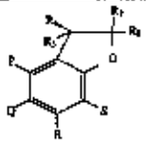


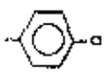
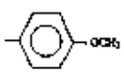
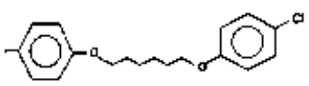
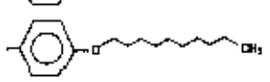
wherein P_a, Q_a, R_a, R_1, R_2, R_3, R_5, R_6, R_7, R_8 and n are as defined above, provided that X_a stands for a group other than a hydrogen atom, are novel compounds not described in any conventional technical literature. Further, when the structural formula representing the compound of the present invention has an asymmetric carbon, the compound of the present invention includes all possible optical isomers.

Examples of compounds comprising specific combinations of groups will now be described for the purpose of more specifically describing the compounds and novel compounds used in the pharmaceutical composition of the present invention. In the following synoptical tables, code G is used according to need to represent the formula:

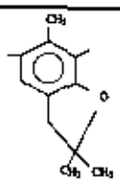
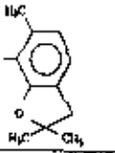
-continued

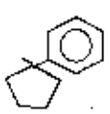
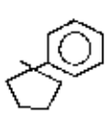
234	P,S = H Q = O(CH$_2$)$_3$CH$_3$ R = O		−CH$_3$	−CH$_3$	−CH$_3$	0



Compound No.	P–S	R_4–R_8	R_1	X_n	n
301	P,R = H R = O(CH$_2$)$_3$CH$_3$ S = O	R_5,R_6 = H R_7,R_8 = CH$_3$		H	1
302	P,R = CH$_3$ Q = NHCO(CH$_2$)$_6$CH$_3$ S = O	R_5,R_6 = H R_7,R_8 = CH$_3$		H	1
303	P,R = CH$_3$ Q = O S = NH(CH$_2$)$_3$CH$_3$	R_5,R_6 = H R_7,R_8 = CH$_3$		H	1
304	P = O R = H Q,S = CH$_3$	R_5,R_6,R_7,R_8 = H		H	1
305	P,R = CH$_3$ Q = H S = O	R_5,R_6 = H R_7,R_8 = CH$_3$		H	1

-continued

306	P,S = H Q = O R = CH$_3$	R_5,R_6 = H R_7,R_8 = CH$_3$		H	1
307	P,Q = H R = CH$_3$ S = O	R_5,R_6 = H R_7,R_8 = CH$_3$		H	1

Compound No.	P–S	R_5–R_8	R_9	R_{10}	R_{11}	R_{12}	n
308	P,Q = H R = CH$_3$ S = O	R_5,R_6 = H R_7,R_8 = CH$_3$	H	H	−(CH$_2$)$_6$CH$_3$	H	1
309	P,Q = H R = CH$_3$ S = O	R_5,R_6 = H R_7,R_8 = CH$_3$	H	H		H	1
310	P,S = H Q = O R = CH$_3$	R_5,R_6 = H R_7,R_8 = CH$_3$	H	H	−(CH$_2$)$_6$CH$_3$	H	1
311	P,S = H Q = O R = CH$_3$	R_5,R_6 = H R_7,R_8 = CH$_3$	H	H		H	1

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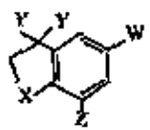
(54) Title: DIHYDROBENZOFURAN AND RELATED COMPOUNDS USEFUL AS ANTI-INFLAMMATORY AGENTS

(57) Abstract

A compound having the structure (A), wherein (a) W is -CO(')-NRR' or -NR-CO(')R'; (b) X and X' are independently O or S; (c) each Y is independently hydrogen or straight, branched or cyclic alkanyl having from 1 to about 3 carbon atoms, or the two Y's are bonded to form an alkanyl ring having from 3 to about 7 carbon atoms; (d) Z is unsubstituted branched or cyclic alkyl, or unsubstituted or alkanyl-substituted phenyl or benzyl, Z having from 3 to about 10 atoms other than hydrogen; (e) R is selected from hydrogen, straight or branched alkyl having from 1 to about 6 carbon atoms, and cyclic alkyl having from 3 to about 6 carbon atoms; and (f) R' is selected from hydrogen, hydroxy, straight or branched alkyl or alkoxy having from 1 to about 6 carbon atoms, and cyclic alkyl having from 3 to about 7 carbon atoms; pharmaceutical compositions comprising such compounds, and methods of treating inflammation or pain using such compounds.



(A)

DIHYDROBENZOFURAN AND RELATED COMPOUNDS USEFUL AS ANTI-INFLAMMATORY AGENTS

TECHNICAL FIELD

The subject invention relates to nonsteroidal anti-inflammatory drugs, particularly to substituted dihydrobenzofuran and related compounds.

BACKGROUND OF THE INVENTION

Certain dihydrobenzofuran compounds and other compounds structurally related thereto have been found to have significant disease altering activities. Such compounds, processes for making them, and uses for them are disclosed in the following references: U.S. Patent No. 4,670,457 issued to Doria, Romeo & Corno on June 2, 1987; U.S. Patent No. 4,849,428 issued to Dobson, Loomans, Mathews & Miller on July 18, 1989; Japanese Patent Publication No. 53-005178 of Yoshitomi Pharm. Ind. KK published January 1, 1978; Hammond, M. L., I. E. Kopka, R. A. Zambias, C. G. Caldwell, J. Boger, F. Baker, T. Bach, S. Luell & D. E. McIntyre, "2,3-Dihydro-5-benzofuranols as Antioxidant-Based Inhibitors of Leukotriene Biosynthesis", J. Med. Chem., Vol. 32 (1989), pp. 1006-1020; Ortiz de Montellano, P. R & M. A. Correia, "Suicidal Destruction of Cytochrome P-450 during Oxidative Drug Metabolism", Ann. Rev. Pharmacol. Toxicol., Vol. 23 (1983), pp. 481-503; Chakrabarti, J.K., R.J. Eggleton, P.T. Gallagher, J. Harvey, T.A. Hicks, E.A. Kitchen, and C.W. Smith, "5-Acyl-3-substituted-benzofuran-2(3H)-ones as Potential Anti-Inflammatory Agents", J. Med. Chem., Vol. 30 (1987), pp. 1663-1666.

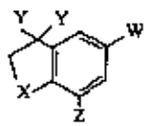
It is an object of the subject invention to provide compounds which have effective anti-inflammatory, analgesic and/or anti-oxidant activity.

It is a further object of the subject invention to provide such compounds which cause few adverse side effects.

It is also an object of the subject invention to provide methods for treating inflammation and/or pain using the subject compounds.

SUMMARY OF THE INVENTION

The subject invention compounds having the structure:



wherein

(a) W is -C(X')-NRR' or -NR-C(X')R';

(b) X and X' are independently O or S;

(c) each Y is independently hydrogen or unsubstituted straight, branched or cyclic alkanyl having from 1 to about 3 carbon atoms, or the two Y's are bonded to form an unsubstituted alkanyl ring having from 3 to about 7 carbon atoms;

(d) Z is unsubstituted branched or cyclic alkyl, or unsubstituted or alkanyl-substituted phenyl or benzyl, Z having from 3 to about 10 atoms other than hydrogen;

(e) R is selected from hydrogen, straight or branched alkyl having from 1 to about 6 carbon atoms, and cyclic alkyl having from 3 to about 6 carbon atoms; and

(f) R' is selected from hydrogen, hydroxy, straight or branched alkyl or alkoxy having from 1 to about 6 carbon atoms, and cyclic alkyl having from 3 to about 7 carbon atoms.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, unless otherwise indicated, "alkyl" means a straight, branched or cyclic hydrocarbon chain, saturated or unsaturated, unsubstituted or substituted. Preferred alkyl are C_1-C_{12}; more preferred are C_1-C_6, more preferred still are C_1-C_3, especially preferred are C_2 and C_1. Preferred alkyl are straight chain. Preferred branched alkyl have one or two branches, preferably one branch. Preferred cyclic alkyl are monocyclic or are a straight chain with a monocyclic terminus. Preferred alkyl are saturated. Unsaturated alkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated alkyl have one or two double bonds or one triple bond, more preferably one double bond. Preferred alkyl are unsubstituted. Preferred substituted alkyl are mono-, di-, or trisubstituted, more preferably monosubstituted. Preferred alkyl substituents include halo, hydroxy, alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy), aryloxy (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, acyloxyphenoxy), acyloxy (e.g., propionyloxy, benzoyloxy, acetoxy), carbamoyloxy, carboxy, mercapto, alkylthio, acylthio, arylthio (e.g., phenylthio, chlorophenylthio, alkylphenylthio, alkoxyphenylthio, benzylthio, alkyloxycarbonylphenylthio), aryl (e.g., phenyl, tolyl, alkyloxphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, heteroaryl, amino (e.g., amino, mono- and di- C_1-C_3 alkanylamino, methylphenylamino, methylbenzylamino, C_1-C_3 alkanylamido, carbamamido, ureido, guanidino).

As used herein, "alkanyl" means a saturated alkyl.

As used herein, "alkoxy" means -O-alkyl.

As used herein, "aryl" means a moiety having an unsubstituted or substituted aromatic ring having 6 to about 10 carbon atoms. Preferred aryl are phenyl and naphthyl; most preferred aryl is phenyl. Preferred aryl are unsubstituted. Preferred substituted aryl are mono-, di-, or trisubstituted, more preferably monosubstituted. Preferred aryl substituents include hydroxy, mercapto, halo, methyl, ethyl and propyl.

As used herein, "heterocyclyl" means a moiety having a saturated or unsaturated non-aromatic ring having from 3 to about 8 ring atoms, including from 2 to about 6 carbon atoms and from 1 to about 4 heteroatoms selected from O, S, and N. Preferred heterocycles are saturated. Preferred heterocycles have 5 or 6 atoms in the ring including 1 or 2 heteroatoms in the ring, also preferably 1 heteroatom in the ring. Specific preferred heterocycles include piperidinyl, tetrahydrothienyl, pyrrolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, tetrahydrofuranyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, oxathiazolidinyl, isothiazolidinyl, azepinyl, oxepinyl, triazolidinyl. Heterocycles are unsubstituted or substituted, preferably unsubstituted. Preferred substituted heterocycles are mono-, di-, or trisubstituted, more preferably monosubstituted. Preferred heterocycle substituents include alkyl, halo, hydroxy, alkoxy, thio, amino, amido, ureido, guanidino, thiocarbamamido, thioureido.

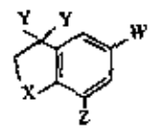
As used herein, "heteroaryl" means a moiety having an aromatic ring having 5 or 6 ring atoms including from 2 to 5 carbon atoms and from 1 to 3 heteroatoms selected from O, S and N. Preferred heteroaryls have 1 or 2 heteroatoms in the ring, also preferably 1 heteroatom in the ring. Specific preferred heteroaryls include pyrrolyl, imidazolyl, pyridyl, pyrimidinyl, pyrazinyl, oxazolyl, isoxazolyl, pyranyl, thienyl, tetrazolyl, thiazolyl, isothiazolyl, furyl, oxathiazolyl. Heteroaryls are unsubstituted or substituted, preferably unsubstituted. Preferred substituted heterocycles are mono-, di-,

or trisubstituted, more preferably monosubstituted. *Preferred* heteroaryl substituents *include* alkyl, halo, hydroxy, alkoxy, thio, amino, amido, ureido, guanidino, thiocarbamamido, thiouredio.

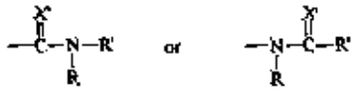
As used herein, "halo" means fluoro, chloro, bromo or iodo. Preferred halo are fluoro, chloro and bromo; *more preferred are chloro* and bromo, *especially chloro*.

Compounds

The subject invention involves compounds having the following structure:



In the above structure, W is:



In the above structure, X and X' are independently O or S. Preferred X is O. Preferred X' is O.

In the above structure, each Y *is independently* selected from hydrogen, *unsubstituted straight* or branched alkanyl having from 1 to about 3 carbon atoms, and cyclic alkyl having about 3 carbon atoms, cyclopropyl, or the Y's are bonded together to form an unsubstituted cyclic alkanyl ring having from 3 to about 7 carbon atoms *in the ring*. Each Y is preferably hydrogen, methyl, *ethyl or cyclopropyl*; more preferably hydrogen or methyl; most preferably methyl. Preferably both Y's are the same. When the Y's are bonded together to form a cyclic ring, the ring is preferably cyclopropyl, cyclobutyl or cyclopentyl, more preferably cyclopropyl.

In the above structure, Z is selected from unsubstituted branched or cyclic alkyl, and unsubstituted or alkanyl-substituted phenyl, or benzyl, Z having from 3 to about 10 atoms other than hydrogen. Z is preferably saturated.

Z *is preferably branched* alkanyl having from about 3 to about 8 carbon atoms, more preferably from about 4 to about 6 carbon atoms. Z is preferably branched alkanyl having 2 or more branches, more preferably 2 branches. Preferred branched alkanyl *Z include* t-butyl, neopentyl,

isopropyl; most preferred is t-butyl. Preferred cyclic alkanyl Z include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, *cycloheptyl*. *Also preferred* cyclic *alkanyl Z include methyl* or ethyl with a terminal cyclopropyl, cyclobutyl or cyclopentyl, especially cyclopropylmethyl or cyclopropylethyl. Also preferred Z is unsubstituted phenyl or benzyl.

In the above structure, R is selected from *hydrogen, straight or* branched *alkyl having from 1 to about* 6 carbon atoms, and cyclic alkyl having from 3 to about 6 carbon atoms. R preferably has from 0 to about 10, more preferably from 0 to about 6, atoms other than hydrogen. Preferably alkyl portions of R are saturated. *More preferred R is hydrogen* or methyl.

In the above structure, R' is selected from hydrogen, hydroxy, straight or branched alkyl or alkoxy having from 1 to about 6 carbon atoms, and cyclic alkyl having from 3 to about 7 carbon atoms. *R' preferably has from* 0 to about *10, more preferably from* 0 to about 6, atoms other than hydrogen. Preferably alkyl portions of R' are saturated. Preferred R' is C_1-C_5 straight or branched alkanyl. Preferred R' is C_1-C_5 straight or branched alkanoxy. Preferred R' is C_3-C_6 cyclic alkanyl. *Also preferred is straight chain* alkanyl, *preferably methyl or ethyl, with* a terminal cyclopropyl, cyclobutyl or cyclopentyl; especially cyclopropyl- methyl and cyclopropylethyl. More preferred R' is selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-methylpropyl, 2-methylpropyl, 1-methylbutyl, ethoxy, benzyl, *phenethyl*, cyclopropyl, *cyclobutyl, cyclopentyl, cyclohexyl*, cyclopropylmethyl and cyclopropylethyl. Most preferred R' is selected from methyl, ethyl, n-propyl, n-butyl and ethoxy.

R is preferably unsubstituted. *R' is preferably unsubstituted.* Preferred *substituents for substituted* alkyl R or R' include hydroxy, mercapto, halo, amino, alkoxy, alkylamino, dialkylamino, carboxy, carboxyalkyl, phenyl, halophenyl, alkylphenyl, alkoxyphenyl, carboxyphenyl, carboxyalkylphenyl, pyridyl, alkylpyridyl, halopyridyl, *alkoxypyridyl*, carboxypyridyl, *and carboxyalkylpyridyl*.

Preferred compounds of the subject invention include those having the above structure with W, X, X', R, R', the two Y's, and Z as indicated in the following table:

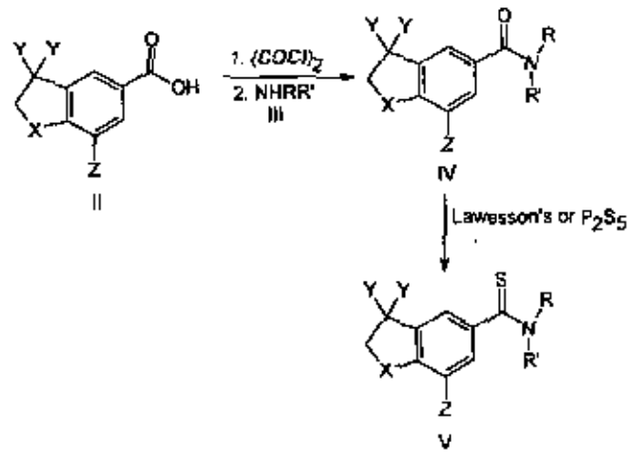
Compound

No.	W	X	X'	R	R'	Y	Z
1	C(X')NRR'	O	O	H	Me	Me, Me	t-Bu

2	C(X')NRR'	O	O	H	Et	Me, Me	t-Bu
3	C(X')NRR'	O	O	H	n-Pr	Me, Me	t-Bu
4	C(X')NRR'	O	O	H	n-Bu	Me, Me	t-Bu
5	C(X')NRR'	O	O	H	2-Pe	Me, Me	t-Bu
6	C(X')NRR'	O	O	H	OEt	Me, Me	t-Bu
7	C(X')NRR'	O	O	H	c-Pr	Me, Me	t-Bu
8	C(X')NRR'	O	O	H	CH_2-c-Pr	Me, Me	t-Bu
9	C(X')NRR'	O	O	Me	Et	Me, Me	t-Bu
10	C(X')NRR'	O	S	H	n-Pr	Me, Me	t-Bu
11	NRC(X')R'	O	O	H	Me	Me, Me	t-Bu
12	NRC(X')R'	O	O	H	Et	Me, Me	t-Bu

In order to determine and assess pharmacological activity, testing of the subject compounds in animals is carried out using various assays known to those skilled in the art. The *anti-inflammatory activity of* the subject compounds can be conveniently demonstrated using an essay designed to test the ability of the subject compounds to antagonize the local edema which is characteristic of the inflammatory response. *Examples* of such known tests include the rat carrageenan edema test, the oxazolone-induced inflamed mouse ear test, and the mouse arachadonic acid-induced inflamed ear test. Analgesic activity may *be tested in art-known models* such as the phenylbenzoquinone-induced writhing test in mice, and the Randall & Selitto test in rats. Another useful art-known test is the rat adjuvant arthritis test which is a useful model *for assessing anti-*inflammatory activity, anti-arthritic and anti-resorptive activity in a chronic, rather than an acute, model.

These and other appropriate tests for pharmacological *activity are* disclosed and/or referred to in U.S. Patent No. 4,130,666 issued to Moore on December 19, 1978; U.S. Patent No. 4,431,656 issued February 14, 1984 to Katsumi, et al.; U.S. Patent No. 4,440,784 issued to Katsumi, *et al.* on April 3, 1984; Japanese Patent Application 85/54315 of Katsumi, et al., published March 28, 1985; European Patent Application No. 0,059,090 of Yamanuchi Pharmaceutical Company Ltd., published September 1, 1982; Opas, E.V., R.J. Bonney & J. L. Humes, "Prostaglandin and Leukotriene Synthesis in Mouse Ears Inflamed by Arachadonic Acid", The Journal of Investigative Dermatology, Vol. 84, No. 4 (1985), pp. 253-256; Swingle, K. F., R. L. Bell & G. G. I. Moore, "Anti-inflammatory Activity of Antioxidants", Anti-inflammatory and Antirheumatic Drugs, Vol. III, Chapter 4, K. D.

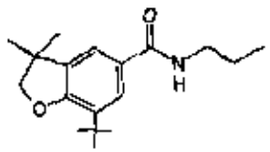


A general method for the preparation of compounds of structure IV in Scheme 1 is the condensation of an appropriate heterocyclic carboxylic acid of structure II with an appropriate amine of structure III under known reaction conditions. For example, this reaction can be performed by activation of the carboxylic acid in an inert halogenated solvent, such as CH_2Cl_2, using an agent such as oxalyl chloride at the appropriate temperature, followed by evaporation of the volatiles, and reaction with the appropriate amine. In general the organic amines useful for this reaction are known, commercially available, or readily prepared. Alternatively, the compounds of structure IV in Scheme I can be prepared by carboamidation of the appropriate heterocyclic bromide of structure I using a catalytic amount of a palladium complex such as bis(triphenylphosphine) palladium dichloride in the presence of carbon monoxide gas and excess of the appropriate amine (structure III) at elevated temperature and pressure. Acids of general structure II may be prepared by a substantially similar method, in which the carbonylation is performed in the presence of a palladium complex, a non-volatile tertiary amine such as tri-n-butylamine and excess alcohol such as ethanol, followed by alkaline hydrolysis and acidification.

Compounds of structure I are made by a series of reactions culminating in a cyclization reaction illustrated in Scheme 1 Reaction

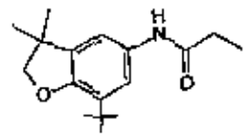
Example 1

Synthesis of N-propyl (7-*tert*-butyl-3,3-dimethyl-2,3-dihydrobenzo[b]furan-5-yl)carboxamide:



2,4-dibromo-6-*tert*-butylphenol. *In a* 2 L 3-neck flask, equipped with *Ar inlet*, reflux condenser, addition funnel, and efficient magnetic stir bar, is placed 2-*tert*-butylphenol (150.2 g, 1.00 mol) and MeOH (300 mL). The stirred solution is cooled in an ice bath as neat Br_2 (321.8 g, 2.01 mol, 2.01 eq) is added *dropwise over* 0.5 h (Caution: this reaction is exothermic. Control with rate of addition.) The reaction is monitored by TLC (2% EtOAc/hexane), and is complete after 2 hrs. The reaction mixture is transfered to a 1 L beaker, along with *a 20-mL rinse of* the reaction flask. *The red solution* solidifies rapidly to a bright orange crystalline mass. The crystalline mass is redissolved by heating over a steam bath, and then a solution of $Na_2S_2O_5$ (1.45 g, 5.4 mmol) in 40 mL H_2O *is added, followed* immediately by fresh MeOH *(80 mL).* The resulting suspension is reheated on the steam bath for 10 min (the mixture does not redissolve), and then is vigorously stirred while allowing to cool to room temperature. After 0.5 h, practically all yellow color has vanished, and *faint orange white* crystals are deposited. *These are filtered* and air dried to yield 2,4-dibromo-6-tert-butylphenol as faint orange-white platelets.

2,4-dibromo-6-*tert*-butylphenyl isobutenyl ether. In a 3000 mL 3-neck flask, equipped with Ar inlet and magnetic *stirrer, is placed* 2,4-dibromo-6-*tert-butylphenol* (70.0 g, 226 mmol), K_2CO_3 (37.6 g, 276 mmol, 1.2 eq), NaI (3.38 g, 22.6 mmol, 0.1 eq), β-methallyl chloride (33.9 mL, 339 mmol, 1.5 eq), and acetone (1500 mL). The reaction mixture is vigorously *stirred at* 23°C for 56 hrs, and monitored *by TLC analysis* (pet. ether). The solids are *removed by* filtration, washed with acetone, and the filtrates rotoevaporated (bath temperature kept below 35°C) to give an oil. The oil is dissolved in hexane (100 mL), and stirred with silica gel (80 g). *The slurry is filtered* through a pad of Celite, *and eluted* with additional hexane (6 x 100 mL). The filtrate is evaporated to give 2,4-dibromo-6-*tert*-butylphenyl isobutenyl



7-*tert*-butyl-3,3-dimethyl-5-nitro-2,3-dihydrobenzo[b]furan. A solution of 7-*tert*-butyl-3,3-dimethyl-2,3-dihydrobenzo[b]furan (10.0 g, 49.0 mmol) in glacial acetic acid 80 mL) is treated with 70 % nitric acid (4.0 mL, 63.7 mmol) dropwise, and allowed *to stir at 24°C for 4 h.* TLC (hexane) is used to *monitor* reaction progress. The reaction mixture is partitioned between Et_2O (100 mL) and H_2O (100 mL). The Et_2O layer is washed with H_2O (50 mL) and saturated Na_2CO_3 (50 mL), dried ($MgSO_4$), filtered and *evaporated to a* red solid *(9.12 g). Crystallization from* hexane provides 7-tert-butyl-3,3-dimethyl-5-nitro-2,3-dihydrobenzo[b]furan as an orange solid.

5-amino-7-*tert*-butyl-3,3-dimethyl-2,3-dihydrobenzo[b]furan. A mixture of *7-tert-butyl-3,3-dimethyl-5-nitro-2,3-dihydrobenzo[b]furan (2.2 g, 8.8 mmol) and 10% Pd on charcoal* (220 mg) in EtOH (60 mL) is hydrogenated at 24°C and 40 psi of H_2 for 3 h. The reaction is monitored by TLC (EtOAC:hexane, 1:19). The reaction mixture is vented to N_2, filtered through Celite, and evaporated to *yield 5-amino-7-tert-butyl-3,3-dimethyl-2,3-dihydrobenzo[b]furan* as a purple solid.

N-(7-tert-butyl-3,3-dimethyl-2,3-dihydrobenzo[b]furan-5-yl)propanamide. To a solution of 5-amino-7-*tert*-butyl-3,3-dimethyl-2,3-dihydrobenzo[b]furan *(400 mg, 1.84 mmol)* and dimethylaminopyridine (61 *mg*, 0.50 mmol) in CH_2Cl_2 (5 mL) is added at 24°C propionyl chloride (160 µL, 1.84 mmol) in a single portion. The reaction is stirred for 1 h, and monitored by TLC (hexane:EtOAc, 9:1). *The mixture is diluted with* Et_2O *(5 mL), and a fine precipitate is* filtered off. The filtrate is evaporated to an orange solid which is purified by preparative TLC (hexane:EtOAc, 9:1) to yield N-(7-tert-butyl-3,3-dimethyl-2,3-dihydrobenzo[b]-furan-5-yl)propanamide as a white solid.

Example 4

Synthesis of N-(7-tert-butyl-3,3-dimethyl-2,3-dihydrobenzo[b]furan-5-yl)-
acetamide:

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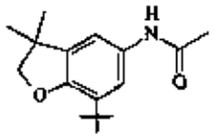

To a solution of 5-amino-7-*tert*-butyl-3,3-dimethyl-2,3-dihydrobenzo[b]-furan (400 mg, 1.84 mmol) and dimethylaminopyridine (247 mg, 2.024 mmol) in CH_2Cl_2 (20 mL) is added at 24°C acetyl chloride (130 µL, 1.84 mmol) in a single portion. The reaction is stirred for 1 h, and monitored by TLC (hexane:EtOAc, 9:1). The mixture is diluted with Et_2O (5 mL), and a fine precipitate is filtered off. The filtrate is evaporated to an orange solid which is purified by preparative TLC (hexane:EtOAc, 9:1) to yield N-(7-tert-butyl-3,3-dimethyl-2,3-dihydrobenzo[b]furan-5-yl)acetamide as a white solid.

Compositions

Compositions of the subject invention comprise a safe and effective amount of the subject compounds, and a pharmaceutically-acceptable carrier. As used herein, "safe and effective amount" means an amount of a compound sufficient to significantly induce a positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. A safe and effective amount of a compound will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

Compositions of the subject invention preferably comprise from about 0.1% to about 99.9% by weight of a compound, more preferably from about 20% to about 80%, and most preferably from about 40% to about 70%.

In addition to the compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a human or lower animal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound,

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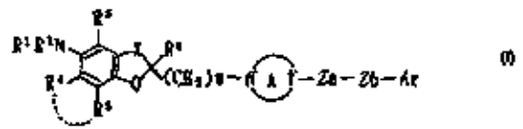
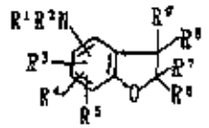


(I)

(57) Abstract

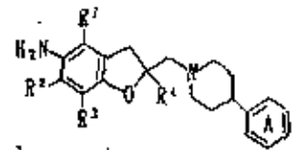
A compound of formula (I) wherein R^1 and R^2 each represents hydrogen, lower alkyl which may be substituted or acyl; R^3, R^4 and R^5 each represents lower alkyl which may be substituted or lower alkoxy which may be substituted or R^4 and R^5 taken together represent a 5- or 6-membered carbocyclic group; R^6 represents lower alkyl; Ar represents an aromatic group which may be substituted; ring A represents a 5- to 8-membered nitrogen-containing heterocyclic ring which may be substituted; X represents lower alkylene which may be substituted; Y represents carbon or nitrogen; Za represents CH_2, $COCH_2$, OCH_2, SCH_2, $NHCH_2$, etc.; Zb represents a bond or a divalent aliphatic hydrocarbon group which may be substituted and may contain O, N or S; and n represents an integer of 1 to 3, or a salt thereof is useful for a pharmaceutical composition for modulating sodium channel.

(EP-A-483772 and its counterpart, JP-A-5-140142).



wherein R^1 and R^2 each represents hydrogen, acyl, alkoxycarbonyl, or an aliphatic or aromatic group which may be substituted; R^3, R^4 and R^5 each represents a hydroxy which may be acylated or an amino, alkoxy or aliphatic group which may be substituted, or two of R^1, R^4 and R^5 may form a carbocycle; R^4 and R^7 each represents an aliphatic group which may be substituted and at least one of R^6 and R^7 has methylene in α-position; R^8 and R^9 each represents hydrogen or an aliphatic or aromatic group which may be substituted.

2) The aminocoumaran compounds of the following formula which has inhibitory activity of lipid peroxidation (JP-A-6-41123).



wherein R^1, R^2, R^3, and R^4 may be the same or different and each represents lower alkyl; ring A represents a benzene ring substituted by at least one substituent selected from among lower alkyl, lower alkoxy and halogen.

3) A crystalline salt of an enantiomer of 5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan having inhibitory activity of lipid peroxidation (USP 5,552,552).

However, there is no report about the relationship of these compounds with sodium channel modulating activity.

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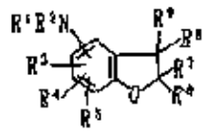
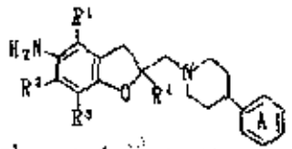


wherein R^1 and R^2 each represents hydrogen, acyl, alkoxycarbonyl, or an aliphatic or aromatic group which may be substituted; R^3, R^4 and R^5 each represents a hydroxy which may be acylated or an amino, alkoxy or aliphatic group which may be substituted, or two of R^3, R^4 and R^5 may form a carbocycle; R^6 and R^7 each represents an aliphatic group which may be substituted and at least one of R^6 and R^7 has methylene in α-position; R^8 and R^9 each represents hydrogen or an aliphatic or aromatic group which may be substituted.

2) The aminocoumaran compounds of the following formula which has inhibitory activity of lipid peroxidation (JP-A-6-41123).



wherein R^1, R^2, R^3, and R^4 may be the same or different and each represents lower alkyl; ring A represents a benzene ring substituted by at least one substituent selected from among lower alkyl, lower alkoxy and halogen.

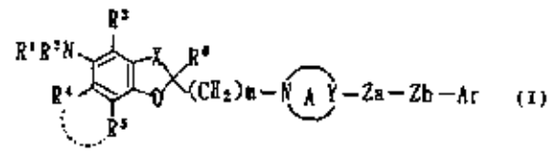
3) A crystalline salt of an enantiomer of 5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan having inhibitory activity of lipid peroxidation (USP 5,552,552).

However, there is no report about the relationship of these compounds with sodium channel modulating activity.

Any sodium channel modulatory substance possessed of satisfactory sodium channel modulating activity coupled with favorable intracranial transfer kinetics and metabolic stability is expected to show good efficacy in central nervous system (CNS) diseases and disorders such as central nervous system ischemia, central nervous system trauma (e.g. brain trauma, spinal cord injury, whiplash injury, etc.), epilepsy, neurodegenerative diseases (e.g. amyotrophic lateral sclerosis [ALS], Alzheimer's disease, Huntington's chorea, Parkinson's disease, diabetic neuropathy, etc.), vascular dementia (e.g. multi-infarct dementia, Binswanger's disease, etc.), manic-depressive psychosis, depression, schizophrenia, chronic pain, trigeminal neuralgia, migraine and cerebral edema. However, no fully satisfactory modulator is available today and there has been a standing need for development of a compound possessed of satisfactory sodium channel modulating activity and qualified for use as a medicine.

The inventors of the present invention explored broadly for compounds having sodium channel modulating activity and succeeded in the creation of a novel compound which is structurally characterized in that the carbon atom in 2-position of a fused cyclic ether has been concurrently substituted by a lower alkyl group and a group of the formula:

wherein each of the symbols has the same meaning as defined below, and is of the formula:



(I)

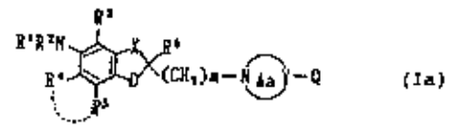
wherein R^1 and R^2 each represents a hydrogen atom, a lower alkyl which may be substituted or an acyl; R^3, R^4 and R^5 each represents a lower alkyl which may be substituted or a lower alkoxy which may be substituted, or R^4 and R^5 taken together represent a 5- or 6-membered carbocyclic group; R^6 represents a lower alkyl; Ar represents an aromatic group which may be substituted; ring A represents a 5- to 8-membered nitrogen-containing heterocyclic ring which may be substituted; X represents a lower alkylene which may be substituted; Y represents a carbon or nitrogen atom; Za represents a group of the formula:

CH_2, $\underset{R^7}{|}$COCH, $\underset{R^7}{|}$OCH, $\underset{R^7}{|}$SCH or $\underset{R^{10}}{|}$N—$\underset{R^7}{|}$CH

wherein R^7 represents a hydrogen atom or an aromatic group which may be substituted; R^{10} represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl; Zb represents a bond or a divalent aliphatic hydrocarbon group which may be substituted and may contain oxygen, nitrogen or sulfur; and m represents an integer of 1 to 3, or a salt thereof [hereinafter referred to briefly as compound (I)].

They discovered surprisingly that a compound of the following formula or a salt thereof [hereinafter referred to briefly as compound (Ia)] including

compound (I) has very favorable properties required of a sodium channel modulator, for example a good affinity for the sodium channel as well as high stability, and as such is fully satisfactory for use as a medicine. The present invention has been developed on the basis of the above findings.



(Ia)

wherein Q represents a hydrogen atom, an aromatic group which may be substituted or a group of the formula: -Zc-Ar wherein Zc represents a divalent aliphatic hydrocarbon group which may be substituted and may contain oxygen, nitrogen or sulfur; Ar has the same meaning as defined above; ring Aa represents a 5- to 8-membered nitrogen-containing heterocyclic ring which may be substituted or the corresponding fused benzologue system thereof; the other respective symbols have the same meanings as defined above.

DISCLOSURE OF INVENTION

The present invention is directed to

(1) compound (I),

(3) a compound of the above (1) wherein R^1 and R^2 each is

i) a hydrogen atom,

ii) a C_{1-6} alkyl which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{3-6} cycloalkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{7-11} aralkyl, C_{1-6} alkoxy, C_{6-10} aryloxy, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, carboxy, C_{1-6} alkoxy-carbonyl, carbamoyl, amidino, imino, amino, mono-C_{1-6} alkylamino,

di-C_{1-6} alkylamino, 3- to 6-membered cyclic amino, C_{1-3} alkylenedioxy, hydroxy, nitro, cyano, mercapto, sulfo, sulfino, phosphono, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{1-6} alkylthio, C_{6-10} arylthio, C_{1-6} alkylsulfinyl, C_{6-10} arylsulfinyl, C_{1-6} alkylsulfonyl and C_{6-10} arylsulfonyl, or

iii) an acyl selected from the group consisting of formyl, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryl-C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-C_{1-6} alkoxy-carbonyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl which may be substituted by 1 to 3 C_{1-6} alkyl and C_{6-10} aryl-C_{1-6} alkylsulfonyl;

R^3, R^4 and R^5 each is

i) a C_{1-6} alkyl which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{3-6} cycloalkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{7-11} aralkyl, C_{1-6} alkoxy, C_{6-10} aryloxy, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, carboxy, C_{1-6} alkoxy-carbonyl, carbamoyl, amidino, imino, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 6-membered cyclic amino, C_{1-3} alkylenedioxy, hydroxy, nitro, cyano, mercapto, sulfo, sulfino, phosphono, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{1-6} alkylthio, C_{6-10} arylthio, C_{1-6} alkylsulfinyl, C_{6-10} arylsulfinyl, C_{1-6} alkylsulfonyl and C_{6-10} arylsulfonyl, or

ii) a C_{1-6} alkoxy which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{3-6} cycloalkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{7-11} aralkyl, C_{1-6} alkoxy, C_{6-10} aryloxy, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, carboxy, C_{1-6} alkoxy-carbonyl, carbamoyl, amidino, imino, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 6-membered cyclic amino, C_{1-3} alkylenedioxy, hydroxy, nitro, cyano, mercapto, sulfo, sulfino, phosphono, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{1-6} alkylthio, C_{6-10} arylthio, C_{1-6} alkylsulfinyl, C_{6-10} arylsulfinyl, C_{1-6} alkylsulfonyl and C_{6-10} arylsulfonyl,

or R^4 and R^5 form, taken together with the respective adjacent carbon atoms, a 5- or 6-membered carbocyclic group selected from the group consisting of a 6-membered aromatic hydrocarbon ring and a 5- or 6-membered cycloalkene;

R^6 is a C_{1-6} alkyl;

Ar is i) a C_{6-14} aryl or ii) a 5- to 10-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from nitrogen, sulfur and oxygen in addition to carbon, each of which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, C_{1-6} alkyl which may be halogenated, C_{3-6} cycloalkyl, C_{1-4} alkoxy which may be halogenated, C_{1-6} alkylthio which may be halogenated, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyl, carboxy, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, sulfo, C_{1-6} alkylsulfonyl, C_{6-10} aryl and C_{6-10} aryloxy;

ring A is a 5- to 8-membered nitrogen-containing heterocyclic ring optionally containing 1 to 4 hetero atoms selected from nitrogen, sulfur and oxygen in addition to nitrogen and carbon, which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, C_{1-6} alkyl which may be halogenated, C_{3-6} cycloalkyl, C_{1-6} alkoxy which may be halogenated, C_{1-6} alkylthio which may be halogenated, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyl, carboxy, C_{1-6} alkoxy-carbonyl, carbamoyl,

mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, sulfo, C_{1-6} alkylsulfonyl, C_{6-10} aryl and C_{6-10} aryloxy;

X represents a C_{1-6} alkylene which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-14} aryl, nitro, cyano, hydroxy, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyl, C_{6-10} aryloxy and oxo;

Y is i) a nitrogen atom or ii) a group of the formula: >C(R^8)-
wherein R^8 is a hydrogen atom, halogen, nitro, cyano, C_{1-6} alkyl which may be halogenated, C_{3-6} cycloalkyl, C_{1-6} alkoxy which may be halogenated, C_{1-6} alkylthio which may be halogenated, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyl, carboxy, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, sulfo, C_{1-6} alkylsulfonyl, C_{6-10} aryl or C_{6-10} aryloxy;

R^7 is a hydrogen atom or i) a C_{6-14} aryl or ii) a 5- to 10-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from nitrogen, sulfur and oxygen in addition to carbon, each of which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{1-3} alkylenedioxy, nitro, cyano, C_{1-6} alkyl which may be halogenated, C_{3-6} cycloalkyl, C_{1-6} alkoxy which may be halogenated, C_{1-6} alkylthio which may be halogenated, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyl, carboxy, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, sulfo, C_{1-6} alkylsulfonyl, C_{6-10} aryl and C_{6-10} aryloxy;

R^{10} is i) a hydrogen atom,
ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen, C_{3-6} cycloalkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{7-11} aralkyl, C_{1-6} alkoxy, C_{6-10} aryloxy, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, carboxy, C_{1-6} alkoxy-carbonyl, carbamoyl, amidino, imino, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 3- to 6-membered cyclic amino, C_{1-3} alkylenedioxy, hydroxy, nitro, cyano, mercapto, sulfo, sulfino, phosphono, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{1-6} alkylthio, C_{6-10} arylthio, C_{1-6} alkylsulfinyl, C_{6-10} arylsulfinyl, C_{1-6} alkylsulfonyl and C_{6-10} arylsulfonyl, or
iii) an acyl selected from the group consisting of formyl, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryl-C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-C_{1-6} alkoxy-carbonyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl which may be substituted by 1 to 3 C_{1-6} alkyl and C_{6-10} aryl-C_{1-6} alkylsulfonyl; and

Zb is a divalent aliphatic hydrocarbon group selected from the group consisting of (i) a C_{1-6} alkylene, (ii) a C_{2-6} alkenylene, (iii) a C_{2-6} alkynylene or (iv) a group of the formula: -$(CH_2)_p$-M-$(CH_2)_q$-
wherein p and q each is an integer of 0 to 6 and p + q is an integer of 1 to 6; M is O, NR^9, S, SO or SO_2, wherein R^9 is a hydrogen atom, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-14} aryl, C_{7-11} aralkyl or an acyl selected from the group consisting of formyl, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryl-C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-C_{1-6} alkoxy-carbonyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl which

may be substituted by 1 to 3 C_{1-6} alkyl and C_{6-10} aryl-C_{1-6} alkylsulfonyl, each of which divalent group may be substituted by 1 to 5 substituents selected from the group consisting of halogen, nitro, cyano, C_{1-6} alkyl which may be halogenated, C_{3-6} cycloalkyl, C_{1-6} alkoxy which may be halogenated, C_{1-6} alkylthio which may be halogenated, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{6-14} aryl, C_{7-11} aralkyl, C_{6-10} aryloxy, oxo, formyl, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryl-C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-C_{1-6} alkoxy-carbonyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl which may be substituted by 1 to 3 C_{1-6} alkyl and C_{6-10} aryl-C_{1-6} alkylsulfonyl,

(3) a compound of the above (1) wherein Za is a group of the formula:

$$CH_2,\ \underset{\displaystyle R^3}{\overset{|}{C}}H,\ \underset{\displaystyle R^3}{\overset{|}{O}}CH \text{ or } \underset{\displaystyle R^3}{\overset{|}{S}}CH$$

wherein R^3 has the same meaning as defined above,

(4) a compound of the above (1) wherein R^3 and R^7 each is a hydrogen atom,

(5) a compound of the above (1) wherein R^3, R^4, and R^5 each is C_{1-4} alkyl,

(6) a compound of the above (1) wherein R^6 is C_{1-6} alkyl,

(7) a compound of the above (1) wherein Ar is a C_{6-14} aryl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{1-6} alkyl and C_{1-6} alkoxy,

(8) a compound of the above (1) wherein ring A is a 6-membered nitrogen-containing heterocyclic ring which may be substituted,

(9) a compound of the above (1) wherein X is methylene,

(10) a compound of the above (1) wherein Y is CH,

(11) a compound of the above (1) wherein Za is a group of the formula:

$$\underset{\displaystyle R^{10}}{\overset{|}{N}}\!\!-\!\!\underset{\displaystyle R^7}{\overset{|}{C}}H$$

wherein respective symbols have the same meanings as defined above,

(12) a compound of the above (1) wherein R^7 is C_{6-10} aryl which may be substituted,

(13) a compound of the above (1) wherein R^{10} is a hydrogen atom,

(14) a compound of the above (1) wherein Zb is a bond,

(15) a compound of the above (1) wherein m is 1,

(16) a compound of the above (1) wherein R^1 and R^7 each is a hydrogen atom;

R^3, R^4, R^5, and R^6 each is a C_{1-6} alkyl;

Ar is a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{1-4} alkyl and C_{1-6} alkoxy;

ring A is a 6-membered nitrogen-containing heterocyclic ring;

X is methylene;

Y is CH or N;

Za is a group of the formula:

$$\underset{\displaystyle R^{10'}}{\overset{|}{N}}\!\!-\!\!\underset{\displaystyle R^{7'}}{\overset{|}{C}}H$$

wherein $R^{7'}$ is a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{1-6} alkyl and C_{1-6} alkoxy; and $R^{10'}$ is a hydrogen atom;

Zb is a bond or a C_{1-6} alkylene which may be substituted by a C_{6-10} aryl; and

m is 1 or 2,

(17) a compound of the above (1) wherein R^1 and R^2 each is a hydrogen atom;
R^3, R^4, R^5, and R^6 each is a C_{1-4} alkyl;
Ar is a C_{6-10} aryl which may be substituted by a methylenedioxy;
ring A is a 6-membered nitrogen-containing heterocyclic ring;
X is methylene;
Y is CH or N;
Za is a group of the formula: CH_2, $\underset{\displaystyle R^{7a}}{\overset{|}{C}}OH$ or $\underset{\displaystyle R^{7a}}{\overset{|}{C}}H$
wherein R^{7a} is a hydrogen atom or C_{6-10} aryl;
Zb is a bond or a (i) C_{1-4} alkylene or (ii) C_{2-6} alkenylene group which may be substituted by a C_{6-10} aryl; and
m is 1,

(18) a compound of the above (1) wherein R^1 and R^2 each is hydrogen;
R^3, R^4, R^5, and R^6 each is a C_{1-4} alkyl;
Ar is a C_{6-10} aryl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, methylenedioxy, C_{1-6} alkyl and C_{1-6} alkoxy;
ring A is a 6-membered nitrogen-containing heterocyclic ring;
X is methylene;
Y is CH or N;
Za is a group of the formula:

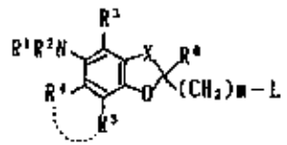
CH_2, $\underset{\displaystyle R^{7b}}{\overset{|}{C}}OH$, $\underset{\displaystyle R^{7a}}{\overset{|}{C}}H$ or $\underset{\displaystyle R^{10a}}{\overset{|}{N}}\!\!-\!\!\underset{\displaystyle R^{7a}}{\overset{|}{C}}H$

wherein R^{7b} is a hydrogen atom or a C_{6-10} aryl which may be substituted by a halogen; and R^{10a} is a hydrogen atom

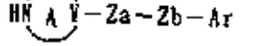
or a C_{7-11} aralkyl;
Zb is a bond or a divalent group selected from the group consisting of (i) a C_{1-6} alkylene, (ii) a C_{2-4} alkenylene and (iii) a group of the formula: $-(CH_2)_{p'}-M'-(CH_2)_{q'}-$ wherein p' and q' each is an integer of 0 to 5, p'+q' is an integer of 1 to 6 and M' is O or NH, each of which divalent group may be substituted by a C_{6-10} aryl; and
m is 1 or 2,

(19) a compound of the above (1) which is
1-[(5-amino-2,3-dihydro-2,4,6,7-tetramethylbenzofuran-2-yl)methyl]-N-(diphenylmethyl)-4-piperidinamine,
(-)-1-[(5-amino-2,3-dihydro-2,4,6,7-tetramethylbenzofuran-2-yl)methyl]-N-(diphenylmethyl)-4-piperidinamine,
(+)-1-[(5-amino-2,3-dihydro-2,4,6,7-tetramethylbenzofuran-2-yl)methyl]-N-(diphenylmethyl)-4-piperidinamine,
1-[(5-amino-2,3-dihydro-7-isopropyl-2,4,6-trimethylbenzofuran-2-yl)methyl]-N-(diphenylmethyl)-4-piperidinamine,
(-)-1-[(5-amino-2,3-dihydro-7-isopropyl-2,4,6-trimethylbenzofuran-2-yl)methyl]-N-(diphenylmethyl)-4-piperidinamine,
(+)-1-[(5-amino-2,3-dihydro-7-isopropyl-2,4,6-trimethylbenzofuran-2-yl)methyl]-N-(diphenylmethyl)-4-piperidinamine, or a salt thereof,

(20) a process for producing a compound of the above (1) which comprises
(i) reacting a compound of the formula:

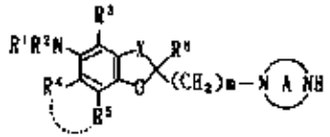


wherein L represents a leaving group; the other symbols have the same meanings as defined above, or a salt thereof with a compound of the formula:



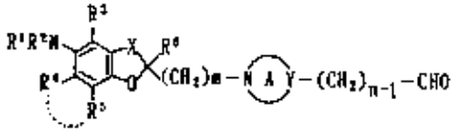
wherein the respective symbols have the same meanings as defined above, or a salt thereof;

(ii) subjecting a compound of the formula:



wherein the respective symbols have the same meanings as defined above, or a salt thereof to (a) alkylation, (b) acylation or (c) acylation followed by reduction;

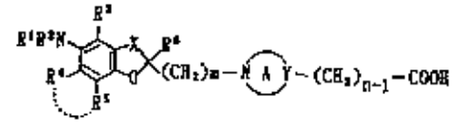
(iii) reacting a compound of the formula:



wherein n represents an integer of 1 to 4; the other symbols have the same meanings as defined above, or a salt thereof with a compound of the formula:

wherein R^{11} represents a hydrogen atom or a hydrocarbon group which may be substituted; Zd represents a divalent aliphatic hydrocarbon group which may be substituted and may contain oxygen, nitrogen or sulfur; Ar has the same meaning as defined above, or a salt thereof,

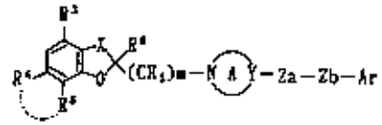
(iv) reacting a compound of the formula:



wherein the respective symbols have the same meanings as defined above, or a salt thereof with a compound of the formula:

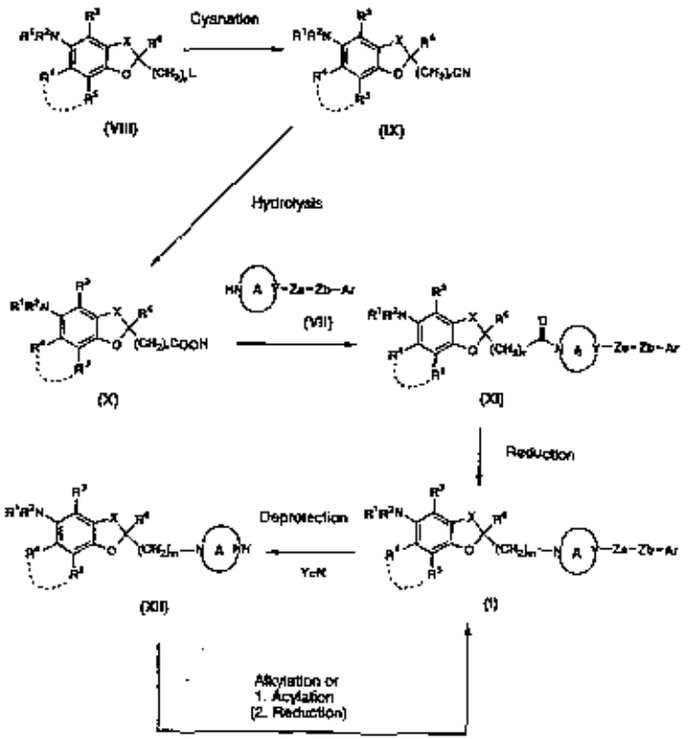
wherein the respective symbols have the same meanings as defined above, or a salt thereof, optionally followed by reduction; or

(v) subjecting a compound of the formula:



wherein the respective symbols have the same meanings as defined above, or a salt thereof to (a) nitration followed by reduction or (b) diazo coupling reaction followed by reduction,

Reaction scheme 2



Referring to compound (IX) (wherein L has the same meaning as defined above; r represents 1 or 2), compound (IX) wherein r=1 can be obtained by reacting compound (VI) wherein m=1, that is to say compound *(VIII) (wherein r has the same meaning as above)* wherein r=1, with a cyano compound. The cyano compound includes, for example, sodium cyanide, potassium cyanide, and a mixture thereof. It is also possible to

produced from compound (XXV) wherein X=methylene in the same manner as the production of compound (VI) from compound (V).

Compound (XXVI) can be produced by subjecting compound (III) and compound (VII) to condensation in the same manner as the production of compound (I) from compound (VI).

Compound (I) can also be produced by nitrating compound (XXVI) in the same manner as in the process for production of compound (IV) from compound (III) and then reducing the nitro group in the same manner as in the process for production of compound (VI) from compound (IV). Moreover, the alkylation and acylation reactions to which compound (VI) is optionally subjected can be carried out in combination or in repetition. The reaction mixture thus obtained can be used, either as it is or in a partially purified form, for the next reaction but the product compound can be easily isolated from the reaction mixture by per se known methods and further purified by such separatory procedures as recrystallization, distillation, chromatography, etc.

Compound (I) can be produced by subjecting compound (XXVI) to diazo coupling reaction with a diazonium salt followed by reduction of the resulting azo compound. The diazonium salt that can be used includes aryldiazonium salts such as benzenediazonium chloride, 4-nitrobenzenediazonium chloride, 2,4-dinitrobenzenediazonium chloride, 4-sulfobenzenediazonium chloride, etc. The diazonium salt can be prepared by the per se known technology, for example by the processes described in JP-A-5-140142 *and other literature or any processes analogous* thereto. This diazonium compound is used in a proportion of about 0.8 to 3 mols per mol of compound (XXVI). This diazo coupling reaction can be carried

added and the mixture was refluxed for 24 hours. After cooling, the reaction mixture was filtered and washed with diethyl ether. The filtrate was extracted with 1N-hydrochloric acid and the aqueous layer was made weakly acidic with saturated aqueous sodium hydrogen carbonate ($NaHCO_3$). This aqueous layer was washed with diethyl ether and made weakly basic with saturated aqueous $NaHCO_3$. This solution was extracted with ethyl acetate and the organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was crystallized from diethyl ether/hexane to provide 0.58 g of the title compound. Yield 28%.

m.p. 118-120°C.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, s), 1.5-1.8 (2H, m), 1.9-2.2 (2H, m), 2.07 (6H, s), 2.10 (3H, s), 2.5-2.7 (4H, m), 2.7-2.9 (1H, m), 2.83 (1H, d, J=15.4 Hz), 2.9-3.05 (1H, m), 3.13 (1H, d, J=15.4 Hz), 7.25 (2H, d, J=8.8 Hz), 7.42 (2H, d, J=8.8 Hz).

Reference Example 6

N-[2,3-dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperidinyl)methyl]benzofuran-5-yl]acetamide

To a suspension of 2,3-dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperidinyl)methyl]-5-benzofuranamine dihydrochloride (1.3 g) in tetrahydrofuran (10 mL) was added a solution of sodium carbonate (0.95 g) in water (5 mL) with ice-cooling and the mixture was stirred for 5 minutes. Then, 0.26 mL of acetyl chloride was added dropwise and the mixture was stirred at room temperature for 15 minutes. This reaction mixture was diluted with water and extracted with 2 portions of ethyl acetate. The pooled organic layer was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate/diisopropyl ether to provide 1.1 g of the

title compound. Yield 90%.

m.p. 94-96°C.

^{1}H-NMR ($CDCl_3$) δ: 1.4-1.5 (3H, m), 1.6-1.9 (4H, m), 2.0-2.7 (17H, m), 2.81 (1H, d, J=15.4 Hz), 2.9-3.3 (3H, m), 6.5-6.7 (1H, m), 7.1-7.4 (5H, m).

Reference Example 7

N-[2,3-dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperazinyl)methyl]benzofuran-5-yl]acetamide hydrochloride

Using 2,3-dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperazinyl)methyl]-5-benzofuranamine, the procedure of Reference Example 6 was otherwise repeated to provide N-[2,3-dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperazinyl)methyl]benzofuran-5-yl]acetamide. Yield 94%. This product was dissolved in tetrahydrofuran and after the solution was diluted with methanol, a stoichiometric excess of 10% HCl solution in methanol was added. The mixture was concentrated under reduced pressure and crystallized from ethanol/diethyl ether to provide the title compound.

m.p. 195-199°C.

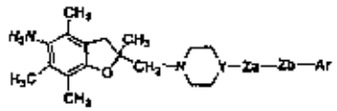
^{1}H-NMR (DMSO-d_6) δ: 1.62 (3H, s), 1.97 (3H, s), 1.99 (3H, s), 2.02 (3H, s), 2.05 (3H, s), 3.01 (1H, d, J=15.8 Hz), 3.1-4.2 (11H, m), 6.85 (1H, t, J=7.1 Hz), 6.99 (2H, d, J=8.2 Hz), 7.26 (2H, t, J=7.7 Hz), 9.11 (0.5 H, s), 10.5-10.9 (0.5 H, br).

Reference Example 8

N-ethyl-2,3-dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperidinyl)methyl]-5-benzofuranamine

To a solution of N-[2,3-dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperidinyl)methyl]benzofuran-5-yl]acetamide (0.56 g) in tetrahydrofuran (8 mL) was added 0.11 g of lithium aluminum hydride in small portions under ice-cooling. The mixture was then refluxed for 30 hours. After this reaction mixture was cooled with ice, 0.42 g Hyflo

Table 1



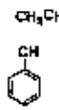
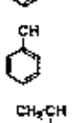
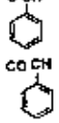
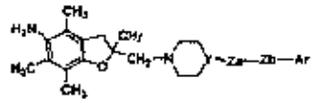
Ex.No.	Y	Za	Zb	Ar	Additive
1	CH	CH_2	CH_2		
2	CH	CH_2	CH_2CH_2		
3	CH	CH_2	$CH_2CH_2CH_2$		
4	N	CH_2	—		3HCl
5	CH	CH_2	—		
6	N	CH_2	—		3HCl
7	CH	OCH_2	—		
8	CH	OCH_2	$CH=CH$		
9	CH	OCH_2	CH_2CH_2		
10	N	$COCH_2$	CH_2CH_2		
11	N	CH_2	$CH_2CH_2CH_2$		3HCl
12	N	$COCH_2$	CH_2		
13	N	CH_2	CH_2CH_2		3HCl
14	N	CH_2			
15	N	$COCH_2$			
16	N	CH_2			3HCl
17	CH		—		$(COOH)_2$
18	N		—		

Table 2



Ex.No.	Y	Za	Zb	Ar	Additive
19	N	CH_2			3HCl
20	N	CH_2			3HCl
21	N	CH_2			3HCl
22	N	CH_2			3HCl
23	N	CH_2			3HCl
24	CH	CH_2			$(COOH)_2$
25	CH	CH_2			$(COOH)_2$
26	CH	CH_2			$(COOH)_2$
27	N	CH_2	CH_3		
28	CH		—		$(COOH)_2$

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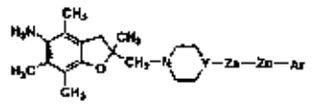
Table 3



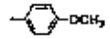
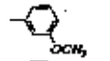
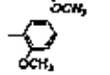
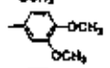
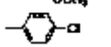
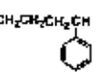
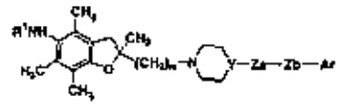
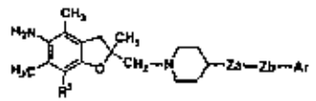
Ex.No.	Y	Za	Zb	Ar	Additive
29	N	CH_2	—		3HCl
30	N	CH_2	—		3HCl
31	N	CH_2	—		3HCl
32	N	CH_2	—		3HCl
33	N	CH_2	—		3HCl
34	N	CH_2	—		3HCl
35	N	$COCH_3$			
36	N	CH_3			3HCl
37	N	$COCH_3$			
38	N	CH_2			3HCl
39	CH	NHCH	—		
40	CH	NHCH	—		3HCl

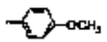
Table 4



Ex.No.	R^1	m	Y	Za	Zb	Ar	Additive
41	H	1	CH	CH_2	CH_2NHCH 		3HCl
42	H	1	CH	CH_2	$CH_2NHCH_2CH_2CH$ 		3HCl
43	H	1	CH	CH_2	NHCH 		2HCl
44	H	1	CH	CH_2	$NHCH_2CH$ 		3HCl
45	H	1	CH	CH_2	$NHCH_2CH_2CH$ 		2HCl
46	H	1	CH	$N(CH_2C_6H_5)CH_2$	CH_2CH 		3HCl
47	H	1	CH	$NHCH_2$	CH_2CH 		$(COOH)_2$
48	H	2	CH	OCH 	—		$(COOH)_2$
49	H	2	CH	CH_2	OCH 		$2(COOH)_2$
50	H	2	CH	CH_2	CH_2OCH 		$(COOH)_2$
51	CH_3CO	1	N	CH_2	$CH_2CH_2CH_2OCH$ 		$(COOH)_2$
52	CH_3CH_2	1	N	CH_2	$CH_2CH_2CH_2OCH$		$(COOH)_2$

Table 5



Ex.No.	Absolute configuration	R^5	Za	Zb	Ar	Additive
53		CH_3	NHCH	—		
54		CH_3	NHCH	—		
55	R	CH_3	NHCH	—		
56	S	CH_3	NHCH	—		
57	R	CH_3	NHCH	—		H_2SO_4
58	S	CH_3	NHCH	—		H_2SO_4
59	S	CH_3	NHCH	—		
60		$CH(CH_3)_2$	NHCH	—		

Formulation Example 1

The compound obtained in Example 5 was dissolved in 30% (w/v) polyethylene glycol 400-saline to prepare a 0.01% solution of the compound. This solution was filtered through a bacterial filter and dispensed into vials, 10 mL per vial, to provide an injectable solution for intravenous administration which contained 1 mg of the compound in each vial.

Formulation Example 2

(S)-2,3-Dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperidinyl)methyl]-5-benzofuranamine dihydrochloride was dissolved in 30% (w/v) polyethylene glycol 400-saline to prepare a 0.01% solution of the compound. The solution was filtered through a bacterial filter and dispensed into vials, 10 mL per vial, to provide an injectable solution for intravenous administration which contained 1 mg of the compound in each vial.

Formulation Example 3

(1) Compound of Example 5	1.0 g
(2) Lactose	60.0 g
(3) Corn starch	35.0 g
(4) Gelatin	3.0 g
(5) Magnesium stearate	2.0 g

Using 30 mL of 10 wt. % aqueous solution of gelatin (3.0 g as gelatin), a mixture of 1.0 g the compound obtained in Example 5, 60.0 g lactose, and 35.0 g corn starch was granulated through a 1 mm-mesh sieve, dried at 40°C, and resieved. The granules thus obtained were mixed with 2.0 g magnesium stearate and the mixture was compressed. The resulting core tablets were coated with a suspension of sucrose, titanium dioxide, talc, and gum arabic in water. The coated tablets were glazed with beeswax to provide 1000 coated tablets.

Formulation Example 4

The compound obtained in Example 40 was dissolved

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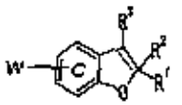
(54) BENZOFURAN DERIVATIVES, PROCESS FOR THE PREPARATION OF THE SAME AND USES THEREOF

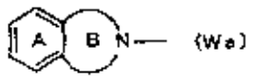
(57) Compounds represented by the formula:



(I)

wherein R^1 and R^2 are hydrogen atom, a hydrocarbon group or a heterocyclic group, or R^1 and R^2 may form, together with the adjacent carbon atom, a 3- to 8-membered homocyclic or heterocyclic ring, W indicates

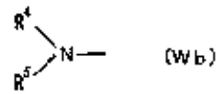
(i) a group represented by the formula:



(Wa)

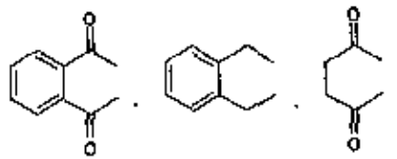
wherein ring B indicates a 5- to 7-membered ring, or

(ii) a group represented by the formula:



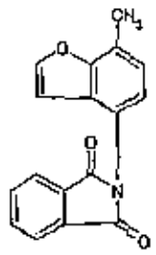
(Wb)

wherein R^4 indicates (1) an aliphatic hydrocarbon group, which may be substituted with an aromatic



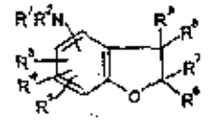
or form pyrrole or pyrrolidine; R^5 is R, lower alkyl, CF_3-, or $ClCH_2$-; and $R^{5'}$ is lower alkyl or CF_3-, or pharmacologically acceptable salts thereof (USP 4,212,865).

5) A compound that is a synthetic intermediate and is represented by the formula:



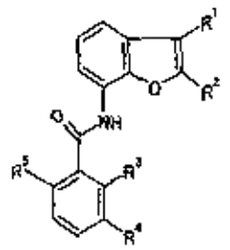
[Tetrahedron Letters, Vol. 37, No. 51, pp. 9183-9186 (1996)].

6) As compounds having an inhibitory activity of lipid peroxide formation, compounds represented by the formula:



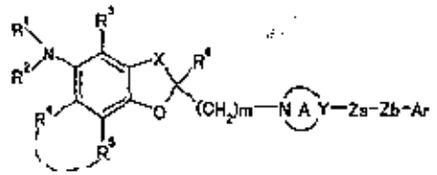
wherein R^1 and R^2 are the same or different and each is hydrogen, acyl, alkoxycarbonyl, or an aliphatic or aromatic group which respectively may be substituted; R^3, R^4, and R^5 are the same or different and each is hydroxyl that may be acylated, or amino, alkoxy or an aliphatic group, which respectively may be substituted, or two of R^3, R^4, and R^5 may form a carbon homocyclic ring that may be substituted, *R^6 and R^7 are the same or different and each* is an aliphatic group that may be substituted, and at least one of R^6 and R^7 has methylene at the α position; and R^8 and R^9 are the same or different and each is hydrogen, or an aliphatic or aromatic group, which respectively may be substituted, or salts thereof (*EP-A-483732* and *JP 5-140142 A*).

7) As compounds having bone resorption inhibitory activity, compounds represented by the formula:



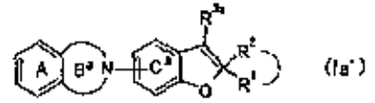
wherein R^1 is formyl, carbamoyl-lower alkyl, thiomorpholinocarbonyl-lower alkyl, thiomorpholinocarbonyl-lower alkyl S-oxide, pyridylaminocarbonyl-lower alkyl, pyrazylaminocarbonyl-lower alkyl, thiazolylaminocarbonyl-lower alkyl, quinolylaminocarbonyl-lower alkyl that may have one or more appropriate substituents, 3-pyridyl-lower alkylaminocarbonyl-lower alkyl, 4-pyridyl-lower alkylaminocarbonyl-lower alkyl, pyridylethylaminocarbonyl-lower alkyl, pyridyl-lower alkylaminocarbonyl-lower alkyl N-oxide, benzimidazolyl-lower alkylaminocarbonyl-lower alkyl, N-pyridyl-lower alkyl-N-acyl-lower alkylaminocarbonyl-lower alkyl, N-pyridyl-N-lower alkylaminocarbonyl-lower alkyl, lower alkylaminocarbonyl-lower alkyl, di-lower alkylaminocarbonylmethyl, quinolyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl, cyano-lower alkyl, di-lower alkylamino-lower alkyl, pyridyl-lower alkyl, thienyl-lower alkyl, pyrazolyl-lower alkyl that may have one or more appropriate substituents, pyrimidinyl-lower alkyl that may have one or more appropriate substituents, dihydrophthalazinyl-lower alkyl that may have one or more appropriate substituents, oxadiazolyl-lower alkyl that may have one or more appropriate substituents, heterocyclic-lower alkanyl that may have one or more appropriate substituents, lower alkoxylower alkylamino-lower alkyl that may have one or more appropriate substituents, aryl-lower alkylaminocarbonyl-lower alkyl that may have one or more appropriate substituents, arylaminocarbonyl-lower alkyl that may have one or more appropriate substituents, arylthio-lower alkyl that may have one or more appropriate substituents, lower alkyl or an imidazolyl-lower alkyl;
R^2 is lower alkyl, protected carboxyl or cyano; R^3 is halogen or lower alkyl; R4 is hydrogen, nitro or amino; and R^5 is halogen, lower alkyl or nitro; provided that, 1) when R^1 is methyl, R^2 is protected carboxyl or cyano and, 2) when R^1 is imidazolylmethyl, R^2 is protected carboxyl or cyano, or salts thereof (JP 9-124633 A).

β) As compounds having sodium channel regulating activity, compounds represented by the formula:



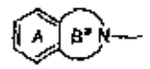
wherein each of R^1 and R^2 is hydrogen atom, lower alkyl that may be substituted or acyl;
each of R^3, R^4 and R^5 is lower alkyl that may be substituted or lower alkoxy that may be substituted, or R^4 and R^5 together may form a 5- or 6-membered homocyclic ring;
R^6 is lower alkyl;
Ar is an aromatic group that may be substituted;
ring A is a 5- to 8-membered nitrogen-containing heterocyclic ring that may be substituted;
X is a lower alkylene that may have substituents;
Y is carbon atom or nitrogen atom;
Za is a group represented by CH_2, $COCH(R^7)$, $OCH_2(R^7)$, $SCH_2(R^7)$, or $N(R^{7a})CH_2(R^7)$ (wherein R^7 is hydrogen

also found that compounds including compounds (Ia) and represented by the formula:



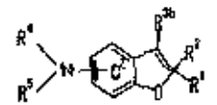
wherein R^1 and R^2 are the same or different and each is hydrogen atom, a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted, or R^1 and R^2 may form, together with the adjacent carbon atom, a 3-to 8-membered homocyclic or heterocyclic ring that may be substituted;
R^{3a} is hydrogen atom, a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted;
--- is a single bond or a double bond;
ring A is benzene ring that may be substituted;
ring B^a indicates a 5- to 7-membered heterocyclic ring that may be substituted;
ring C^a is benzene ring that may be substituted in addition to the group represented by the formula:

(wherein each symbol is as defined above), or salts thereof (hereinafter, sometimes, abbreviated as compounds (Ia')) have, on the basis of the specific chemical structure of the substituent on ring C^a,

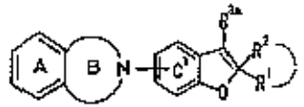


a neurotrophic factor-like activity, a neurotrophic factor enhancing activity, an inhibitory activity of cytotoxicity of β-amyloid, etc. and, further that these compounds (Ia) and compounds (Ia') have extremely low toxicity, are excellent in the brain penetrability and have an inhibitory activity of neurodegeneration, etc., thereby being fully satisfactory as pharmaceuticals.

[0011] Moreover, the present inventors have synthesized for the first time novel compounds represented by the formula:



wherein R^1 and R^2 are the same or different and each is hydrogen atom, a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted, or R^1 and R^2 may form, together with the adjacent carbon atom, a 3-(6 8-membered homocyclic or heterocyclic ring that may be substituted;
R^{3b} is C_{6-14} aryl that may be substituted;
R^4 is (1) an aliphatic hydrocarbon group which may be substituted with an aromatic group that may be substituted and, further, may be substituted, or (2) acyl containing an aromatic group that may be substituted;
R^5 is hydrogen atom, C_{1-6} alkyl or acyl;
--- indicates a single bond or a double bond;
ring C^a is benzene ring that may be substituted in addition to a group represented by formula $-NR^4(R^5)$ (wherein

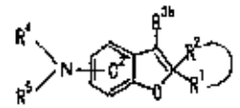


(Ia)

wherein R^1 and R^2 are the same or different and each is hydrogen atom, a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted, or R^1 and R^2 may form, together with the adjacent carbon atom, a 3-to 8-membered homocyclic or heterocyclic ring that may be substituted;
R^{3a} is hydrogen atom, a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted,
--- is a single bond or a double bond;
ring A is benzene ring that may be substituted,
ring B is a 5- to 7-membered nitrogen containing heterocyclic ring which may be substituted with halogen or a hydrocarbon group that may be substituted;
ring C' is benzene ring that may further be substituted with a substituent selected from halogen, lower alkyl that may be halogenated, lower alkoxy that may be halogenated and lower alkylthio that may be halogenated, in addition to the group represented by the formula:

(wherein each symbol is as defined above), or a salt thereof;

3. A compound represented by the formula:



(Ib)

wherein R^1 and R^2 are the same or different and each is hydrogen atom, a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted, or R^1 and R^2 may form, together with the adjacent carbon atom, a 3-to 8-membered homocyclic or heterocyclic ring that may be substituted;
R^{3b} is a C_{6-14} aryl group that may be substituted,
R^4 is (1) an aliphatic hydrocarbon group which is substituted with an aromatic group that may be substituted and, may further be substituted, or (2) an acyl group containing an aromatic group that may be substituted;
R^5 is hydrogen atom, a C_{1-6} alkyl group, or an acyl group;
--- is a single bond or a double bond;
ring C' is benzene ring that may further be substituted, in addition to the group represented by -$NR^4(R^5)$ (each symbol is as defined above), or a salt thereof;

4. The compound according to the above 1, wherein R^1 and R^2 are the same or different and each is (i) hydrogen atom, (ii) a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{3-6} cycloalkyl group, or a C_{6-14} aryl group, which respectively may have 1 to 5 substituents selected from (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) C_{1-6} alkyl that may be halogenated, (6) C_{2-6} alkenyl that may be halogenated, (7) C_{2-6} alkynyl that may be halogenated, (8) C_{3-6} cycloalkyl that may be halogenated, (9) C_{6-14} aryl, (10) C_{1-6} alkoxy that may be halogenated, (11) C_{1-6} alkylthio that may be halogenated or mercapto, (12) hydroxyl, (13) amino, (14) mono-C_{1-6} alkylamino, (15) mono-C_{6-14} arylamino, (16) di-C_{1-6} alkylamino, (17) di-C_{6-14} arylamino, (18) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{6-14} aryl-carbonyl, C_{7-18} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocyclic carbonyl containing, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-14} aryl-carbamoyl, thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl containing, in addition to carbon atom(s), 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl, C_{6-14} arylsulfinyl, and C_{6-14} arylsulfinyl, (19) acylamino selected from formylamino, C_{1-6} alkyl-carbonylamino, C_{6-14} aryl-carbonylamino, C_{1-6} alkoxy-carbonylamino, C_{1-6} alkylsulfonylamino, and C_{6-14} arylsulfonylamino, (20) acyloxy selected from C_{1-6} alkyl-carbonyloxy, C_{6-14} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-14} aryl-carbamoyloxy and nicotinoyloxy, (21) 5- to 7-membered saturated cyclic amino, which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl, and 5- to 10-membered aromatic heterocyclic group containing, in addition to carbon atom(s), 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (22) 5- to 10-membered aromatic heterocyclic group containing, in addition to carbon atom(s), 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (23) sulfo, and (24) C_{6-14} arylcoxy, or
(iii) 5- to 14-membered heterocyclic group containing, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, which respectively may have 1 to 5 substituents selected from (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) C_{1-6} alkyl that may be halogenated, (6) C_{2-6} alkenyl that may be halogenated, (7) C_{2-6} alkynyl that may be halogenated, (8) C_{3-6} cycloalkyl that may be halogenated, (9) C_{6-14} aryl, (10) C_{1-6} alkoxy that may be halogenated or mercapto, (12) hydroxyl, (13) amino, (14) mono-C_{1-6} alkylamino, (15) mono-C_{6-14} arylamino, (16) di-C_{1-6} alkylamino, (17) di-C_{6-14} arylamino, (18) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocyclic carbonyl containing, in addition to carbon atom(s), 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkylcarbamoyl, C_{6-14} aryl-carbamoyl, thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl containing, in addition to carbon atom(s), 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl and C_{6-14} arylsulfinyl, (19) acylamino selected from formylamino, C_{1-6} alkylcarbonylamino, C_{6-14} aryl-carbonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkylsulfonylamino and C_{6-14} arylsulfonylamino, (20) acyloxy selected from C_{1-6} alkylcarbonyloxy, C_{6-14} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-14} aryl-carbamoyloxy and nicotinoyloxy, (21) 5-to 7-membered saturated cyclic amino, which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl and 5- to 10-membered aromatic heterocyclic group containing, in addition to carbon atom(s), 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (22) 5- to 10-membered aromatic heterocyclic group containing, in addition to carbon atom(s), 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (23) sulfo, and (24) a C_{6-14} arylcoxy, or
(iv) R^1 and R^2 form, together with the adjacent carbon atom, C_{3-6} cycloalkane or a 5- to 8-membered heterocyclic ring containing, in addition to carbon atom(s), 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, which respectively may have 1 to 5 substituents selected from (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) C_{1-6} alkyl that may be halogenated, (6) C_{2-6} alkenyl that may be halogenated, (7) C_{2-6} alkynyl that may be halogenated, (8) C_{3-6} cycloalkyl that may be halogenated, (9) C_{6-14} aryl, (10) C_{1-6} alkoxy that may be halogenated, (11) C_{1-6} alkylthio that may be halogenated or mercapto, (12) hydroxyl, (13) amino, (14) mono-C_{1-6} alkylamino, (15) mono-C_{6-14} arylamino, (16) di-C_{1-6} alkylamino, (17) di-C_{6-14} arylamino, (18) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocyclic carbonyl containing, in addition to carbon atom, 1 to 4 heteroatoms selected from nitrogen atom, sulfur atom, and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, thiocarbamoyl, C_{6-14} aryl-carbamoyl, 5- or 6-membered heterocyclic carbamoyl containing, in addition to carbon atom, 1 to 4 heteroatoms selected from nitrogen atom, sulfur atom, and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl, and C_{6-14} arylsulfinyl, (19) acylamino selected from formylamino, C_{1-6} alkylcarbonylamino, C_{6-14} arylcarbonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkylsulfonylamino, and C_{6-14} arylsulfonylamino, (20) acyloxy selected from C_{1-6} alkylcarbonyloxy, C_{6-14} arylcarbonyloxy, C_{1-6} alkoxycarbonyloxy, mono-C_{1-6} alkylcarbamoyloxy, di-C_{1-6} alkylcarbamoyloxy, C_{6-14} arylcarbamoyloxy and nicotinoyloxy,
(21) 5- to 7-membered saturated-cyclic amino, which may have 1 to 3 substituents selected from a C_{1-6} alkyl, C_{6-14} aryl, and a 5- to 10-membered aromatic heterocyclic group containing, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (22) a 5- to 10-membered aromatic heterocyclic group containing, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom, and oxygen atom, (23) sulfo, and (24) C_{6-14} arylcoxy;

(I) when W is Wa,
R^{3a} is (i) hydrogen atom, (ii) a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{3-6} cycloalkyl

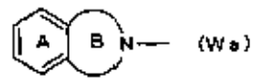
group or a C_{6-14} aryl group which respectively may have 1 to 5 substituents selected from (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) C_{1-6} alkyl that may be halogenated, (6) C_{2-6} alkenyl that may be halogenated, (7) C_{2-6} alkynyl that may be halogenated, (8) C_{3-6} cycloalkyl that may be halogenated, (9) C_{6-14} aryl, (10) C_{1-6} alkoxy that may be halogenated, (11) C_{1-6} alkylthio that may be halogenated or mercapto, (12) hydroxyl, (13) amino, (14) mono-C_{1-6} alkylamino, (15) mono-C_{6-14} arylamino, (16) di-C_{1-6} alkylamino, (17) di-C_{6-14} arylamino, (18) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocyclic carbonyl containing, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-14} arylcarbamoyl, thiocarbamoyl, 5- or 6-membered, heterocyclic carbamoyl containing, in addition to carbon atom, 1 to 4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl and C_{6-14} arylsulfinyl, (19) acylamino selected from formylamino, C_{1-6}alkyl-carboxamido, C_{6-14} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino and C_{6-14} arylsulfonylamino, (20) acyloxy selected from C_{1-6} alkyl-carbonyloxy, C_{6-14} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, a mono-C_{1-6} alkyl-carbamoyloxy, a di-C_{1-6} alkyl-carbamoyloxy, C_{6-14} aryl-carbamoyloxy and nicotinoyloxy, (21) 5- to 7-membered saturated-cyclic amino, which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl, and a 5- to 10-membered aromatic heterocyclic group containing, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (22) a 5- to 10-membered aromatic heterocyclic group containing, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (23) sulfo, and (24) C_{6-14} aryloxy, or

(iii) a 5- to 14-membered heterocyclic group containing, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, which may have 1 to 5 substituents selected from (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) C_{1-6} alkyl that may be halogenated, (6) C_{2-6} alkenyl that may be halogenated, (7) C_{2-6} alkynyl that may be halogenated, (8) C_{3-6} cycloalkyl that may be halogenated, (9) C_{6-14} aryl, (10) C_{1-6} alkoxy that may be halogenated, (11) C_{1-6} alkylthio that may be halogenated or mercapto, (12) hydroxyl, (13) amino, (14) mono-C_{1-6} alkylamino, (15) mono-C_{6-14} arylamino, (16) di-C_{1-6} alkylamino, (17) di-C_{6-14} arylamino, (18) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocyclic carbonyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-14} aryl-carbamoyl, thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl and C_{6-14} arylsulfinyl, (19) acylamino selected from formylamino, C_{1-6} alkylcarbonylamino, C_{6-14} aryl-carbonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkylsulfonylamino and C_{6-14} arylsulfonylamino, (20) acyloxy selected from C_{1-6} alkylcarbomyloxy, C_{6-14} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-14} aryl-carbamoyloxy and nicotinoyloxy, (21) 5- to 7-membered saturated-cyclic amino, which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl and a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (22) a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (23) sulfo, and (24) a C_{6-14} aryloxy;

ring A is benzene ring, which respectively may have 1 to 5 substituents selected from (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) C_{1-6} alkyl that may be halogenated, (6) C_{2-6} alkenyl that may be halogenated, (7) C_{2-6} alkynyl that may be halogenated, (8) C_{3-6} cycloalkyl that may be halogenated, (9) C_{6-14} aryl, (10) C_{1-6} alkoxy that may be halogenated, (11) C_{1-6} alkylthio that may be halogenated or mercapto, (12) hydroxyl, (13) amino, (14) mono-C_{1-6} alkylamino, (15) mono-C_{6-14} arylamino, (16) di-C_{1-6} alkylamino, (17) di-C_{6-14} arylamino, (18) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocyclic carbonyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-14} aryl-carbamoyl, thiocarbamoyl, 5- or 6-membered, heterocyclic carbamoyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl and C_{6-14} arylsulfinyl, (19) acylamino selected from formylamino, C_{1-6} alkyl-carboxamido, C_{6-14} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino and C_{6-14} arylsulfonylamino, (20) acyloxy selected from C_{1-6} alkyl-carbonyloxy, C_{6-14} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-14} aryl-carbamoyloxy and nicotinoyloxy, (21) 5- to 7-membered saturated-cyclic amino, which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl and a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (22) a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (23) sulfo, and (24) a C_{6-14} aryloxy;

ring B is a 5- to 7-membered nitrogen-containing heterocyclic ring that may be substituted with (i) halogen or (ii) a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{3-6} cycloalkyl group, or a C_{6-14} aryl group, which respectively may have 1 to 5 substituents selected from (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) C_{1-6} alkyl that may be halogenated, (6) C_{2-6} alkenyl that may be halogenated, (7) C_{2-6} alkynyl that may be halogenated, (8) C_{3-6} cycloalkyl that may be halogenated, (9) C_{6-14} aryl, (10) C_{1-6} alkoxy that may be halogenated, (11) C_{1-6} alkylthio that may be halogenated or mercapto, (12) hydroxyl, (13) amino, (14) mono-C_{1-6} alkylamino, (15) mono-C_{6-14} arylamino, (16) di-C_{1-6} alkylamino, (17) di-C_{6-14} arylamino, (18) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocyclic carbonyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-14} aryl-carbamoyl, thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl and C_{6-14} arylsulfinyl, (19) acylamino selected from formylamino, C_{1-6} alkyl-carboxamido, C_{6-14} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino and C_{6-14} arylsulfonylamino, (20) acyloxy selected from C_{1-6} alkylcarbonyloxy, C_{6-14} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-14} aryl-carbamoyloxy and nicotinoyloxy, (21) 5- to 7-membered saturated-cyclic amino, which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl and a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (22) a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (23) sulfo, and (24) a C_{6-14} aryloxy;

ring C is benzene ring that may be substituted with a substituent selected from halogen, C_{1-6} alkyl that may be halogenated, C_{1-6} alkoxy that may be halogenated, and C_{1-6} alkylthio that may be halogenated in addition to the group represented by the formula:



(ii) when W is Wa,

R^a is C_{6-14} aryl, which respectively may have 1 to 5 substituents selected from (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) C_{1-6} alkyl that may be halogenated, (6) C_{2-6} alkenyl that may be halogenated, (7) C_{2-6} alkynyl that may be halogenated, (8) C_{3-6} cycloalkyl that may be halogenated, (9) C_{6-14} aryl, (10) C_{1-6} alkoxy that may be halogenated, (11) C_{1-6} alkylthio that may be halogenated or mercapto, (12) hydroxyl, (13) amino, (14) mono-C_{1-6} alkylamino, (15) mono-C_{6-14} arylamino, (16) di-C_{1-6} alkylamino, (17) di-C_{6-14} arylamino, (18) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocyclic carbonyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-14} aryl-carbamoyl, thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl and C_{6-14} arylsulfinyl, (19) acylamino selected from formylamino, C_{1-6} alkylcarbonylamino, C_{6-14} aryl-carbonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkylsulfonylamino and C_{6-14} arylsulfonylamino, (20) acyloxy selected from C_{1-6} alkylcarbonyloxy, C_{6-14} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-14} aryl-carbamoyloxy and nicotinoyloxy, (21) 5- to 7-membered saturated-cyclic amino, which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl and a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (22) a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (23) sulfo, and (24) a C_{6-14} aryloxy;

R^4 is a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, or a C_{3-5} cycloalkyl group, which has 1 to 3 groups of a C_{6-14} aryl group and a 5- to 14-membered, aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, which respectively may have 1 to 5 substituents selected from (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) C_{1-6} alkyl that may be halogenated, (6) C_{2-6} alkenyl that may be halogenated, (7) C_{2-6} alkynyl that may be halogenated, (8) C_{3-6} cycloalkyl that may be halogenated, (9) C_{6-14} aryl, (10) C_{1-6} alkoxy that may be halogenated, (11) C_{1-6} alkylthio that may be halogenated or mercapto, (12) hydroxyl, (13) amino, (14) mono-C_{1-6} alkylamino, (15) mono-C_{6-14} arylamino, (16) di-C_{1-6} alkylamino, (17) di-C_{6-14} arylamino, (18) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocyclic carbonyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-14} aryl-carbamoyl, thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl and C_{6-14} arylsulfinyl, (19) acylamino selected from formylamino, C_{1-6} alkylcarbonylamino, C_{6-14} aryl-carbonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkylsulfonylamino and C_{6-14} arylsulfonylamino, (20) acyloxy selected from C_{1-6} alkylcarbonyloxy, C_{6-14} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-14} aryl-carbamoyloxy and nicotinoyloxy, (21) 5- to 7-membered saturated-cyclic amino, which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl, and a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (22) a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (23) sulfo, and (24) a C_{6-14} aryloxy, and further may have 1 to 5 substituents selected from (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) C_{1-6} alkyl that may be halogenated, (6) C_{2-6} alkenyl that may be halogenated, (7) C_{2-6} alkynyl that may be halogenated, (8) C_{3-6} cycloalkyl that may be halogenated, (9) C_{6-14} aryl, (10) C_{1-6} alkoxy that may be halogenated, (11) C_{1-6} alkylthio that may be halogenated or mercapto, (12) hydroxyl, (13) amino, (14) mono-C_{1-6} alkylamino, (15) mono-C_{6-14} arylamino, (16) di-C_{1-6} alkylamino, (17) di-C_{6-14} arylamino, (18) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocyclic carbonyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-14} aryl-carbamoyl, thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl, and C_{6-14} arylsulfinyl, (19) acylamino selected from formylamino, C_{1-6} alkyl-carbonylamino, C_{6-14} aryl-carbonylamino, C_{1-6} alkoxy-carbonylamino, C_{1-6} alkylsulfonylamino and C_{6-14} arylsulfonylamino, (20) acyloxy selected from C_{1-6} alkylcarbonyloxy, C_{6-14} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-14} aryl-carbamoyloxy and nicotinoyloxy, (21) 5- to 7-membered saturated-cyclic amino which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl and 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (22) a 5- to 10-membered, aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (23) sulfo, and (24) a C_{6-14} aryloxy, or

(ii) an acyl group that is selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbamyl, C_{3-6} cycloalkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryl-oxycarbonyl, C_{7-16} aralkyl-oxycarbonyl, 5- or 6-membered heterocyclic carbonyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom, and oxygen atom, mono-C_{1-6} alkylcarbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-14} aryl-carbamoyl, thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl that contains, in addition to carbon atom, 1 to 4 hetero atom selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl and C_{6-14} arylsulfinyl,

which has 1 to 3 groups of a C_{6-14} aryl group and a 5- to 14-membered aromatic heterocyclic group that contains, in addition to the carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, which respectively may have 1 to 5 substituents selected from (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) C_{1-6} alkyl that may be halogenated, (6) C_{2-6} alkenyl that may be halogenated, (7) C_{2-6} alkynyl that may be halogenated, (8) C_{3-6} cycloalkyl that may be halogenated, (9) C_{6-14} aryl, (10) C_{1-6} alkoxy that may be halogenated or mercapto, (12) hydroxyl, (13) amino, (14) mono-C_{1-6} alkylamino, (15) mono-C_{6-14} arylamino, (16) di-C_{1-6} alkylamino, (17) di-C_{6-14} arylamino, (18) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or

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6-membered heterocyclic carbonyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkylcarbamoyl, C_{6-14} aryl-carbamoyl, thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{6-14} arylsulfinyl, C_{1-6} alkylsulfinyl and C_{6-14} arylsulfinyl, (18) acylamino selected from formylamino, C_{1-6} alkylcarbonylamino, C_{6-14} arylcarbonyl-amino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkylsulfonylamino and C_{6-14} arylsulfonylamino, (20) acyloxy selected from C_{1-6} alkylcarbonyloxy, C_{6-14} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-14} aryl-carbamoyloxy, and nicotinoyloxy, (21) 5- to 7-membered saturated-cyclic amino, which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl, and a 5- to 10-membered, aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (22) a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (23) sulfo, and (24) C_{6-14} aryloxy.

R^5 is (i) hydrogen atom, (ii) a C_{1-6} alkyl group, or (iii) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocyclic carbonyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkylcarbamoyl, C_{6-14} aryl-carbamoyl, thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl and C_{6-14} arylsulfinyl; and ring C is, in addition to a group represented by the formula $-NR^4(R^5)$, benzene ring, which may have 1 to 3 substituents selected from (1) halogen, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) C_{1-6} alkyl that may be halogenated, (6) C_{2-6} alkenyl that may be halogenated, (7) C_{2-6} alkynyl that may be halogenated, (8) C_{3-6} cycloalkyl that may be halogenated, (9) C_{6-14} aryl, (10) C_{1-6} alkoxy that may be halogenated, (11) hydroxyl, (12) amino, (13) mono-C_{1-6} alkylamino, (14) mono-C_{6-14} arylamino, (15) di-C_{1-6} alkylamino, (16) di-C_{6-14} arylamino, (17) acyl selected from formyl, carboxyl, carbamoyl, C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocyclic carbonyl that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-14} aryl-carbamoyl, thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl that contains, in addition to carbon atom, 1 to 4 hetero atom selected from nitrogen atom, sulfur atom and oxygen atom, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl, and C_{6-14} arylsulfinyl, (18) acylamino selected from formylamino, C_{1-6} alkyl-carboxamido, C_{6-14} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino and C_{6-14} arylsulfonylamino, (19) 5- to 7-membered saturated-cyclic amino, which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl and a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, (20) a 5- to 10-membered aromatic heterocyclic group that contains, in addition to carbon atom, 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom, and (21) sulfo;

5. The compound according to the above 2, wherein R^1 and R^2 are the same or different and each is hydrogen atom or a C_{1-6} alkyl group that may have substituents, or R^1 and R^2 may form, together with the adjacent carbon atom, a 3- to 8-membered heterocyclic ring that may be substituted;

6. The compound according to the above 2, wherein each of R^1 and R^2 is a C_{1-6} alkyl group;

7. The compound according to the above 2, wherein R^{2a} is a C_{6-14} aryl group that may be substituted;

8. The compound according to the above 2, wherein R^{2a} is phenyl group that may have C_{1-6} alkyl or halogen;

9. The compound according to the above 2, wherein ring A is benzene ring that may be substituted selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} alkylenedioxy;

10. The compound according to the above 2, wherein ring B is a 5- to 7-membered nitrogen-containing heterocyclic ring that may be substituted with C_{1-6} alkyl;

11. The compound according to the above 2, wherein ring C^1 is benzene ring that may be further substituted with C_{1-6} alkyl or C_{1-6} alkoxy;

12. The compound according to the above 2, wherein a group represented by the formula:

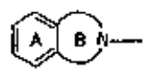

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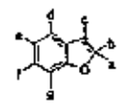
Table 1



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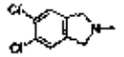
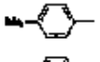
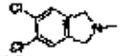
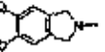
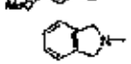
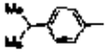
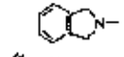
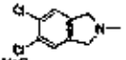
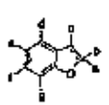
2a	Me	Me		Me		Me	Me	—
3a	Me	Me		Me		Me	Me	—
4a	Me	Me		Me		Me	Me	—
5a	Me	Me		Me		Me	Me	—
6a	Me	Me		Me		Me	Me	—
7a	Me	Me		Me		Me	Me	—
8a	Me	Me		Me		Me	Me	—
9a	Me	Me		Me		Me	Me	—
10a	Me	Me		Me		Me	Me	—
11a	Me	Me		Me		Me	Me	—
12a	Me	Me		Me		Me	Me	—

Table 2



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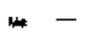
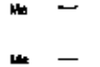
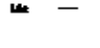
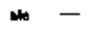
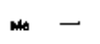
13a	Me	Me		Me		Me	Me	—	
14a	Me	Me		Me		Me	Me	—	
15a	Me	Me	H	Me		Me	Me	—	
16a	Me	Me		Me		Me	Me	—	
17a	Me	Me		Me		Me	Me	—	
18a	Me	Me		Me		Me	Me	—	
19a	Me	Me		Me		Me	Me	—	HCl
20a	Me	Me		Me		Me	Me	—	HCl
21a	Me	Me		Me		Me	Me	—	HBr
22a	Me	Me		Me		Me	Me	—	HBr

Formulation Example 1a

[0829]

(1) The compound obtained in Example 14a	50 mg
(2) Lactose	34 mg
(3) Corn starch	10.6 mg
(4) Corn starch (paste)	5 mg
(5) Magnesium Stearate	0.4 mg
(6) Calcium carboxymethyl cellulose	20 mg
Total	120 mg

[0830] According to a conventional method, tablets were prepared by mixing the above-described substances, (1) to (5), and then subjecting the resulting mixture to a tablet compression process By using a tablet compression machine.

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US006172085B1

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

(10) **Patent No.: US 6,172,085 B1**
(45) **Date of Patent: Jan. 9, 2001**

(54) **CYCLIC ETHER COMPOUNDS AS SODIUM CHANNEL MODULATORS**

(75) Inventors: **Shigenori Ohkawa**; **Tsutomu Hashimoto**, both of Osaka; **Kuniji Fukatsu**, Hyogo, all of (JP)

(73) Assignee: **Takeda Chemical Industries, Ltd.**, *Osaka (JP)*

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **09/242,067**

(22) PCT Filed: **Aug. 28, 1997**

(86) PCT No.: **PCT/JP97/03087**

§ 371 Date: **Feb. 8, 1999**

§ 102(e) Date: **Feb. 8, 1999**

(87) PCT Pub. No.: **WO98/08842**

PCT Pub. Date: **Mar. 5, 1998**

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Apr. 4, 1997 (JP) 9-086496

(51) **Int. Cl.**[7] **C07D 405/06**; A61K 31/343

(52) **U.S. Cl.** 514/320; 514/217.03; 514/307; 514/318; 514/322; 514/417; 540/596; 546/150; 546/196; 546/199; 546/201; 546/204; 548/477

(58) **Field of Search** 540/596; 546/150, 546/196, 199, 201, 204; 548/477; 514/212, 217.03, 318, 307, 320, 322, 417

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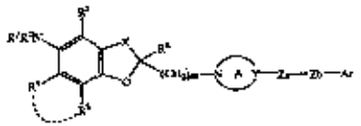
(57) **ABSTRACT**

A compound of the formula:



wherein R^1 and R^2 each represents hydrogen, lower alkyl which may be substituted or acyl; R^3, R^4 and R^5 each represents lower alkyl which may be substituted or lower alkoxy which may be substituted or R^4 and R^5 taken together represent a 5- or 6-membered carbocyclic group; R^6 represents lower alkyl; Ar represents an aromatic group which may be substituted; ring A represents a 5- to 8-membered nitrogen-containing heterocyclic ring which may be substituted; X represents lower alkylene which may be substituted; Y represents carbon or nitrogen; Za represents CH_2, $COCH_2$, OCH_2, SCH_2, $NHCH_2$, etc.; Zb represents a bond or a divalent aliphatic hydrocarbon group which may be substituted and may contain O, N or S; and m represents an integer of 1 to 3, or a salt thereof is useful for a pharmaceutical composition for modulating sodium channel.

23 Claims, No Drawings

with inorganic acids are salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc. The preferred salts with organic acids are salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc. The preferred salts with basic amino acids are salts with arginine, lysine, ornithine, etc. The preferred salts with acidic amino acids are salts with aspartic acid, glutamic acid, etc.

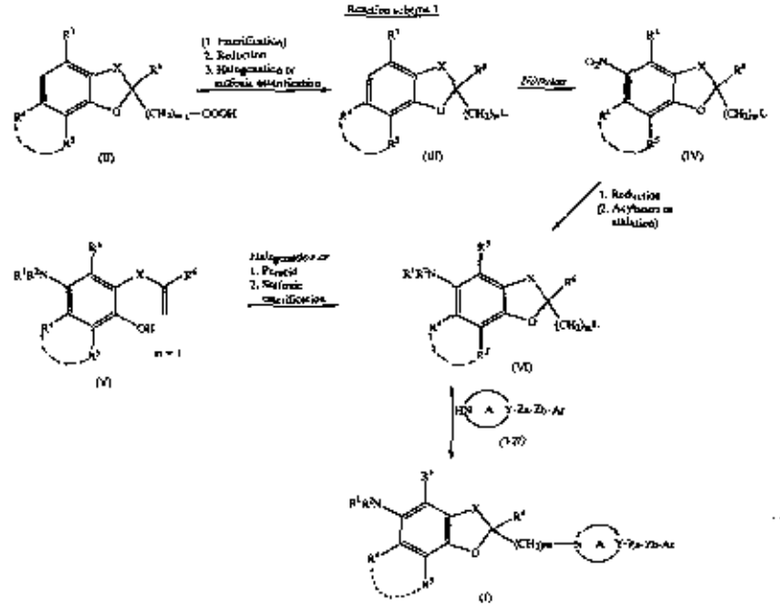
Particularly preferred salts are pharmacologically acceptable salts. When compound (I) or ((a) contains a basic functional group, the preferred salt includes the corresponding salts with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc. and salts with organic acids such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, etc. When an acidic functional group is present, the preferred salt includes the corresponding salts with alkali metals such as sodium, potassium, etc., salts with alkaline earth metals such as calcium, magnesium, etc., and ammonium salts.

The process for producing compound (I) of the present invention is not described.

Compound (I) of the invention can be produced by the per se known methods or analogous thereto, or the processes represented by the reaction schemes presented hereinafter. Compound (Ia) can be produced by the per se known methods (e.g. the processes disclosed in EP-A-483772, JP-A-5-140142 and JP-A-6-41123, U.S. Pat. No. 5,552,552, etc.), or analogous thereto, or the processes represented by the reaction schemes presented below.

In the following reaction schemes, the respective symbols have the same meanings as defined hereinbefore. The compounds (II) through (XXVIII) in the reaction schemes include their salts which may be of the same kinds as those mentioned for compound (I).

Reaction scheme 1

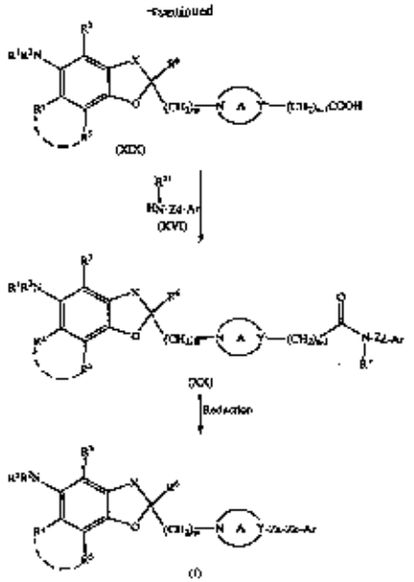


Compound (II) can be obtained by the per se known method, for example any of the processes disclosed in JP-A-62-87585, JP-A-5-140142, J. Am. Oil Chem. Soc., 51, 200–203, 1974, etc., or any process analogous thereto.

Compound (V) can be obtained by the per se known method, for example the process disclosed in JP-A-5-140142, or any process analogous thereto.

Compound (VII) may be purchased from a commercial source if it is available on the market, to be obtained by the per se known method, for example the processes disclosed in Eur. J. Med. Chem. 15, 363–370, 1980, JP-A-2-49726, etc., or any process analogous thereto.

Compound (III) (wherein L represents a leaving group) can be obtained by a process which comprises reducing the carboxyl group of compound (II) either directly or after



Compound (XVIII) (wherein R^{32} represents a hydrogen atom or a hydrocarbon group; n has the same meaning as defined above) can be produced by subjecting compound (VI) and compound (XVII) (wherein the respective symbols have the same meanings as defined above) to a condensation similar to that used in the production of compound (I) from compound (VI).

The "hydrocarbon group" for R^{32} may be similar to the "hydrocarbon group" of the "hydrocarbon group which may be substituted" as mentioned for R^{30}.

Compound (XVII) can be purchased and used, when it is commercially available or be obtained by per se known method, for example the method described in J. Am. Chem. Soc., 75, 6249, 1953, etc.

Compound (XIX) (wherein n has the same meaning as defined above) can be produced by subjecting compound (XVIII) to acid or alkaline hydrolysis. The acid hydrolysis can be carried out using, for example, a mineral acid such as hydrochloric acid, sulfuric acid, etc., a Lewis acid such as boron trichloride, boron tribromide, etc., a combination of a Lewis acid with either a thiol or a sulfide, or an organic acid such as trifluoroacetic acid, p-toluenesulfonic acid, etc. The alkaline hydrolysis can be carried out using a metal hydroxide such as sodium hydroxide, potassium hydroxide, barium hydroxide, etc., a metal carbonate such as sodium carbonate, potassium carbonate, etc., a metal alkoxide such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc., or an organic base such as triethylamine, imidazole, formamidine, etc., for instance. The acid or base is used in a proportion of about 0.5 to 20 mols, preferably about 0.5 to 10 mols, per mol of compound (XVIII). This reaction can be advantageously carried out in the absence of a solvent or in an inert solvent. There is no particular limitation on the kind of solvent that can be used unless the reaction is interefered with. Preferred are alcohols such as methanol, ethanol, propanol, etc., aromatic hydrocarbons such as benzene, toluene, etc., saturated hydrocarbons such as cyclohexane, hexane, etc., organic acids such as formic acid, acetic acid, etc., ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., nitriles such as acetonitrile, propionitrile, etc., ketones such as acetone, methyl ethyl ketone, etc., sulfoxides such as dimethyl sulfoxide etc., water, and mixtures of such solvents. The reaction time is generally 10 minutes to 60 hours, preferably 10 minutes to 12 hours. The reaction temperature is generally −10–200° C., preferably 0–120° C. Thus obtained compound (XIX) can be submitted to the next reaction either as the reaction mixture or after partial purification but can be easily isolated by per se known method and purified by the routine purification procedure such as recrystallization, distillation, chromatography, etc.

Compound (XX) (wherein n and ZD have the same meanings as respectively defined above) can be produced by subjecting compound (XVI) to condensation with compound (XIX), a reactive derivative of compound (XIX) or a salt of compound (XIX) in the same manner as described for the production of compound (XI) from compound (X).

Reference Example 51

Ethyl 4[N-benzyl-N(3,3-diphenylpropyl)amino]-1-piperidinecarboxylate

In a reactor equipped with a water trap, a solution of 3,3-diphenylpropylamine (4.9 g) and 1-ethoxycarbonyl-4-piperidone (4.0 g) in toluene (100 mL) was refluxed for 2 hours. This reaction mixture was concentrated under reduced pressure and the residue was dissolved in 80 mL of ethanol. After this solution was cooled with ice, 1.8 g of sodium cyanoborohydride and a small amount of bromocresol green were added. Then, 4N-hydrogen chloride solution in ethanol was added dropwise until the reaction mixture had turned yellow and, after completion of dropwise addition, the mixture was further stirred for 30 minutes. This reaction mixture was poured into an excess of aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure to give ethyl 4-[(3,3-diphenylpropyl)amino]-1-piperidinecarboxylate. This product was dissolved in 80 mL of N,N-dimethylformamide, followed by addition of 2.8 mL of benzyl bromide and 3.2 g of potassium carbonate, and the mixture was stirred at room temperature for 2 hours. This reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=6:1 to 3:1) to provide 7.8 g of the title compound. Yield based on 3,3-diphenylpropylamine was 73%.

Oil.

^{1}H-NMR ($CDCl_3$) δ: 1.18–1.40 (5H, m), 1.59–1.68 (2H, m), 2.10–2.20 (2H, m), 2.49–2.62 (5H, m), 3.60 (2H, s), 3.98–4.27 (5H, m), 7.10–7.35 (15H, m).

Reference Example 52

N-Benzyl-N-(3,3-diphenylpropyl)-4-piperidinamine

Using ethyl 4-[N-benzyl-N(3,3-diphenylpropyl)amino]-1-piperidinecarboxylate, the procedure of Reference Example 40 was otherwise repeated to provide the title compound. Yield 99%.

Oil.

^{1}H-NMR ($CDCl_3$) δ: 1.22–1.43 (2H, m), 1.63–1.75 (2H, m), 2.08–2.19 (2H, m), 2.40–2.61 (5H, m), 3.02–3.08 (2H, m), 3.62 (2H, s), 3.97 (1H, t, J=7.4 Hz), 7.10–7.36 (15H, m).

Reference Example 53

N-(2-Cyanomethyl-2,3-dihydro-2,4,6,7-tetramethylbenzofuran-5-yl)formamide

A solution of N-(2-bromomethyl-2,3-dihydro-2,4,6,7-tetramethylbenzofuran-5-yl)formamide (20 g) and sodium cyanide (17 g) in dimethyl sulfoxide (100 mL) was stirred under argon gas at 100° C. for 13 hours. This reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/diisopropyl ether to provide 14 g of the title compound. Yield 84%.

m.p. 183–185° C.

^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, s), 2.08–2.17 (9H, m), 2.73–2.75 (2H, m), 3.03–3.22 (2H, m), 6.65–6.76 (1H, m), 7.96 (0.4H, d, J=12.2 Hz), 8.41 (0.6H, d, J=1.4 Hz)

Reference Example 54

5-Amino-2,3-dihydro-2,4,6,7-tetramethyl-2-benzofuranacetic acid

To a solution of N-(2-cyanomethyl-2,3-dihydro-2,4,6,7-tetramethylbenzofuran-5-yl)formamide (14 g) in methanol (50 mL) was added 120 mL of 4.6N-aqueous sodium hydroxide and the mixture was refluxed under argon gas for 40 hours. This reaction mixture was neutralized with concentrated hydrochloric acid and extracted with chloroform. The extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was crystallized from chloroform/diisopropyl ether to provide 11 g of the title compound. Yield 82%.

m.p. 186–188° C.

^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, s), 1.95 (9H, s), 2.60 (2H, s), 2.84 (1H, d, J=15.6 Hz), 3.18 (1H, d, J=15.6 Hz).

Reference Example 55

5-[(Tert-butoxycarbonyl)amino]-2,3-dihydro-2,4,6,7-tetramethyl-2-benzofuranacetic acid

To a suspension of 5-amino-2,3-dihydro-2,4,6,7-tetramethyl-2-benzofuranacetic acid (8.3 g) in tetrahydrofuran (50 mL) was added a solution of di-tert-butyl dicarbonate (7.6 g) in a tetrahydrofuran (5 mL) as well as 34 mL of 1N-aqueous sodium hydroxide and the mixture was stirred at room temperature for 30 minutes. After ice-cooling, the reaction mixture was made acidic with 0.5M aqueous citric acid and extracted with ethyl acetate. The extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=2:1) to provide 11 g of the title compound. Yield 92%.

Oil.

^{1}H-NMR ($CDCl_3$) δ: 1.50–1.53 (9H, m), 1.58 (3H, s), 2.08–2.09 (6H, m), 2.13 (3H, s), 2.78 (2H, br s), 2.98 (1H, d, J=15.4 Hz), 3.25 (1H, d, J=15.4 Hz), 5.80 (1H, s).

Reference Example 56

Tert-butyl [2,3-dihydro-2-(2-hydroxyethyl)-2,4,6,7-tetramethylbenzofuran-5-yl]carbamate

To a solution of 5-[(tert-butoxycarbonyl)amino]-2,3-dihydro-2,4,6,7-tetramethyl-2benzofuranacetic acid (11 g) in 50 mL tetrahydrofuran was added 64 mL of 1M borane-tetrahydrofuran complex solution in tetrahydrofuran dropwise under ice-cooling and the mixture was stirred at room temperature for 12 hours. This reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with aqueous saturated NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=2:1) to provide 7.8 g of the title compound. Yield 76%.

Oil.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, s), 1.50 (9H, s), 1.89–2.16 (2H, m), 2.07 (3H, s), 2.10 (3H, s), 2.13 (3H, s), 2.35 (1H, br s), 2.91 (1H, d, J=15.4 Hz), 3.06 (1H, d, J=15.6 Hz), 3.71–3.97 (2H, m), 5.79 (1H, br s).

Reference Example 57

Tert-butyl [2-(2-bromoethyl)-2,3-dihydro-2,4,6,7-tetramethylbenzofuran-5-yl]carbamate

To a solution of tert-butyl [2,3-dihydro-2-(2-hydroxyethyl)-2,4,6,7-tetramethylbenzofuran-5-yl]

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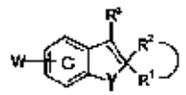
(54) PROMOTERS FOR THE PROLIFERATION AND DIFFERENTIATION OF STEM CELLS AND/OR NEURON PRECURSOR CELLS

(57) An agent for promoting the proliferation or differentiation of a stem cell and/or neural progenitor cell comprising a compound represented by Formula:



wherein each of R^1 and R^2 is H, a hydrocarbon group or a heterocyclic group, or taken together with the adjacent carbon atom to form a ring, R^3 is H, a hydrocarbon group or a heterocyclic group, W is a group represented by Formula:

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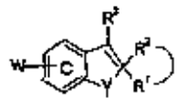
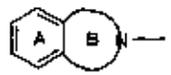
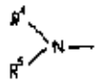


(I)

wherein R^1 and R^2 are same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R^1 and R^2 are taken together with the adjacent carbon atom to form an optionally substituted 3- to 8-membered homocyclic or heterocyclic ring,
R^3 is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group,
— is a single bond or a double bond,
W is (i) a group represented by Formula:



wherein Ring A is an optionally substituted benzene ring, Ring B is an optionally substituted 5- to 7-membered nitrogen-containing heterocyclic ring,
(ii) a group represented by Formula:



wherein R^4 is (1) an aliphatic hydrocarbon group which is substituted by an optionally substituted aromatic group and which may have a further substituent or (2) an optionally substituted aromatic ring-containing acyl group, R^5 is a hydrogen atom, a C_{1-6} alkyl or an acyl group, or,
(iii) a group represented by Formula:

$$R^{4c}-X- \qquad \text{(Wc)}$$

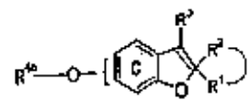
wherein R^{4c} is an optionally substituted aromatic group, an optionally substituted aliphatic hydrocarbon group or an acyl group, X is an oxygen atom or an optionally oxidized sulfur atom,
Y is an oxygen atom, an optionally oxidized sulfur atom or an optionally substituted imino,
Ring C is a benzene ring which may have a further substituent in addition to the group represented by W, or a salt or prodrug thereof has an unexpectedly excellent promoting effect on the proliferation or differentiation of a stem cell and neural progenitor cell, and based on this finding, made a further effort and established the present invention.

[0008] Thus, the present invention relates to:

(1) an agent for promoting the proliferation or differentiation of a stem cell and/or neural progenitor cell comprising a compound represented by Formula (I), or a salt or prodrug thereof;
(2) the agent according to the above-mentioned (1) wherein the stem cell is an embryonic stem cell or a neural stem cell;
(3) the agent according to the above-mentioned (1) which is an agent for promoting the engraftment or differentiation in neural stem cell, neural progenitor cell and/or neurocyte transplantation;
(4) the agent according to the above-mentioned (1) which is an agent for promoting the proliferation or differentiation of a neural stem cell, neural progenitor cell and/or neurocyte for transplantation;
(5) the agent according to the above-mentioned (1) which is an agent for promoting the proliferation or differentiation

of an intrinsic neural stem cell;
(6) the agent according to the above-mentioned (1) which is an agent for preventing or treating a central nervous system disease;
(7) the agent according to the above-mentioned (1) which is a nerve regeneration-promoting agent;
(8) the agent according to the above-mentioned (1) which is a nerve neogenesis-promoting agent;
(9) the agent according to the above-mentioned (1) wherein — is a single bond;
(10) the agent according to the above-mentioned (1) wherein Y is an oxygen atom;
(11) the agent according to the above-mentioned (1) wherein W is a group represented by Formula (We);
(12) the agent according to the above-mentioned (11) wherein each of R^1 and R^2 is a hydrogen atom or a C_{1-6} alkyl group, R^3 is a hydrogen atom or a phenyl group which may have 1 to 3 substituents selected from C_{1-6} alkyl and halogen, the Ring C is a benzene ring which may further have 1 to 3 substituents selected from C_{1-6} alkyl and C_{1-6} alkoxy, — is a single bond, Y is an oxygen atom, the group represented by Formula (We) is a group represented by Formula:

wherein Ring A^1 is a benzene ring which may have 1 to 3 substituents selected from halogen, C_{1-6} alkoxy and C_{1-6} alkylenedioxy;
(13) the agent according to the above-mentioned (12) wherein the group represented by Formula (We) is a substituent on the 5-position of the benzofuran ring;
(14) the agent according to the above-mentioned (11) comprising [1] 2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline, [2] 5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline, [3] 5,6-dimethoxy-2-[3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl]isoindoline, [4] 5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]-2H-isoindole, [5] 6-[3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl]-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]isoindole, [6] 6-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]-6H-[1,3]dioxolo[4,5-f]isoindole, [7] 6-[2,2,4,6,7-pentamethyl-3-phenyl-2,3-dihydro-1-benzofuran-5-yl]-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]isoindole, [8] (R)-5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline or [9] (R)-5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline hydrochloride;
(15) the agent according to the above-mentioned (11) comprising (R)-5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline,
(16) the agent according to the above-mentioned (1) wherein W is a group represented by Formula (We);
(17) the agent according to the above-mentioned (16) wherein each of R^1 and R^2 is a methyl group, R^3 is a phenyl group which may have 1 to 3 substituents selected from fluorine, methyl and isopropyl, the Ring C is a benzene ring which may further have 1 to 3 substituents selected from C_{1-6} alkyl and C_{1-6} alkoxy, Y is an oxygen atom, R^4 is a benzyl or phenethyl group which may have 1 to 3 substituents selected from fluorine, methoxy and methylenedioxy and R^5 is a hydrogen atom or a methyl group;
(18) the agent according to the above-mentioned (16) comprising (1) N-(4-fluorobenzyl)-2,2,4,6,7-pentamethyl-3-phenyl-2,3-dihydro-1-benzofuran-5-amine, (2) N-benzyl-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine, (3) 3-(4-isopropylphenyl)-N-(4-methoxybenzyl)-N,2,2,4,6,7-hexamethyl-2,3-dihydro-1-benzofuran-5-amine, (4) 3-(4-isopropylphenyl)-N-[2-(4-methoxyphenyl)ethyl]-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine, (5) N-(4-fluorobenzyl)-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine, (6) N-[1,3-benzodioxol-5-ylmethyl]-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine, (7) N-(4-fluorobenzyl)-3-(4-fluorophenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine, (8) N-(4-methoxybenzyl)-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine, (9) N-(4-fluorobenzyl)-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine, (10) 3-(4-isopropylphenyl)-N-(4-methoxybenzyl)-2,4,6,7-tetramethyl-1-benzofuran-5-amine, (11) N-(4-fluorobenzyl)-3-(4-isopropylphenyl)-2,4,6,7-tetramethyl-1-benzofuran-5-amine, (12) N-(4-fluorobenzyl)-3-(4-fluorophenyl)-2,4,6,7-tetramethyl-1-benzofuran-5-amine, (13) N-(4-fluorobenzyl)-3-(4-isopropylphenyl)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine]-5-amine or (14) (R)-N-(4-fluorobenzyl)-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine hydrochloride;
(19) the agent according to the above-mentioned (1) wherein W is a group represented by Formula (Wc);
(20) the agent according to the above-mentioned (19) comprising a compound represented by Formula:



wherein each of R^1 and R^2 is C_{1-6} alkyl which may have phenyl-substituted 6-membered saturated cyclic amino, *or R^1 and R^2 are taken together with the adjacent carbon atom to form a C_{1-6}* alkyl- or C_{2-6} alkyl-substituted pyperidine;
R^3 is (i) a hydrogen atom, or,
(ii) phenyl which may have 1 to 3 substituents selected from (1) C_{1-6} alkyl, (2) di-C_{1-6} alkylamino and (3) 6-membered saturated cyclic amino which may have C_{1-6} alkyl;
R^{4a} is (i) phenyl which may have 1 to 3 substituents selected from nitro and C_{1-6} alkyl-carbonamide,
(ii) C_{1-6} alkyl or C_{2-6} alkenyl having 1 to 3 phenyl, quinolyl or pyridyl which may have 1 to 3 substituents selected from C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxy-carbonyl, C_{1-6} alkylsulfonyl and C_{1-6} alkylsulfinyl and optionally further *having phenyl, carboxy or C_{1-6} alkoxy-carbonyl as additional substituents*, or,
(iii) acyl represented by Formula: -(C=O)-$R^{5'}$ wherein $R^{5'}$ is C_{1-6} alkoxy-substituted phenyl; and,
the Ring C is a benzene ring which may further have 1 to 3 C_{1-6} alkyl, or a salt or prodrug thereof;
(21) the agent according to the above-mentioned (16) comprising:
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran, 3-(4-methylphenyl)-2,4,6,7-tetramethylbenzofuran-5-yl 4-methoxybenzoate, 3-(4-isopropylphenyl)-2,4,6,7-tetramethylbenzofuran-5-yl 4-methoxybenzoate, 3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,4,6,7-tetramethylbenzofuran, 3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine] or a salt thereof;
(22) a method for culturing a stem cell, neural progenitor cell and/or neurocyte, comprising culturing the stem cell, neural progenitor cell and/or neurocyte in the presence of a compound according to the above-mentioned (1) or a salt thereof;
(23) the method according to the above-mentioned (22) wherein the stem cell is an embryonic stem cell or a neural stem cell;
(24) the method according to the above-mentioned (22) whereby a cell for transplantation therapy is prepared;
(25) a cell obtained by the method according to the above-mentioned (22);
(26) an agent for promoting proliferation or differentiation used in the culture of a stem cell, neural progenitor cell and/or neurocyte for transplantation, comprising a compound according to the above-mentioned (1) or a salt thereof;
(27) the agent according to the above-mentioned (1) which is an agent for treating a cognitive impairment or a memory impairment;
(28) the agent according to the above-mentioned (1) which is an agent for treating a mild cognitive impairment or a mild memory impairment;
(29) a use of a compound according to the above-mentioned (1) or a salt or prodrug thereof in the production of *an agent for promoting the proliferation or differentiation* in neural stem cell and/or neurocyte transplantation;
(30) a use of a compound according to the above-mentioned (1) or a salt or prodrug thereof in the production of an agent for promoting the proliferation or differentiation of a neural stem cell and/or neurocyte for transplantation;
(31) a use of a compound according to the above-mentioned (1) or a salt or prodrug thereof in the production of an agent for preventing or treating a central nervous system disease;
(32) a method for transplantation therapy of a stem cell, neural progenitor cell and/or neurocyte, comprising administering a compound according to the above-mentioned (1) or a salt or prodrug thereof; and
(33) a method for preventing or treating a central nervous system disease in a mammal, comprising administering *a compound* according to the above-mentioned (1) or a salt or prodrug thereof to the mammal in need of such a treatment.

Brief Description of Drawings

[0009] Figure 1 shows a graph indicating a differentiation promoting effect of a test compound on a neural stem cell in an Experimental Example described below.

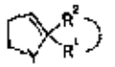
Detailed Description of the Invention

[0010] In the formula shown above, — is a single bond or a double bond. Preferably, — is a single bond.

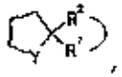
[0011] In the formula shown above, R^1 and R^2 are same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group or R^1 and R^2 may be taken together with the adjacent carbon atom to form an optionally substituted 5- to 8-membered homocyclic or heterocyclic ring.

[0012] In the formula shown above, when — is a double bond, then R^2 is not present. Thus, in the formula shown above:

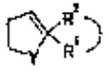
(i) when — is a single bond, the moiety:



is the moiety:

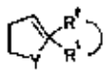


(ii) when — is a double bond, the moiety:



is the moiety:

but in this specification (i) and (ii) are sometimes unified to be represented just by Formula:



[0013] A "hydrocarbon group" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 may for example be a linear or branched or cyclic hydrocarbon group (e.g., alkyl, alkenyl, alkynyl, cycloalkyl, aryl). Among those listed above, a linear or branched or cyclic hydrocarbon group having 1 to 16 carbon atoms is preferred.

[0014] Preferred "alkyl" may for example be C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl).

[0015] Preferred "alkenyl" may for example be C_{2-6} alkenyl (e.g., vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl).

[0016] Preferred "alkynyl" may for example be C_{2-6} alkynyl (e.g., ethynyl, propargyl, butynyl, 1-hexynyl).

[0017] Preferred "cycloalkyl" may for example be C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl).

[0018] Preferred "aryl" may for example be C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-anthryl).

[0019] A "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 may for example be (1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine), (2) C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy), (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated C_{2-6} alkenyl, (7) optionally halogenated C_{2-6} alkynyl (8) optionally halogenated C_{3-6} cycloalkyl, (9) C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-anthryl), (10) optionally halogenated C_{1-6} alkoxy, (11) optionally halogenated C_{1-6} alkylthio or mercapto, (12) hydroxy, (13) amino, (14) mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino and the like), (15) mono-C_{6-14} arylamino (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino), (16) di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino), (17) di-C_{6-14} arylamino (e.g., diphenylamino), (18) acyl, (19) acylamino, (20) acyloxy, (21) optionally substituted 5- to 7-membered saturated cyclic amino, (22) a 5- to 10-membered aromatic heterocyclic group (e.g., 2- or 3-thienyl, 2-, 3-or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl), (23) sulfo, (24) C_{6-14} aryloxy (e.g., phenoxy, naphthyloxy).

[0020] The "hydrocarbon group" may have 1 to 5, preferably 1 to 3 of the above listed substituents in any substitutable positions, and when the number of the substituents is 2 or more, then each substituent may be same to or different from each other.

[0021] The "optionally halogenated C_{1-6} alkyl" mentioned above may for example be C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine). Those exemplified typically are methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl and the like.

[0022] The "optionally halogenated C_{2-6} alkenyl" mentioned above may for example be C_{2-6} alkenyl (e.g., vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine). Those exemplified typically are vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, 3,3,3-trifluoro-1-propenyl, 4,4,4-trifluoro-1-butenyl and the like.

[0023] The "optionally halogenated C_{2-6} alkynyl" mentioned above may for example be C_{2-6} alkynyl (e.g., ethynyl, propargyl, butynyl, 1-hexynyl) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine). Those exemplified typically are ethynyl, propargyl, butynyl, 1-hexynyl, 3,3,3-trifluoro-1-propynyl, 4,4,4-trifluoro-1-butynyl and the like.

[0024] The "optionally halogenated C_{3-6} cycloalkyl" mentioned above may for example be C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine). Those exemplified typically are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dichlorocyclohexyl, 2,2,3,3-tetrafluorocyclopentyl, 4-chlorocyclohexyl and the like.

[0025] The "optionally halogenated C_{1-6} alkoxy" mentioned above may for example be C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine). Those exemplified typically are methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy and the like.

[0026] The "optionally halogenated C_{1-6} alkylthio" mentioned above may for example be C_{1-6} alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine). Those exemplified typically are methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio and the like.

[0027] The "acyl" mentioned above may for example be formyl, carboxy, carbamoyl, C_{1-5} alkyl-carbonyl (e.g., acetyl, propanoyl), C_{3-6} cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl), C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, isopoxycarbonyl, tert-butoxycarbonyl), C_{6-14} aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl), C_{7-16} aralkyl-carbonyl (e.g., phenylacetyl, phenylpropionyl), C_{6-14} aryloxy-carbonyl (e.g., phenoxycarbonyl), C_{7-16} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl), 5- or 8-membered heterocyclic carbonyl (e.g., nicotinoyl, isonicotinoyl, 2-thenoyl, 3-thenoyl, 2-furoyl, 3-furoyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperidinocarbonyl, 1-pyrrolidinylcarbonyl), mono-C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl), di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl), C_{6-14} aryl-carbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl), thiocarbamoyl, 5- or 6-membered heterocyclic carbamoyl (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl), C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl), C_{6-14} arylsulfonyl (e.g., phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl), C_{1-6} alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl), C_{6-14} arylsulfinyl (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl).

[0028] The "acylamino" mentioned above may for example be formylamino, C_{1-5} alkyl-carbonylamino (e.g., acetylamino), C_{6-14} aryl-carbonylamino (e.g., phenylcarbonylamino, naphthylcarbonylamino), C_{1-6} alkoxy-carbon-

ylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino), C_{1-6} alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino), C_{6-14} arylsulfonylamino (e.g., phenylsulfonylamino, 2-naphthylsulfonylamino, 1-naphthylsulfonylamino).

[0029] The "acyloxy" mentioned above may for example be formyloxy, C_{1-6} alkyl-carbonyloxy (e.g., acetoxy, propionyloxy), C_{6-14} aryl-carbonyloxy (e.g., benzoyloxy, naphthylcarbonyloxy), C_{1-6} alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy), mono-C_{1-6} alkyl-carbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy), di-C_{1-6} alkyl-carbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy), C_{6-14} arylcarbamoyloxy (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy), nicotinoyloxy and the like.

[0030] A "5- to 7-membered saturated cyclic amino" in the "optionally substituted 5- to 7-membered saturated cyclic amino" mentioned above may for example be morpholino, thiomorpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl and the like. A "substituent" in such an "optionally substituted 5- to 7-membered saturated cyclic amino" may for example be C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl), C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-anthryl), 5- to 10-membered aromatic heterocyclic group (e.g., 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl), 1 to 3 of which may be employed.

[0031] A "substituent" in the "optionally substituted heterocyclic group" represented by R^1 or R^2 may for example be a 5- to 14-membered heterocyclic group (aromatic heterocyclic group, saturated or unsaturated non-aromatic heterocyclic group) containing 1 to 4 heteroatoms selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms.

[0032] Such "aromatic heterocyclic group" may for example be a 5- to 14-membered, preferably 5- to 10-membered aromatic heterocyclic group containing one or more (for example 1 to 4) heteroatoms selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Those exemplified typically are a monovalent group formed by removing any hydrogen atom from an aromatic heterocyclic ring such as thiophene, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furane, isoindolizine, xanthalene, phenoxathiine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, 4H-quinolizine, isoquinoline, quinoline, phthalazine, naphthylidine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, oxazole, isoxazole, furazane or phenoxazine, or a ring formed by condensation of any of the ring listed above (preferably monocyclic ring) with one or more (preferably 1 or 2) aromatic rings (e.g., benzene ring, etc.) and the like.

[0033] A preferred "aromatic heterocyclic group" may for example be a 5- or 6-membered aromatic heterocyclic group which may be fused with a single benzene ring. Those exemplified typically are 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, 2- or 3-thienyl and the like. Those employed more preferably are 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 3-quinolyl, 1-isoquinolyl, 1- or 2-indolyl, 2-benzothiazolyl and the like.

[0034] A "non-aromatic heterocyclic group" may for example be a 3- to 8-membered (preferably 5- to 6-membered) saturated or unsaturated (preferably saturated) non-aromatic heterocyclic group (aliphatic heterocyclic group) such as oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl and the like.

[0035] A "substituent" in the "optionally substituted heterocyclic group" represented by R^1 or R^2 is similar to the "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above, and the same numbers of such substituents is employed.

[0036] A "3- to 8-membered homocyclic ring" in the "optionally substituted 3- to 8-membered homocyclic ring" formed from R^1 and R^2 may for example be a C_{3-8} cycloalkane such as cyclopropane, cyclobutane, cyclopentan, cyclohexane and the like.

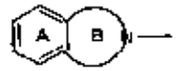
[0037] A "3- to 8-membered heterocyclic ring" in the "optionally substituted 3- to 8-membered heterocyclic ring" formed from R^1 and R^2 may for example be a 3- to 8-membered heterocyclic ring containing 1 to 4 heteroatoms selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms, such as aziridine, azetidine, morpholine, thiomorpholine, piperazine, piperidine, pyrrolidine, hexamethyleneimine, heptamethyleneimine, hexahydropyridothione and the like.

[0038] A "substituent" in the "optionally substituted 3- to 8-membered homocyclic or heterocyclic ring" formed from R^1 and R^2 is similar to the "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above, and the same number of such substituents is employed.

[0039] The "optionally substituted hydrocarbon group" and "optionally substituted heterocyclic group" represented by R^3 are similar to the "optionally substituted hydrocarbon group" and "optionally substituted heterocyclic group" represented by R^1 or R^2 described above.

[0040] In the formula shown above, W is:

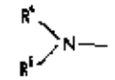
(i) a group represented by Formula:



(Wa)

wherein Ring A is an optionally substituted benzene ring, Ring B is an optionally substituted 5- to 7-membered nitrogen-containing heterocyclic ring,

(ii) a group represented by Formula:



(Wb)

wherein R^4 is (1) an aliphatic hydrocarbon group which is substituted by an optionally substituted aromatic group and which may have a further substituent or (2) an optionally substituted aromatic ring-containing acyl group, R^5 is a hydrogen atom, a C_{1-6} alkyl or an acyl group, or,

(iii) a group represented by Formula:

$$R^{4c}—X— \quad \text{(Wc)}$$

wherein R^{4c} is an optionally substituted aromatic group, an optionally substituted aliphatic hydrocarbon group or an acyl group, X is an oxygen atom or an optionally oxidized sulfur atom

[0041] When W is Wa, R^3 in the formula shown above is preferably a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group (hereinafter sometimes referred to as R^{3a}).

[0042] In the formula shown above, the Ring A is an optionally substituted benzene ring.

[0043] A "substituent" in the "optionally substituted benzene ring" represented by the Ring A is similar to the "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above, and the "optionally substituted benzene ring" may have 1 to 4 (preferably 1 or 2) such substituents at any substitutable positions, and when the number of such substituents is 2 or more, the substituents may be the same as or different from each other.

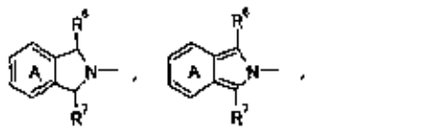
[0044] In the formula shown above, the Ring B is an optionally substituted 5- to 7-membered nitrogen-containing heterocyclic ring.

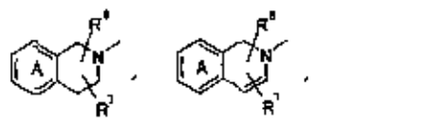
[0045] The "5- to 7-membered nitrogen-containing heterocyclic ring" represented by the Ring B may for example be a 5- to 7-membered nitrogen-containing heterocyclic ring such as pyrrole (e.g., 1H-pyrrole), dihydropyrrole (e.g., 2,5-dihydro-1H-pyrrole), dihydropyridine (e.g., 1,2-dihydropyridine), tetrahydropyridine (e.g., 1,2,3,4-tetrahydropyridine), azepine (e.g., 1H-azepine), dihydroazepine (e.g., 2,3-dihydro-1H-azepine, 2,5-dihydro-1H-azepine, 2,7-dihydro-1H-azepine), tetrahydroazepine (e.g., 2,3,6,7-tetrahydro-1H-azepine, 2,3,4,7-tetrahydro-1H-azepine) and the like.

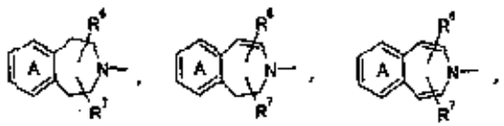
[0046] A "substituent" in the "optionally substituted 5- to 7-membered nitrogen-containing heterocyclic ring" represented by the Ring B is similar to the "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above, and the same number of such substituents is employed. The substituent on the Ring B may also be an oxo group and the like.

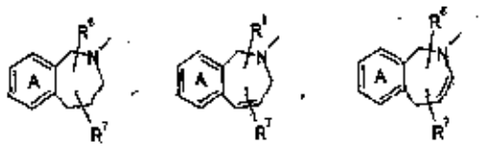
[0047] A group represented by Formula:

wherein each symbol is as defined above, is more typically a group represented by Formulae:

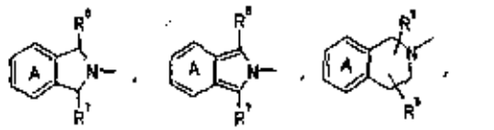


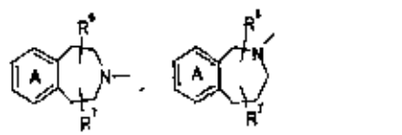




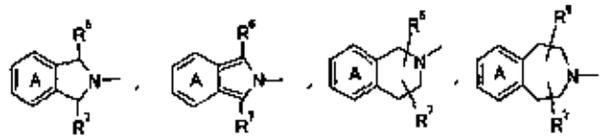


wherein R^6 and R^7 are same or different and each is a hydrogen atom, a halogen or an optionally substituted hydrocarbon group, and Ring A is as defined above, preferably a group represented by Formulas:

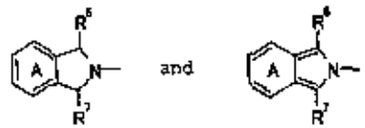




wherein each symbol is as defined above, more preferably a group represented by Formulas:



wherein each symbol is as defined above, especially a group represented by Formulas:



and

wherein each symbol is as defined above.

[0046] The "halogen" or "optionally substituted hydrocarbon group" represented by R^6 and R^7 is similar to the "halogen" or "optionally substituted hydrocarbon group" as "substituent" on the Ring B described above.

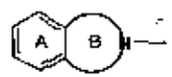
[0049] In the formula shown above, the Ring C is a benzene ring which may further have a substituent in addition to the group represented by W.

[0050] The Ring C may have 1 to 3 (preferably 1) groups represented by W at any substitutable positions, and when the number of the substituents is 2 or more, then they may be the same as or different from each other.

[0051] A "substituent" which the Ring C may further have is similar to the "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above. A "C_{1-6} alkyl" group as a "substituent" on the Ring C may be substituted for example by a "4- to 8-membered lactone which may be substituted for example by hydroxy (for example, 3-hydroxy-5-valerolactone)" or the like. The Ring C may have 1 to 3 (preferably 3) such substituents at any substitutable positions, and when the number of the substituents is 2 or more, then they may be the same as or different from each other.

[0052] The Ring C is preferably a benzene ring substituted by three C_{1-6} alkyl groups such as methyl.

[0053] When W is W_a, then the Ring C in the formula shown above is preferably a benzene ring which may further have a substituent selected from a halogen, optionally halogenated lower alkyl, optionally halogenated lower alkoxy and optionally halogenated lower alkylthio in addition to a group represented by Formula:



wherein each symbol is as defined above. (hereinafter sometimes referred to as Ring C^1).

[0054] The ring C^1 may have 1 to 3 (preferably 1) substituents represented by Formula:

at any substitutable positions, and when the number of the substituents is 2 or more, then they may be the same as or different from each other.

[0055] The "halogen" as a "substituent" which the ring C^1 may further have may for example be fluorine, chlorine, bromine or iodine. The "optionally halogenated lower alkyl" may for example be C_{1-6} alkyl (e.g., methyl, ethyl, propyl,

isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine), and those exemplified typically are methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl and the like.

[0056] The "optionally halogenated lower alkoxy" may for example be C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine). Those exemplified typically are methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy and the like. An "optionally halogenated lower alkylthio" group mentioned above may for example be C_{1-6} alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine). Those exemplified typically are methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio and the like.

[0057] The Ring C^1 may have 1 to 3 (preferably 3) such substituents at any substitutable positions, and when the number of the substituents is 2 or more, then they may be the same as or different from each other.

[0058] When W is W^b, then R^3 in the formula shown above is preferably an optionally substituted C_{6-14} aryl group (hereinafter sometimes referred to as R^{3b}).

[0059] A "C_{6-14} aryl" group in the "optionally substituted C_{6-14} aryl" represented by R^{3b} may for example be C_{6-14} aryl such as phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, anthryl and the like.

[0060] A "substituent" in such "optionally substituted C_{6-14} aryl" is similar to the "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above, and the same number of such substituents is employed.

[0061] In the formula shown above, R^4 is (1) an aliphatic hydrocarbon group which is substituted by an optionally substituted aromatic group and which may further have a substituent, or (2) an acyl group which may contain an optionally substituted aromatic group.

[0062] An "aromatic group" in the "optionally substituted aromatic group" as a substituent on the "aliphatic hydrocarbon group which has an optionally substituted aromatic group and which may further have a substituent" represented by R^4 may for example be an aromatic hydrocarbon group and an aromatic heterocyclic group.

[0063] Such "aromatic hydrocarbon group" may for example be a monocyclic or fused polycyclic (dicyclic or tricyclic) aromatic hydrocarbon group having 6 to 14 carbon atoms. Those exemplified typically are C_{6-14} aryl groups such as phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, anthryl and the like, preferably C_{6-10} aryl such as phenyl, 1-naphthyl, 2-naphthyl and the like.

[0064] Such "aromatic heterocyclic group" may for example be a 5- to 14-membered, preferably 5- to 10-membered aromatic heterocyclic group containing one or more (for example 1 to 4) heteroatoms selected from nitrogen, sulfur and oxygen atoms, in addition to carbon atoms. Those exemplified typically are a monovalent group formed by removing any hydrogen atom from an aromatic heterocyclic ring such as thiophene, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzothiadiazole, naphtho[2,3-b]thiophene, furfurane, isoindolidine, xantholene, phenoxathiine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, 4H-quinolidine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, oxazole, isoxazole, furazane or phenoxazine, or a ring formed by condensation of any of the ring listed above (preferably monocyclic ring) with one ore more (preferably 1 or 2) aromatic rings (e.g., benzene ring, etc.) and the like.

[0065] A preferred "aromatic heterocyclic group" may for example be a 5- or 6-membered aromatic heterocyclic group which may be fused with a single benzene ring. Those exemplified typically are 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, 2- or 3-thienyl and the like. Those employed more preferably are 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 3-quinolyl, 1-isoquinolyl, 1- or 2-indolyl, 2-benzothiazolyl and the like.

[0066] A "substituent" in the "optionally substituted aromatic group" is similar to the "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above, and the same number of such substituents is employed.

[0067] An "aliphatic hydrocarbon group" in the "aliphatic hydrocarbon group which has an optionally substituted aromatic group and which may further have a substituent" represented by R^4 may for example be alkyl, alkenyl, alkynyl, cycloalkyl and the like. Those preferred especially are C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalky and the like.

[0068] Preferred "alkyl" may for example be C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl).

[0069] Preferred "alkenyl" may for example be C_{2-6} alkenyl (e.g., vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl).

[0070] Preferred "alkynyl" may for example be C_{2-6} alkynyl (e.g., ethynyl, propargyl, butynyl, 1-hexynyl).

[0071] Preferred "cycloalkyl" may for example be C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl).

[0072] Among those listed above, a C_{1-6} alkyl group is preferred.

[0073] The "aliphatic hydrocarbon group" mentioned above may have 1 to 3 "optionally substituted aromatic groups" at any substitutable positions, and when the number of such substituents is 2 or more, then they may be the same as or different from each other.

[0074] A "substituent" which the "aliphatic hydrocarbon group" may further have is similar to the "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above, and the same number of such substituents is employed.

[0075] An "acyl group" in the "acyl group which may contain an optionally substituted aromatic group" represented by R^4 is similar to the "acyl group" as "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above.

[0076] An "optionally substituted aromatic group" in the "acyl group which may contain an optionally substituted aromatic group" represented by R^4 is similar to the "optionally substituted aromatic group" in the "aliphatic hydrocarbon group which has an optionally substituted aromatic group and which may further have a substituent" represented by R^4 described above.

[0077] Those exemplified typically as the "acyl group which may contain an optionally substituted aromatic group" represented by R^4 are preferably C_{6-14} aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl), C_{7-15} aralkyl-carbonyl (e.g., phenylacetyl, phenylpropionyl), C_{6-14} aryloxy-carbonyl (e.g., phenoxycarbonyl), C_{7-16} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl), 5- or 6-membered heterocyclic carbonyl (e.g., nicotinoyl, isonicotinoyl, 2-thenoyl, 3-thenoyl, 2-furoyl, 3-furoyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperidinocarbonyl, 1-pyrrolidinylcarbonyl), C_{6-14} aryl-carbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl), 5- or 6-membered heterocyclic carbamoyl (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl), C_{6-14} arylsulfonyl (e.g., phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl), C_{6-14} arylsulfinyl (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl).

[0078] In the formula shown above, R^5 is a hydrogen atom, a C_{1-6} alkyl group or an acyl group.

[0079] The C_{1-6} alkyl group represented by R^5 may for example be methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl and the like.

[0080] The "acyl group" represented by R^5 is similar to the "acyl group" as "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above.

[0081] When W is W^b, the Ring C in the formula shown above is a benzene ring which may further have a substituent in addition to a group represented by Formula: $-NR^4(R^5)$ (hereinafter sometimes referred to as ring C^2).

[0082] The Ring C^2 may have 1 to 3 groups represented by Formula: $-NR^4(R^5)$ at any substitutable positions, and when the number of the substituents is 2 or more, then each substituent may be same to or different from each other.

[0083] A "substituent" which the Ring C^2 may further have in addition to a group represented by Formula: $-NR^4(R^5)$ may for example be a halogen atom (e.g., fluorine, chlorine, bromine, iodine), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy), nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated C_{3-6} cycloalkyl, C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-anthryl), optionally halogenated C_{1-6} alkoxy, hydroxy, amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino), mono-C_{6-14} arylamino (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino), di-C_{6-14} arylamino (e.g., diphenylamino), acyl, acylamino, optionally substituted 5- to 7-membered saturated cyclic amino, 5- to 10-membered aromatic heterocyclic group (e.g., 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl), sulfo and the like.

[0084] Such "optionally halogenated C_{1-6} alkyl", "optionally halogenated C_{2-6} alkenyl", "optionally halogenated C_{2-6} alkynyl", "optionally halogenated C_{3-6} cycloalkyl", "optionally halogenated C_{1-6} alkoxy", "acyl", "acylamino" and "optionally substituted 5- to 7-membered saturated cyclic amino" may for example be similar to those described as "substituents" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above.

[0085] R^{4c} is an optionally substituted aromatic group, an optionally substituted aliphatic hydrocarbon group or an acyl group.

[0086] An "aromatic group" in the "optionally substituted aromatic group" represented by R^{4c} may for example be an aromatic hydrocarbon group, aromatic heterocyclic group and the like.

[0087] Such "aromatic hydrocarbon group" may for example be a monocyclic or fused polycyclic (dicyclic or tricyclic) aromatic hydrocarbon group having 6 to 14 carbon atoms. Those exemplified typically are C_{6-14} aryl groups such as phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, anthryl and the like.

[0088] Such "aromatic heterocyclic group" may for example be a 5- to 14-membered, preferably 5- to 10-membered

aromatic heterocyclic group containing one or more (for example 1 to 4) heteroatoms selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Those exemplified typically are a monovalent group formed by removing any hydrogen atom from an aromatic heterocyclic ring such as thiophene, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furane, isoindolidine, xantholene, phenoxathiine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, 4H-quinolidine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, oxazole, isoxazole, furazane or phenoxazine, or a ring formed by condensation of any of the ring listed above (preferably monocyclic ring) with one ore more (preferably 1 or 2) aromatic rings (e.g., benzene ring, etc.) and the like.

[0089] A preferred "aromatic heterocyclic group" may for example be a 5- or 6-membered aromatic heterocyclic group which may be fused with a single benzene ring. Those exemplified typically are 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, 2- or 3-thienyl and the like. Those employed more preferably are 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 3-quinolyl, 1-isoquinolyl, 1- or 2-indolyl, 2-benzothiazolyl and the like.

[0090] A "substituent" in the "optionally substituted aromatic group" may for example be a halogen atom (e.g., fluorine, chlorine, bromine, iodine), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy), nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino), optionally substituted 5- to 7-membered saturated cyclic amino, acyl, acylamino, acyloxy, sulfo, C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl), C_{6-14} aryloxy (e.g., phenyloxy, naphthyloxy) and the like.

[0091] Such "optionally halogenated C_{1-6} alkyl", "optionally halogenated C_{2-6} alkenyl", "optionally halogenated C_{2-6} alkynyl", "optionally halogenated C_{3-6} cycloalkyl", "optionally halogenated C_{1-6} alkoxy", "optionally halogenated C_{1-6} alkylthio", "optionally substituted 5- to 7-membered saturated cyclic amino", "acyl", "acylamino" and "acyloxy" may for example be similar to those described as "substituents" in an "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above.

[0092] The "aromatic group" mentioned above may have 1 to 3 substituents listed above at any substitutable positions, and when the number of the substituents is 2 or more, then they may be the same as or different from each other.

[0093] The "optionally substituted aromatic group" mentioned above is preferably phenyl, 2-, 3- or 4-pyridyl, 2- or 3-quinolyl, 1-isoquinolyl which may be substituted by 1 to 3 substituents selected from a halogen atom, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, optionally halogenated C_{2-6} alkynyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, optionally substituted 5- to 7-membered saturated cyclic amino, acyl, acylamino, acyloxy, sulfo, C_{6-14} aryl and C_{6-14} aryloxy.

[0094] An "aliphatic hydrocarbon group" in the "optionally substituted aliphatic hydrocarbon group" represented by R^{4C} may for example be alkyl, alkenyl, alkynyl, cycloalkyl and the like. Those preferred especially are C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalky and the like.

[0095] Preferred "alkyl" may for example be C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl).

[0096] Preferred "alkenyl" may for example be C_{2-6} alkenyl (e.g., vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl).

[0097] Preferred "alkynyl" may for example be C_{2-6} alkynyl (e.g., ethynyl, propargyl, butynyl, 1-hexynyl).

[0098] Preferred "cycloalkyl" may for example be C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl).

[0099] Among those listed above, a C_{1-6} alkyl group is preferred.

[0100] A "substituent" which the "aliphatic hydrocarbon group" may have is similar to the "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above, and the same number of such substituents is employed

[0101] Such "substituent" may for example be acyl (e.g., carboxy, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl) and the like.

[0102] The "acyl group" represented by R^{4C} is similar to the "acyl group" as "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above.

[0103] The "optionally oxidized sulfur atom" represented by X or Y may for example be S, SO and SO_2.

[0104] A "substituent" in the "optionally substituted imino" represented by Y may for example be optionally substituted hydrocarbon group and acyl.

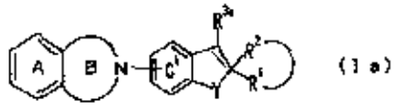
[0105] Such "optionally substituted hydrocarbon group" may for example be similar to the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above.

[0106] Such "acyl" may for example be the "acyl group" as "substituent" in the "optionally substituted hydrocarbon group" represented by R^1 or R^2 described above.

[0107] The "optionally substituted amino" represented by Y is preferably imino, C_{1-6} alkylimino (e.g., methylimino, ethylimino), C_{6-14} arylimino (e.g., phenylimino, 1-naphthylimino, 2-naphthylimino), C_{7-16} aralkylimino (e.g., benzylimino) and the like.

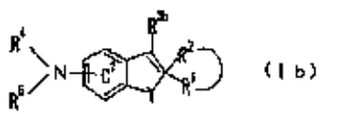
[0108] Each of X and Y is preferably an oxygen atom.

[0109] As described above, a compound (I) of the present invention includes a compound (Ia) represented by Formula:



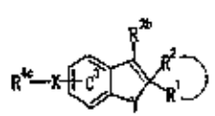
(Ia)

wherein each symbol is as defined above, a compound (Ib) represented by Formula:



(Ib)

wherein each symbol is as defined above and a compound (Ic) represented by Formula:



(Ic)

wherein each symbol is as defined above.

[0110] In the compound (Ia) shown above, R^1 and R^2 are same or different and preferably each is a hydrogen atom or an optionally substituted C_{1-6} alkyl group (especially a C_{1-3} alkyl group such as methyl), or R^1 and R^2 are taken together with the adjacent carbon atom to form an optionally substituted 5- to 8-membered homocyclic or heterocyclic ring, and more preferably each of R^1 and R^2 is a C_{1-6} alkyl group. When — is a double bond, then R^2 is not present, and R^1 is preferably an optionally substituted C_{1-6} alkyl group, especially a C_{1-3} alkyl group such as methyl.

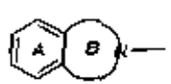
[0111] A preferred R^3 may for example be an optionally substituted C_{6-14} aryl group.

[0112] A preferred Ring A may for example be a benzene ring which may have 1 to 3 substituents selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkylenedioxy.

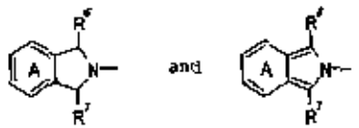
[0113] A preferred Ring B may for example be a 5- to 7-membered nitrogen-containing heterocyclic ring which may be substituted by 1 to 2 C_{1-6} alkyl groups.

[0114] A preferred Ring C^1 may for example be a benzene ring which may further be substituted by 1 to 3 substituents selected from C_{1-6} alkyl and C_{1-6} alkoxy groups.

[0115] A group represented by Formula:

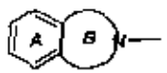


wherein each symbol is as defined above is preferably a group represented by Formulas:



wherein each symbol is as defined above. Specifically, in the above formulae, each of R^6 and R^7 is preferably a hydrogen atom, and the Ring A is preferably a benzene ring which may have 1 to 3 substituents selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkylenedioxy.

[0116] *The position at which the* Ring C^1 *is* substituted by a group represented by Formula:



wherein each symbol is as defined in Claim 1, is preferably the 5-position on the benzofuran ring or dihydrobenzofuran ring.

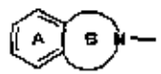
[0117] In an especially preferred Compound (Ia), each of R^1 and R^2 is a hydrogen atom or a C_{1-6} alkyl group (especially a C_{1-3} alkyl group such as methyl), R^{2a} is a hydrogen atom or a phenyl group which may have 1 to 3 substituents selected from C_{1-6} alkyl (especially a C_{1-3} alkyl group such as methyl, ethyl, propyl, isopropyl) and halogen atoms (especially fluorine), the Ring A is a benzene ring which may have 1 to 3 substituents selected from halogen, C_{1-6} alkyl (especially a C_{1-3} alkyl such as methyl) , C_{1-6} alkoxy (especially, a C_{1-3} alkoxy such as methoxy) and C_{1-6} alkylenedioxy (especially, a C_{1-3} alkylenedioxy such as methylenedioxy), the Ring B is a 5- to 7-membered nitrogen-containing heterocyclic ring which may be substituted by 1 or 2 C_{1-6} alkyl groups, the Ring C^1 is a benzene ring which may further have 1 to 3 substituents selected from C_{1-6} alkyl (especially a C_{1-3} alkyl such as methyl) and C_{1-6} alkoxy (especially, a C_{1-3} alkoxy such as methoxy) groups, and Y is an oxygen atom, and in a particularly preferred compound the group represented by Formula:

wherein each symbol is as defined above is a group represented by Formula:

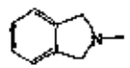
wherein Ring A^1 is a benzene ring which may have 1 to 3 substituents selected from halogen, C_{1-6} alkoxy and C_{1-6} alkylenedioxy.

[0118] When — is a double bond, then R^2 is not present, and a preferred R^1 may for example be a C_{1-6} alkyl group, especially a C_{1-3} alkyl group such as methyl. *While other symbols are preferably as defined above, a* particularly preferred compound is a compound wherein R^{2a} is a phenyl group which may have 1 to 3 C_{1-6} alkyl (especially C_{1-3} alkyl such as methyl, ethyl, propyl, isopropyl) groups, the Ring A is a benzene ring which may be substituted by 1 to 3 C_{1-6} alkoxy (especially methoxy) groups, the Ring B is a 5- to 7-membered nitrogen-containing heterocyclic ring, the Ring C^1 is a benzene ring which may further be substituted by 1 to 3 C_{1-6} alkyl (especially C_{1-3} alkyl *such as methyl*) groups (especially a benzene ring substituted by 3 C_{1-6} alkyl groups such as methyl groups), and Y is an oxygen atom.

One *especially preferred is a compound* wherein the group represented by Formula:



wherein each symbol is as defined above is a group represented by Formula:



[0119] *Examples of a Compound (Ib)* are preferably the compounds produced in the Example 1a to Example 22a described below, among those preferred are:

[1] 2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline (Example 4a) or a salt thereof,
[2] 5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline (Example 5a) or a salt thereof,
[3] 5,6-dimethoxy-2-[3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl]-isoindoline (Example 11a) or a salt thereof,
[4] 6-[3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl]-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]isoindole (Example 12a) or a salt thereof,
[5] 6-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]-6H-[1,3]dioxolo[4,5-f]isoindole (Example 14a) or a salt thereof,
[6] 6-[2,2,4,6,7-pentamethyl-3-phenyl-2,3-dihydro-1-benzofuran-5-yl]-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]isoindole (Example 15a) or a salt thereof,
[7] (R)-5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline (Example 17a),
[8] (R)-5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline hydrochloride (Example 18a),
[9] 5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]-2H-isoindole (Example 23a) or a salt thereof, among which those preferred especially are:

[1] 5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline (Example 5a),
[2] 6-[3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl]-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]isoindole (Example 12a),
[3] (R)-5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline (Example 17a),
[4] (R)-5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline hydrochloride (Example 18a),
[5] 5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]-2H-isoindole (Example 23a),

[0120] *In the Compound (Ib) described above, preferably* R^1 and R^2 are same or different and each is a hydrogen atom or an optionally substituted C_{1-6} alkyl group (especially C_{1-3} alkyl group such as methyl) or R^1 and R^2 are taken together with the adjacent carbon atom to form an optionally substituted 3- to 8-membered homocyclic ring (a C_{3-8} cycloalkane such as cyclopropane, cyclobutane, cyclopentane, cyclohexane), and more preferably R^1 and R^2 are same or different and each is a hydrogen atom or a C_{1-6} alkyl group (*especially* C_{1-3} *alkyl group such as methyl*) or R^1 and R^2 are taken together with the adjacent carbon atoms to form a 3-to 8-membered homocyclic ring. Among those, each of R^1 and R^2 is preferably a C_{1-6} alkyl group, especially methyl.

[0121] A preferred R^{2a} may for example be a phenyl group which may have 1 to 3 substituents selected from halogen (especially, fluorine) and C_{1-6} alkyl (especially C_{1-3} alkyl such as methyl, ethyl, propyl, isopropyl), and more preferred

one is a phenyl group which may be substituted by fluorine, methyl or isopropyl.

[0122] A preferred R^4 may for example be (1) a C_{1-6} alkyl group substituted by an aromatic group (especially, a C_{6-14} aryl group such as phenyl or a 5- or 6-membered aromatic heterocyclic group containing 1 to 3 heteroatoms selected from nitrogen, oxygen, sulfur and the like in addition to carbon atoms such as thienyl and pyridyl) which may have 1 to 3 substituents selected from halogen, C_{1-6} alkoxy and C_{1-3} alkylenedioxy, or (2) an acyl group containing an aromatic group (especially, a C_{6-14} aryl group such as phenyl) which may have 1 to 3 substituents selected from halogen, C_{1-6} alkoxy and C_{1-3} alkylenedioxy, and more preferably (1) a C_{1-6} alkyl group (especially C_{1-3} alkyl such as methyl) substituted by a C_{6-14} aryl group (especially, phenyl), thienyl or pyridyl which may have 1 to 3 substituents selected from halogen (especially, fluorine, chlorine), C_{1-6} alkoxy (especially C_{1-3} alkoxy such as methoxy) and C_{1-3} alkylenedioxy (especially, methylenedioxy) or (2) a C_{6-14} aryl-carbonyl group (especially, phenylcarbonyl group), C_{7-16} aralkyl-carbonyl group (especially, benzylcarbonyl group), C_{6-14} aryl-sulfonyl group (especially, phenylsulfonyl group), nicotinoyl group or thenoyl group which may have 1 to 3 substituents selected from halogen (especially, fluorine, chlorine), C_{1-6} alkoxy (especially C_{1-3} alkoxy such as methoxy) and C_{1-3} alkylenedioxy (especially, methylenedioxy). One preferred especially is a benzyl group or a phenethyl group which may have 1 to 3 substituents selected from fluorine, methoxy and methylenedioxy.

[0123] A preferred R^5 may for example be a hydrogen atom, a C_{1-6} alkyl group (especially C_{1-3} alkyl such as methyl) or a C_{1-6} alkyl-carbonyl group (especially C_{1-3} alkyl-carbonyl group such as acetyl), more preferably it is a hydrogen atom or a methyl group.

[0124] A preferred Ring C^2 may for example be a benzene ring which may be further substituted by 1 to 3 C_{1-6} alkyl (especially C_{1-3} alkyl such as methyl) groups, more preferably it is a benzene ring substituted further by 3 methyl groups.

[0125] In an especially preferred Compound (Ib), R^1 and R^2 are same or different and each is a hydrogen atom or a C_{1-6} alkyl group (especially C_{1-3} alkyl group such as methyl) or R^1 and R^2 are taken together with the adjacent carbon atom to form a 3- to 8-membered homocyclic ring;

R^{3b} is a phenyl group which may have 1 to 3 substituents selected from halogen (especially, fluorine) and C_{1-6} alkyl (especially C_{1-3} alkyl such as methyl, ethyl, propyl, isopropyl);

R^4 is (1) a C_{1-6} alkyl group (especially C_{1-3} alkyl such as methyl) substituted by a C_{6-14} aryl group (especially, phenyl), thienyl or pyridyl which may have 1 to 3 substituents selected from halogen (especially, fluorine, chlorine), C_{1-6} alkoxy (especially C_{1-3} alkoxy such as methoxy) and C_{1-3} alkylenedioxy (especially, methylenedioxy) or (2) a C_{6-14} aryl-carbonyl group (especially, phenylcarbonyl group), C_{7-16} aralkyl-carbonyl group (especially, benzylcarbonyl group), C_{6-14} aryl-sulfonyl group (especially, phenylsulfonyl group), nicotinoyl group or thenoyl group which may have 1 to 3 substituents selected from halogen (especially, fluorine, chlorine), C_{1-6} alkoxy (especially C_{1-3} alkoxy such as methoxy) and C_{1-3} alkylenedioxy (especially, methylenedioxy);

R^5 is a hydrogen atom, a C_{1-6} alkyl group (especially C_{1-3} alkyl such as methyl) or a C_{1-6} alkyl-carbonyl group (especially C_{1-3} alkyl-carbonyl group such as acetyl);

Y is an oxygen atom; and,

the ring C^2 is a benzene ring further substituted by 1 to 3 C_{1-6} alkyl (especially C_{1-3} alkyl such as methyl) groups, and in a further preferred Compound,

each of R^1 and R^2 is a methyl group;

R^{3b} is a phenyl group optionally substituted by fluorine, methyl or isopropyl;

R^4 is a benzyl group or a phenethyl group optionally substituted by fluorine, methoxy or methylenedioxy;

R^5 is a hydrogen atom or a methyl group;

-- is a single bond;

Y is an oxygen atom; and,

the Ring C^2 is a benzene ring further substituted by 3 methyl groups.

[0126] When -- is a double bond, then R^2 is not present, and R^1 is preferably a C_{1-6} alkyl group or the like, especially a C_{1-3} alkyl group such as methyl. While other symbols are preferably as defined above, a particularly preferred compound is a compound wherein R^{3b} is a phenyl group which may have 1 to 3 substituents selected from halogen (especially, fluorine) and C_{1-6} alkyl (especially C_{1-3} alkyl such as methyl, ethyl, propyl, isopropyl); R^4 is (1) a C_{1-6} alkyl group (especially C_{1-3} alkyl such as methyl) substituted by a C_{6-14} aryl group (especially, phenyl) which may have 1 to 3 substituents selected from halogen (especially, fluorine) and C_{1-6} alkoxy (especially C_{1-3} alkoxy such as methoxy) or (2) a C_{6-14} aryl-carbonyl group (especially, phenylcarbonyl group) or a C_{7-16} aralkyl-carbonyl group (especially, benzylcarbonyl group) which may have 1 to 3 substituents selected from halogen (especially, fluorine) and C_{1-6} alkoxy (especially C_{1-3} alkoxy such as methoxy); R^5 is a hydrogen atom; Y is an oxygen atom; and the Ring C^2 is a benzene ring substituted further by 1 to 3 C_{1-6} alkyl (especially C_{1-3} alkyl such as methyl) groups (especially a benzene ring substituted by 3 C_{1-3} alkyl groups such as methyl).

[0127] Examples of a Compound (Ib) are preferably the compounds produced in the *Example 1b to Example 57b* described below, among which those preferred are:

(1) N-(4-fluorobenzyl)-2,2,4,6,7-pentamethyl-3-phenyl-2,3-dihydro-1-benzofuran-5-amine (Example 4b) or a salt thereof,

(2) N-benzyl-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine (Example 6b) or a salt thereof,

(3) 3-(4-isopropylphenyl)-N-(4-methoxybenzyl)-N,2,2,4,6,7-hexamethyl-2,3-dihydro-1-benzofuran-5-amine (Example 9b) or a salt thereof,

(4) 3-(4-isopropylphenyl)-N-[2-(4-methoxyphenyl)ethyl]-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine (Example 11b) or a salt thereof,

(5) N-(4-fluorobenzyl)-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine (Example 15b) or a salt thereof,

(6) N-(1,3-benzodioxol-5-ylmethyl)-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine (Example 23b) or a salt thereof,

(7) N-(4-fluorobenzyl)-3-(4-fluorophenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine (Example 31b) or a salt thereof,

(8) N-(4-methoxybenzyl)-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine (Example 33b) or a salt thereof,

(9) N-(4-fluorobenzyl)-2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-amine (Example 35b) or a salt thereof,

(10) 3-(4-isopropylphenyl)-N-(4-methoxybenzyl)-2,4,6,7-tetramethyl-1-benzofuran-5-amine (Example 45b) or a salt thereof,

(11) N-(4-fluorobenzyl)-3-(4-isopropylphenyl)-2,4,6,7-tetramethyl-1-benzofuran-5-amine (Example 47b) or a salt thereof,

(12) N-(4-fluorobenzyl)-3-(4-fluorophenyl)-2,4,6,7-tetramethyl-1-benzofuran-5-amine (Example 51b) or a salt thereof,

(13) N-(4-fluorobenzyl)-3-(4-isopropylphenyl)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine]-5-amine (Example 55b) or a salt thereof,

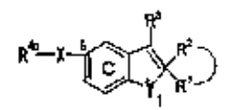
(14) (R)-N-(4-fluorobenzyl)-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine hydrochloride (Example 61b) or other salts thereof, and among those preferred especially are:

(1) N-(4-fluorobenzyl)-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine (Example 15b),

(2) N-(4-fluorobenzyl)-3-(4-isopropylphenyl)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine]-5-amine (Example 55b),

(3) (R)-N-(4-fluorobenzyl)-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-amine hydrochloride (Example 61b) and the like.

[0128] A group represented by Formula: -X-R^{4b} preferably substitute the 5-position on the backbone structure as shown below,



[0129] In a preferred Compound (Ic), each of R^1 and R^2 is C_{1-6} alkyl which may have 1 to 3 substituents selected from (1) C_{6-14} aryl, (2) C_{1-6} alkoxy, (3) C_{1-6} alkylthio, (4) hydroxy, (5) amino, (6) mono-C_{1-6} alkylamino, (7) mono-C_{6-14} arylamino, (8) di-C_{1-6} alkylamino, (9) di-C_{6-14} arylamino, (10) carboxy, (11) C_{1-6} alkylsulfonyl, (12) C_{6-14} arylsulfonyl, (13) C_{1-6} alkylsulfinyl, (14) C_{6-14} arylsulfinyl and (15) 5- to 7-membered saturated cyclic amino which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl and 5- to 10-membered aromatic group, or,

R^1 and R^2 are taken together with the adjacent carbon atom to form a 3- to 8-membered homocyclic or heterocyclic ring which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl, C_{7-16} aralkyl and 5- to 10-membered aromatic heterocyclic group;

R^3 is phenyl, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 4-isoquinolyl, 1-indolyl, 2-indolyl or 2-benzothiazolyl which may have 1 to 3 substituents selected from (1) halogen atom, (2) C_{1-6} alkyl, (3) C_{1-6} alkoxy, (4) amino, (5) mono-C_{1-6} alkylamino, (6) di-C_{1-6} alkylamino and (7) 5- to 7-mem-

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bered saturated cyclic amino which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl and 5- to 10-membered aromatic group;

R^{4c} is (i) C_{1-6} alkyl which has a phenyl, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 1-indolyl, 2-indolyl or 2-benzothiazolyl which may have 1 to 3 substituents selected from (1) halogen atom, (2) C_{1-6} alkyl, (3) C_{1-6} alkoxy, (4) hydroxy, (5) amino, (6) mono-C_{1-6} alkylamino, (7) di-C_{1-6} alkylamino, (8) carboxy and (9) 5-to 7-membered saturated cyclic amino which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl and 5- to 10-membered aromatic group and which may further have carboxy or C_{1-6} alkoxycarbonyl; or,

(ii) C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{6-14} aryl-carbonyl or C_{7-16} aralkyl-carbonyl which may have 1 to 3 substituents selected from (1) halogen atom, (2) C_{1-6} alkyl, (3) C_{1-6} alkoxy, (4) hydroxy, (5) amino, (6) mono-C_{1-6} alkylamino, (7) di-C_{1-6} alkylamino and (8) carboxy;

X is an oxygen atom;

Y is an oxygen atom;

the ring C^2 is a benzene ring which may have 1 to 3 substituents selected from a halogen atom, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino and di-C_{1-6} alkylamino.

[0130] In a more preferred compound, each of R^1 and R^2 is a C_{1-6} alkyl group which may have 1 to 3 substituents selected from C_{6-14} aryl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, mono-C_{7-14} aryl amino, di-C_{1-6} alkylamino, di-C_{6-14} arylamino, carboxy, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl and C_{6-14} arylsulfinyl, or,

R^1 and R^2 are taken together with the adjacent carbon atom to form a piperidine which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{6-14} aryl and C_{7-16} aralkyl;

R^3 is phenyl which may have 1 to 3 substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino and di-C_{1-6} alkylamino;

R^4 is (i) C_{1-6} alkyl having a phenyl or pyridyl which may have 1 to 3 substituents selected from a halogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino and carboxy, or,

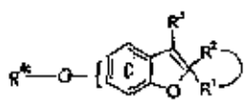
(ii) acyl represented by Formula: -(C=O)-$R^{4'}$ wherein $R^{4'}$ is phenyl or phenyl-C_{1-6} alkyl which may have 1 to 3 substituents selected from a halogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino and carboxy;

X is an oxygen atom;

Y is an oxygen atom;

the Ring C^3 is a benzene ring which may have 1 to 3 substituents selected from a halogen atom, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino and di-C_{1-6} alkylamino.

[0131] One also preferred is a compound represented by Formula:



wherein each of R^1 and R^2 is C_{1-6} alkyl which may have 6-membered saturated cyclic amino substituted by phenyl, or R^1 and R^2 are taken together with the adjacent carbon atom to form a piperidine substituted by C_{1-6} alkyl or C_{7-16} aralkyl;

R^3 is (i) a hydrogen atom, or,

(a) phenyl which may have 1 to 3 substituents selected from (1) C_{1-6} alkyl, (2) di-C_{1-6} alkylamino and (3) 6-membered saturated cyclic amino which may have C_{1-6} alkyl;

R^{4c} is (i) phenyl which may have 1 to 3 substituents selected from nitro and C_{1-6} alkyl-carbonamide,

(ii) C_{1-6} alkyl or C_{2-6} alkenyl having 1 to 3 phenyl, quinolyl or pyridyl which may have 1 to 3 substituents selected from C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxy-carbonyl, C_{1-6} alkylsulfonyl and C_{1-6} alkylsulfinyl and optionally further having phenyl, carboxy or C_{1-6} alkoxy-carbonyl as additional substituents, or,

(iii) acyl represented by Formula: -(C=O)-$R^{5'}$ wherein $R^{5'}$ is C_{1-6} alkoxy-substituted phenyl; and,

the Ring C is a benzene ring which may further have 1 to 3 C_{1-6} alkyl (especially, a benzene ring substituted by 3 C_{1-6} alkyl groups such as methyl).

[0132] Examples of a Compound (Ic) are preferably the compounds produced in the Example 1c to 33c described below. Among those preferred are

3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran, 3-(4-methylphenyl)-2,4,6,7-tetramethylbenzofuran-5-yl 4-methoxybenzoate,
3-(4-isopropylphenyl)-2,4,6,7-tetramethylbenzofuran-5-yl 4-methoxybenzoate,
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,4,6,7-tetramethylbenzofuran,
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine],
3-(4-isopropylphenyl)-5-(3-pyridylmethyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran and their salts.

[0133] Among those listed above, the preferred compounds are:

3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran, 3-(4-methylphenyl)-2,4,6,7-tetramethylbenzofuran-5-yl 4-methoxybenzoate,
3-(4-isopropylphenyl)-2,4,6,7-tetramethylbenzofuran-5-yl 4-methoxybenzoate,
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,4,6,7-tetramethylbenzofuran,
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine] and their salts.

[0134] A salt of a compound described above having an acidic group such as -COOH may for example be a metal salt, ammonium salt and a salt with an organic base, while one having a basic group such as $-NH_2$ may for example be a salt with an inorganic acid, organic acid, basic or acidic amino acid and the like as well as an intramolecular salts. A preferred metal salt may for example be an alkaline metal salt such as sodium and potassium salts; an alkaline earth metal salt such as calcium salt, magnesium salt and barium salt; as well as aluminum salt. A preferred salt with an organic base may for example be a salt with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine or N,N'-dibenzylethylenediamine. A preferred salt with an inorganic acid may for example be a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. A preferred salt with an organic acid may for example be a salt with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. A preferred salt with a basic amino acid may for example be a salt with arginine, lysine or ornithine. A preferred salt with acidic amino acid may for example be a salt with aspartic acid or glutamic acid.

[0135] Among those listed above, pharmaceutically acceptable salts are preferred. For example, a compound having an acidic functional group therein is presented as an inorganic salt such as an alkaline metal salt (e.g., sodium salt, potassium salt), alkaline earth metal salt (e.g., calcium salt, magnesium salt, barium salt) as well as ammonium salt, while one having a basic functional group therein is presented as an inorganic salt such as hydrochloride, sulfate, phosphate and hydrobromide or an organic salt such as acetate, maleate, fumarate, succinate, methanesulfonate, p-toluenesulfonate, citrate, tartrate and the like.

[0136] A Compound (I) (including Compound (Ia), (Ib) and (Ic)) can be produced by a method known per se, such as those described for example in WO99/55454, WO00/35262, WO95/28907, JP-A-5-194468, USP4,881,967, USP4,212,885 and Tetrahedron Letters, Vol.37, No.51, page 9183-9186 (1996) or analogous methods.

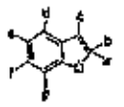
[0137] A prodrug of a Compound (I) may be a compound which is converted into a Compound (I) by a reaction with an enzyme or gastric acid or the like under an in vivo physiological condition, that is a compound undergoing an enzymatic oxidation, reduction or hydrolysis to form the Compound (I) and a compound being hydrolyzed by gastric acid or the like to form the Compound (I).

[0138] A prodrug for a Compound (I) may for example be a compound obtained by subjecting an amino group of the Compound (I) to acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group of the Compound (I) to eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation and tert-butylation); a compound obtained by subjecting a hydroxyl group of the Compound (I) to acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting a hydroxyl group of the Compound (I) to acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation, or dimethylaminomethylcarbonylation); a compound obtained by subjecting a carboxyl group of a compound, which is obtained by esterifying or amidating the carboxyl group of the Compound (I), to ethylesterification, phenylesterification, carboxymethylesterification, dimethylaminoesterification, pivaloyloxymethylesterification, ethoxycarbonyloxyethylesterification, phthalidylesterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylesterification, cyclohexyloxycarbonylethylesterification and methylamidation) and the like. Any of these compounds can be produced from a Compound (I) by a method known per se.

[0139] A prodrug for a Compound (I) may also be one which is converted into the Compound (I) under a physiological condition, such as those described in "IYAKUHIN no KAIHATSU (Development of Pharmaceuticals)", Vol.7, Design of Molecules, p.163-198, Published by HIROKAWA SHOTEN (1990).

[0140] A Compound (I) or a salt or prodrug thereof (hereinafter sometimes just referred to as Compound (I)) has excellent pharmaceutical effects such as neural stem cell auto-replication-promoting effect, neural progenitor cell dif-

Table 2



example number	a	b	c	d	e	f	g	mp
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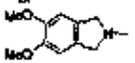
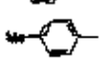
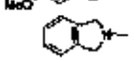
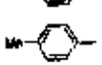
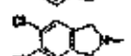
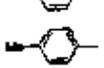
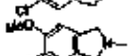
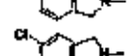
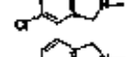
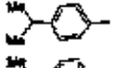
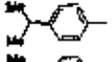
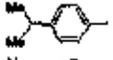
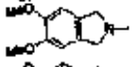
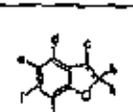
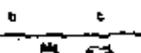
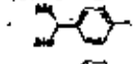
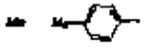
2a	Me	Me		Me		Me	Me	—
3a	Me	Me		Me		Me	Me	—
4a	Me	Me		Me		Me	Me	—
5a	Me	Me		Me		Me	Me	—
6a	Me	Me		Me		Me	Me	—
7a	Me	Me		Me		Me	Me	—
8a	Me	Me		Me		Me	Me	—
9a	Me	Me		Me		Me	Me	—
10a	Me	Me		Me		Me	Me	—
11a	Me	Me		Me		Me	Me	—
12a	Me	Me		Me		Me	Me	—

Table 2



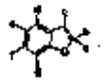
example number	a	b	c	d	e	f	g	mp	salt
13a	Me	-		Me		Me	Me	—	
14a	Me	Me		Me		Me	Me	—	
15a	Me	Me	N	Me		Me	Me	—	
16a	Me	Me		Me		Me	Me	—	
17a	Me	Me		Me		Me	Me	—	
18a	Me	Me		Me		Me	Me	—	
19a	Me	Me		Me		Me	Me	—	HCl
20a	Me	Me		Me		Me	Me	—	HCl
21a	Me	Me		Me		Me	Me	—	HBr
22a	Me	Me		Me		Me	Me	—	HBr
23a	Me	Me		Me		Me	Me	—	

Formulation Example 1a

[0256]

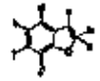
(1) The compound obtained in Example 14a	50 mg
(2) Lactose	34 mg
(3) Corn starch	10.6 mg
(4) Corn starch (Paste)	5 mg
(5) Magnesium Stearate	0.4 mg
(6) Calcium carboxymethyl cellulose	20 mg
Total	120 mg

Table 3



example number	a	b	c	d	e	f	g	m
10								—
11								—
12								—
13								—
14								—
15								—
16								—
17								—
18								—
19								—
19a								—
19b								—
19c								—
19d								—
19e								—
19f								—
19g								—
19h								—
19i								—

Table 4



example number	a	b	c	d	e	f	g	m
19j								—
19k								—
19l								—
19m								—
19n								—
19o								—
19p								—
19q								—
19r								—
19s								—
19t								—
19u								—
19v								—
19w								—
19x								—
19y								—
19z								—
19aa								—
19ab								—

Table 5

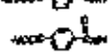
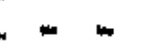
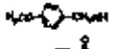
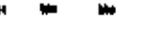
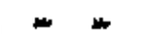
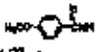
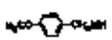
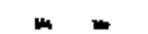
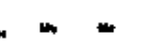
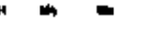
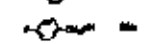
Example number	a	b	c	d	e	f	g	—
365	Me	Me		Me		Me	Me	—
366	Me	Me		Me		Me	Me	—
367	Me	Me		Me		Me	Me	—
368	Me	-		Me		Me	Me	—
369	Me	-		Me		Me	Me	—
370	Me	-		Me		Me	Me	—
371	Me	-		Me		Me	Me	—
372	Me	-		Me		Me	Me	—
373	Me	-		Me		Me	Me	—
374	Me	-		Me		Me	Me	—
375	Me	-		Me		Me	Me	—
376	Me	-		Me		Me	Me	—
377	Me	-		Me		Me	Me	—
378	Me	-		Me		Me	Me	—
379	Me	-		Me		Me	Me	—
380	Me	-		Me		Me	Me	—
381	Me	-		Me		Me	Me	—
382	Me	-		Me		Me	Me	—
383	Me	-		Me		Me	Me	—
384	Me	-		Me		Me	Me	—
385	Me	-		Me		Me	Me	—
386	Me	-		Me		Me	Me	—
387	Me	-		Me		Me	Me	—
388	Me	-		Me		Me	Me	—
389	Me	-		Me		Me	Me	—
390	Me	-		Me		Me	Me	—
391	Me	-		Me		Me	Me	—
392	Me	-		Me		Me	Me	—

Table 6

Example number	c	d	e	f	g	h
525		Me		Me	Me	Me
526		Me		Me	Me	Me
545		Me		Me	Me	Me
546		Me		Me	Me	Me
547		Me		Me	Me	Me
578		Me		Me	Me	Me

Table 7

example number	a	b	c	d	e	f	g	optical rotatory power
10a	ph	Me		ph		Me	ethyl	—
10b	ph	Me		ph		Me	ethyl	—
10c	ph	Me		ph		Me	Me	—
10d	ph	Me		ph		Me	Me	—
10e	ph	Me		ph		Me	Me	—
10f	ph	Me		ph		Me	Me	—
10g	ph	Me		ph		Me	Me	—
10h	ph	Me		ph		Me	Me	—
10i	ph	Me		ph		Me	Me	—
10j	ph	Me		ph		Me	Me	—

Formulation Example 1b

[0350]

(1) The compound obtained in Example 10b	50 mg
(2) Lactose	34 mg
(3) Corn starch	14.8 mg
(4) Corn starch (paste)	5 mg
(5) Magnesium Stearate	0.4 mg
(6) Calcium carboxymethyl cellulose	20 mg
Total	120 mg

[0351] According to a conventional method, tablets were prepared by mixing the above-described substances (1) to (6), and then subjecting the resulting mixture to a tablet compression process By using a tablet compression machine.

[Compounds (Ic)]

Reference Example 1c

Methyl α-bromophenylacetate

[0352] Concentrated sulfuric acid (0.5 mL) was added to a solution of α-bromophenylacetic acid (3.00 g, 13.9 mmol) in ethanol (30 mL) at room temperature, and the mixture was heated under reflux for 1 hour. The reaction mixture was cooled, and extracted twice with ethyl acetate. The organic layers were combined, washed with an aqueous saturated sodium hydrogencarbonate, then dried over magnesium sulfate, filtered, and concentrated under reduced pressure to